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Association of oxidative stress status, IL-13 and immunoglobulines levels in COVID-19 patients with or without vaccination in Babylon Governorate

A Thesis Submitted to the Council of the College of Science for Women University of Babylon in a Partial Fulfilments of the Requirements for the Degree of Master of Science in Chemistry

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ ﴾

سورة الشعراء الاية (80)

- صدق الله العظيم

Dedication

To the lord of the worlds Allah,..

To my great teacher and messenger,Mohammed (May Allah bless and grant him),..

To the souls of the martyrs of Iraq whose blood we live in safety ,..
To my homeland Iraq..
To my Mother and Father ...by their prayers things will be easy .
To my husband ...whow helped me during difficult circumstances and encouraged me

To my daughter and sons (Tuka , Takee AL- Deen ,Mohamed)
To all my brothers and sisters and all family I dedicate my scientific thesis to you

Bushra

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Finally, I would like to express my extreme love and appreciation to everyone who has supported this work .

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Summary

The pandemic corona virus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome corona virus 2 (SARS- CoV-2) is the most formidable challenge to humanity in the 21 century. Although much remains to be understood regarding the immune response to SARS- CoV-2, and vaccine- induced protective immunity may differ from natural immunity owing to the immune evasion strategies of the virus, improved understanding of the natural immune response will be instrumental in developing effective vaccine and therapeutic strategies. we have laid out the pros and cons of the mRNA vaccine platform. The present study deals with laboratory tests and results for serum collected amounted to corona virus patients group (20(6 males and 14 females)) , control group (30(9 males and 21 females)), cured corona virus patients group (20 (11males and 9 females)) , receiving dose 1 Pfizer vaccine group (20 (10 males and 10 females)), receiving dose 2 Pfizer vaccine group (20 (13 males and 7 females)). during the period between October 2021 to November 2021 in Mahaweel hospital . The age range of all male and female subjects (20- 45 years old) with excluded patients which have any chronic diseases, smoker, systematic immune disease, gestational diabetes and also thyroid gland diseases and to complete the work the following parameters were done for all studied groups (patients covid -19 , cured , vaccination and control to evaluation of specific activity against viral infection) .

The result of biochemical test have to Human Total Antioxidant Capacity in group Covid -19 patients compared with control group statistical analysis show level high significant , in group cured Covid -19 patients compared with group control statistical analysis Show level no significant, in group

receiving dose 1 compared with group control statistical analysis show level high significant and in group receiving dose 2 compared with group control statistical analysis Show level no significant .in present study when patients with covid 19 and receiving dose 1 pfizer vaccine the relationship between antioxidants and sex see the male no significantly compare the female. The female have level of antioxidants increase than the level in male, in cured patients COVID-19and receiving dose 2 Pfizer vaccine group the relationship between antioxidants and sex show level the male no significantly compare to female .The female have level of antioxidants low than the level in male, in study Human Malondialdehyde (MDA) test that in Covid-19 patients group compared with group control statistical analysis show level high significant , In cured group when compared with group control statistical analysis Show level significant , In receiving dose1(people who received the first dose) when compared with group control statistical analysis Show level low significant and in receiving dose2 (those who received the second dose) when compared with group control statistical analysis Show level no significant. The results of biochemical test Human Immunoglobulin M (IgM) and G (IgG) in Covid-19 patients group compared in control group show level of Immunoglobulin M (IgM) parameter significant, and show level of Immunoglobulin G (IgG) high significant, show the cured patients(IgM) when compared with control group show level no significant and (IgG) show no significant.

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List of Abbreviation

Abbreviations.	Full name
ACE2	Angiotensin Converting Enzyme 2
ATP	Adenosine triphosphate
BCR	B cell receptor
COVID19	Corona virus Disease 2019
CD	cluster of differentiation
DNA	Deoxyribonucleic acid
ELISA	enzyme – linked immunosorbent assay
EREs	estrogen response elements
EAE	experimental autoimmune encephalomyelitis
HA	Hyaluronan
HBEs	Human bronchial epithelial cells
HAS1	Hyaluronan synthase 1
ICU	intensive care unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IFN	Interferon
IL	Interleukins
LNP	lipid nanoparticle
LSD	least significant difference
mRNA	Messenger Ribonucleic acid
MHC	major histocompatibility complex
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-KB	Nuclear factor kappa B
N P	Nucleocapsid Protein
OST	Oxidative stress th
PUFAs	Polyunsaturated fatty acids
PRRs	pattern recognition receptors
PRR	pattern recognition receptors
PD1	Programmed cell death protein 1

List of Abbreviation

Abbreviations.	Full name
PEG	Polyethylene glycol
ROS	reactive oxygen species
RNA	Ribonucleic acid
RNS	reactive nitrogen species
RBD	receptor-binding domain
SOD	super oxide dismutase
S- 2P	Subunit- 2 prolen
S P	Spike Protein
SPSS	Statistical Package for the Social Sciences
SARS-CoV-2	Severe acute respiratory syndrome corona virus
SOFA	(score of sequence organ failure assessment)
TMPRSS	transmembrane protease serine protease
(TGF-β)	The transforming growth factor
TL	types of lymphocytes
TL4	Toll-like receptor 4
TAOC	Total Antioxidant capacity
TNFα	Tumor necrosis factor alpha
(TCR)	T cell receptor
TXA_2	thromboxane A_2
UV	Ultraviolet
VD	Vitamine D
WT	Wild type

ChapterOne

Introduction & Literature Review

1. Introduction

1. 1 Severe Acute respiratory Syndrome Corona Virus(Sars-Cov2)

1. 1.1 History

The name "corona virus" is derived from Latin word *corona*, meaning "crown" or "wreath", The name was put by June Almeida and David Tyrrell who first notes and studied human corona viruses. Seven human corona viruses (HCoVs) have been so far identified, namely HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and the novel corona virus (2019-nCoV, SARS-CoV-2)**(Liu, *et al,* 2021)** . In fig (1-1) show the stages of disease onset **(Al-Osail et al , 2017)** the disease was later named severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and corona virus disease 2019 (COVID-19). The WHO announced the spread world health emergency on 2020 . COVID-19 has become a world epidemic because it spreads easily and quickly through close contact. The main transmission via respiratory droplets containing infectious virus particles. These droplets are transmitted during breathing, coughing, sneezing, and speaking **(Johnson *et al.*, 2022).**

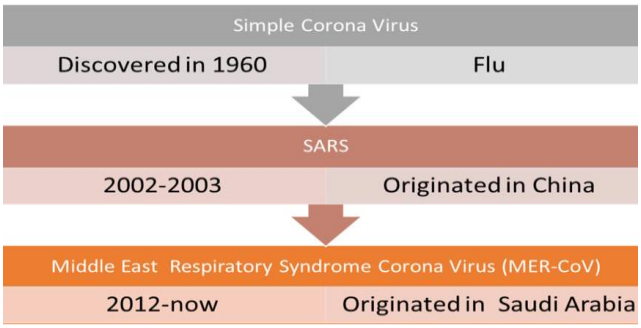


fig (1-1) :- The stages of disease onset **(Al-Osail et al , 2017)**

1.1. 2 Structure of the Sars-Cov2 Protein

The corona virus structure contains in figure (1-2), (N) protein, Membrane (M) protein, Spike (S) protein and Envelop (E) protein and several non-structural proteins (nsp)). The capsid is the protein shell, inside the capsid, there is nuclear capsid or N-protein which is bound to the virus single positive strand RNA that allows the virus to hijack human cells and turn them into virus factories. The N protein coats the viral RNA genome which plays a vital role in its replication and transcription **(Boopathi, *et al* , 2020)**. The M-protein is most abundant in the viral surface and it is believed to be the central organizer for the corona virus assembly and is a type III membrane protein. It consists of 218 to 263 amino acid residues and forms a layer 7.8 nm thick **(Lalchhandama, 2020)**. The molar ratio of E:S:M (in the lipid bilayer is approximately 1:20 - 300 **(Godet *et al.*, 2020).**

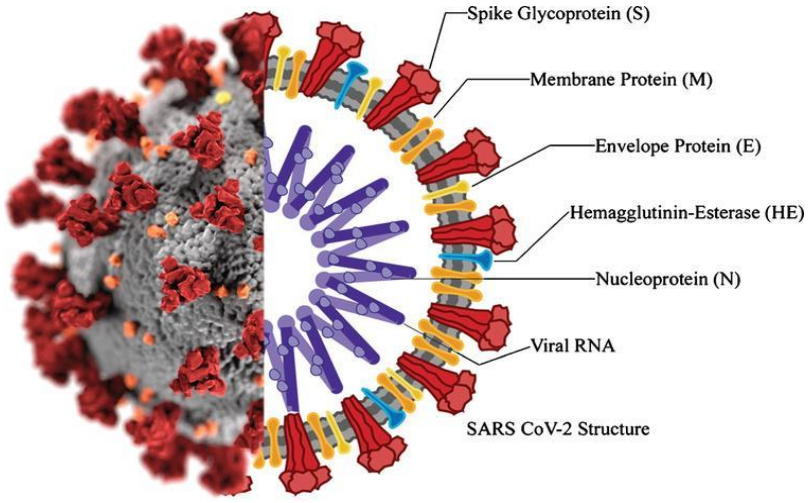


Fig (1-2) :- SARSCoV- 2 Structure **(Yamamoto *et al.*, 2020).**

The ACE2 receptors are located in different parts of our body, including oral mucosa, nasal epithelium, vascular endothelium, lungs, kidney, small intestine, testis, colon, heart, and brain , found that 32 different ACE2 receptors, including seven hotspot variants specified in the different populations **(Sarker *et al.*, 2021)**.

1.1. 3 Life Cycle of Sars-Cov2 Virus.

The virus particle seems to follow two stages of their complete lifespan: (1) early stage (entry and initiation, S protein cleavage, membrane fusion) and (2) advanced stage (translation and RNA replication, virion release)show in figure (1-3).**(Sarker *et al.*, 2021)**

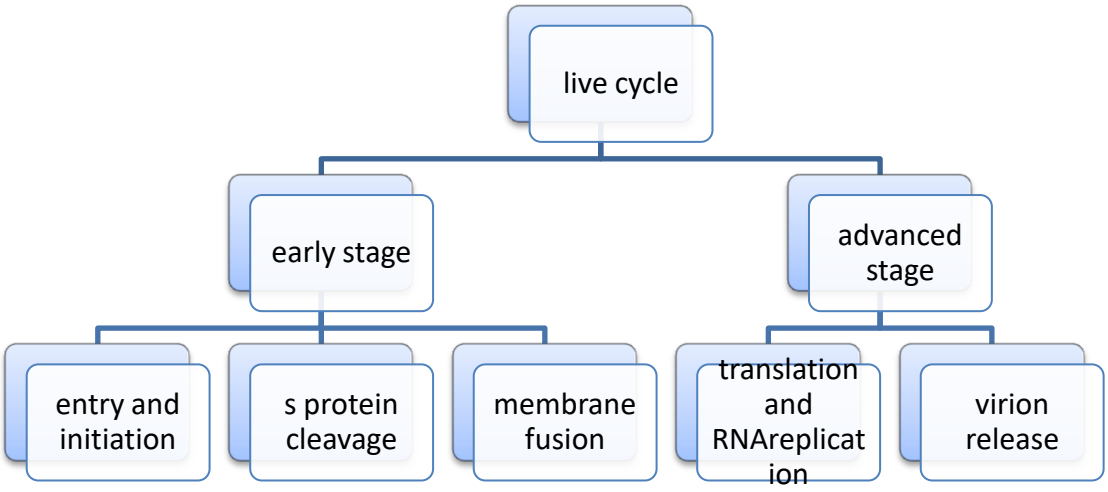


Fig (1-3):- The Schematic Live Cycle of Sars - Cov 2**(Sarker *et al.*, 2021)**

1.1.4 The ACE2 Receptor (Angiotensin-converting enzyme 2)

The ACE2 receptors are located in different parts of our body, including oral mucosa, nasal epithelium, vascular endothelium, lungs, kidney, small intestine, testis, colon, heart, and brain. As ACE2 is an essential intracellular receptor that binds to the S protein encoded by SARS-

CoV-2 to cause an infection, understanding the status and mechanism of ACE2 gene expression is essential. Generally, ACE2 is expressed in various human organs, and its organ- and cell-specific expression suggests that it is involved in regulating cardiovascular and renal function and fertility . Interestingly, single-cell RNA sequence datasets revealed that ACE2 was coexpressed with TMPRSS2 within lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells .It is also known that young children exhibit lower ACE2 expression compared to the adults ,the low risk of infection in children may thus be attributed to this age-dependent ACE2 expression.its prohibits releasing pro-inflammatory cytokines, lung injury, and inflammation**(Pouremamali *et al*., 2022)**.

1.1.5 Entry of Sars-Cov2 Virus.

The SARS-CoV-2 possess an S protein that goes through a cleavage event by fusion proteins . An RBD (receptor-binding domain) at the spike protein enables ACE2 (Angiotensin-converting enzyme 2), the host receptor protein, to initiate membrane fusion activity transmembrane protease serine protease (TMPRSS) assist in proteolytic cleaving of the S protein into S1/S2 subunits,**(Zhang, Yan and Zhou, 2020)** . The entry of the virus particle is initiated by binding of Spike (S) glycoprotein to the ACE2 receptor of the host cell. The S glycoprotein is cleaved into S1/S2 either by TMPRSS2 or by the furin protease, in association with some cofactors**(Jackson *et al.*, 2022)**. S2 stalk domain undergoes a conformational change and facilitates the fusion between the host cell membrane and the virus envelope protein. In this advanced stage, host cell machinery is used by the virus to translate viral polyprotein into nsps. The RNA genome and N protein are made in the host cell cytoplasm and the S,

E, and M structural proteins are packaged in the endoplasmic reticulum (ER)**(Yadav *et al.*, 2021)**. The mature virion is transferred to the Golgi body followed by exocytosis, budding, or cell death this mechanism show in figure (1-4)**.(Sarker *et al.*, 2021)**.

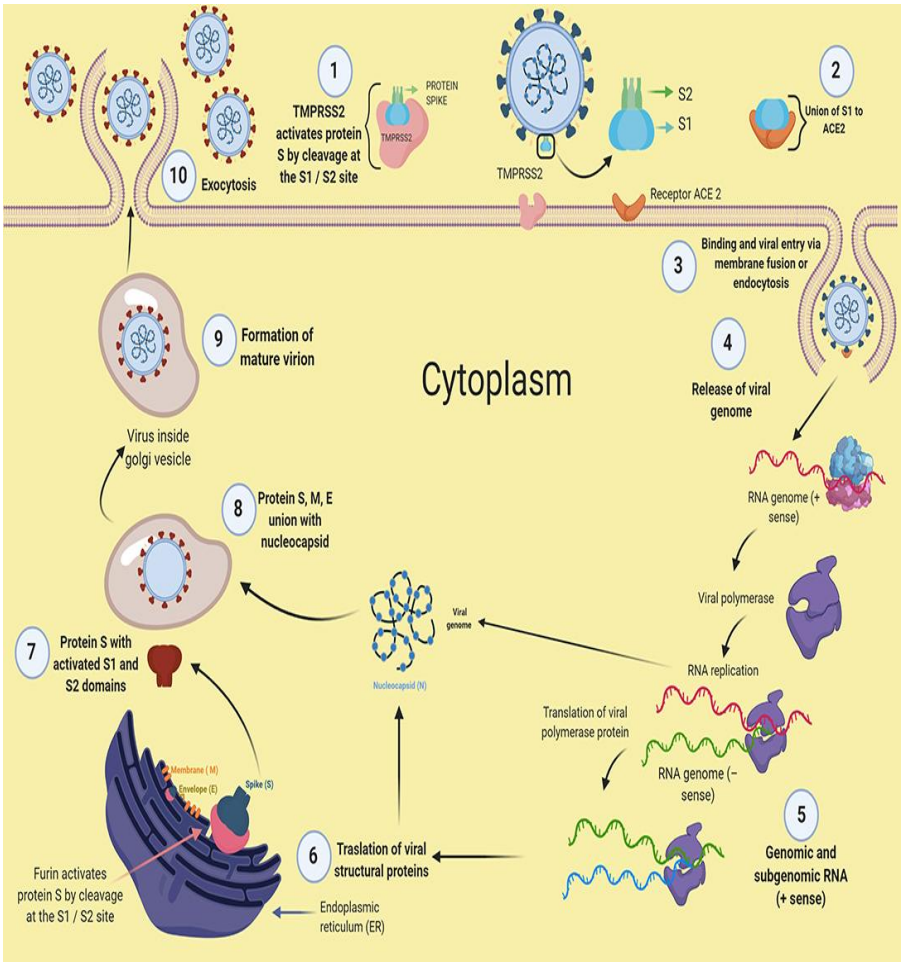


Fig (1-4) :-| Mechanisms of Infection of SARS-CoV-2. **(Guadarrama-Ortiz *et al.*, 2020)**

1.1.6 Covid – 19 Symptoms

Symptoms of COVID-19 that cause destroy the respiratory system, and multiple organ failure systematic, Symptoms of COVID-19 are variable, but often include fever shortness of breath, cough (either with or without sputum), sore throat, nasal congestion, dizziness, chills, muscle ache, arthralgia, weakness, fatigue or myalgia, chest tightness, excessive mucus production with expectoration, hemoptysis, and dyspnea **(Public Health Ontario, 2021).**

The disease can take three main pathways. First, it can pass as a mild illness similar to a common upper respiratory infection. The second possibility is pneumonia, that is, infection of the lower part of the respiratory system. The third and most dangerous, route is the rapid progression of the disease into acute respiratory syndrome**(Al., 2020)** .

The disease can take three main pathways. First, it can pass as a mild illness similar to a common upper respiratory infection. The second possibility is pneumonia, that is, infection of the lower part of the respiratory system. The third, and most dangerous, route is the rapid progression of the disease into acute respiratory syndrome**(Volz *et al*, 2004)**. Advanced age is associated with an elevated Dimer-D value (an indicator of activation of the circulatory coagulation reflex) above 1 µg/ml on admission, and a higher SOFA (score of sequence organ failure assessment)(a clinical scale that assesses the function of a number of metabolic systems and organs such as lungs, heart, liver, kidneys ..etc)**(Cheng *et al.*, 2020)**. With the increased likelihood of disease progression for the worse. In addition, elevated levels of interleukin-6, the highly sensitive cardiac enzyme troponin I, lactate dehydrogenase, and decreased lymphocytes in the blood count are associated

with more severe forms of the disease. Complications of COVID-19 include sepsis and cardiac complications (heart failure or arrhythmias), which are more likely to occur in people with pre-existing heart conditions. In addition, a case of hyper coagulability was observed in 90% of patients with pneumonia caused by the virus **(Nishiga *et al.*, 2020)** . People aged 60 years and over, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, obesity or cancer, are at higher risk of developing serious illness.

However, anyone can get sick with COVID-19 and become seriously ill or die at any age. The Symptoms began to appear on most peopel who were infected about fifth day. And any one doesnot appear The Symptoms with in 12 day its unlikely that they but remain carries to virus **(Özdemir, 2020)**.

1.2.1 Relationship between Reactive Oxygen Species (ROS) and Oxidative stress

Oxygen gas is necessary for energy production via the electron transport chain in living organisms, a mechanism by which energy (ATP) is released to enable the cell carry out its normal physiological functions. This is attributed to its high redox potential which makes it a brilliant oxidizing agent capable of easily accepting electrons from reduced substrates**(Phaniendra, *et al* , 2015)**. This contradictory effect of oxygen in living organisms necessitated the evolution of antioxidant system to protect against over oxidation and combat reactive oxygen species (ROS) Free radicals are small diffusible molecules that are highly reactive because of the unpaired electron). Free radicals were initially thought to be oxygen centered radicals reactive oxygen species (ROS)

but also include a subgroup of reactive nitrogen species (RNS) and are all a product of normal cellular metabolism)**(Kurutas, 2016)**. ROS and RNS have been established to play a double role as beneficial and harmful specie based on their beneficial and deleterious effect on biological systems. The beneficial roles occur at low to moderate concentrations while the deleterious effects occur at high concentrations where the ROS/RNS production surpasses the antioxidant ability to balance it**(Juan *et al.*, 2021)**. As secondary messengers, these free radicals interrupt normal physiological processes at different stages which initiate a series of harmful chain reactions that lead to molecular damage of biological tissues and signalling mechanism. The deleterious effect caused by ROS/RNS that results in biological damage is termed oxidative stress and nitrosative stress of the reactive oxygen species . Exogenous sources of free radicals are radiation, drugs, xenobiotics, toxins. Endogenous sources of free radicals involve mechanisms that are usually more complex **(Alkadi, 2018)**.

The Source of ROS first mitochondria are the most vital source of ROS production. During the physiological process of ATP generation via the respiratory chain, molecular oxygen is reduced to two water molecule Superoxide radical chemical reactivity is relatively weak due to its inability to pass through lipid membrane and its quick conversion to hydrogen peroxide by the antioxidant super oxide dismutase (SOD)**(Sharifi-Rad *et al.*, 2020)**. The Cellular Oxidase Although mitochondrial respiratory chain is the main source of superoxide, this free radical specie can also be produced by one- electron reduction of oxygen by numerous different oxidases under certain conditions **(Alkadi, 2018)**. Oxidative stress is a condition that occurs when the rate of reactive oxygen

species (ROS) formation exceeds the rate of the antioxidant defence system . Reactive oxygen species is generated as natural by-products of normal oxygen metabolism and has important roles in cell signalling and homoeostasis in normal conditions .In figure (1- 5) oxidative Stress-induced diseases in humans . However, at times during disease states (such as inflammation or infection) and environmental stress (e.g. UV or heat exposure) or ionizing radiation, ROS levels could increase dramatically and may result in significant damage to cellular structures .the sex differences associated with oxidative stress**(Mehta *et al* , 2015).**

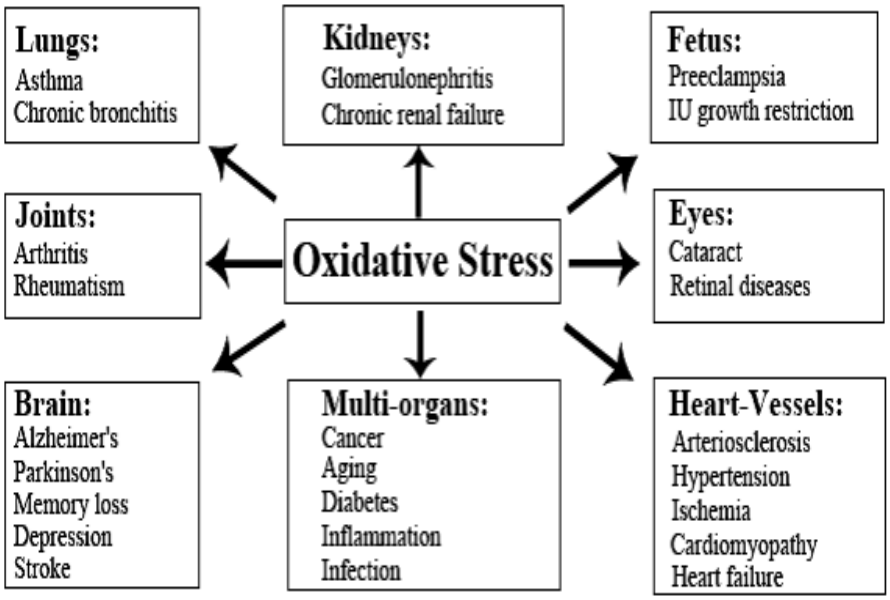


Fig (1- 5):Oxidative Stress-induced Diseases in Humans**(Mehta,*et al* 2015).**

1. 2.2 Oxidative Mechanisms in Covid -19 Pathogenesis

Infection of experimental animals with corona viruses has provided evidence for the involvement of the oxidative stress machinery, with enhancement of ROS production and weakening of defence mechanisms.

Many lines of evidence suggest that overproduction of ROS and a deprivation of antioxidant system play a major role also in the pathogenesis of SARS-CoV-2 infections in humans as well as in the progression and severity of the related diseases **(Forcados *et al.*, 2021) (Solleiro-Villavicencio *et al* , 2018)** as a result of increased inflammatory cell recruitment at the site of infection. Also, viral infections disrupt antioxidant mechanisms, leading unbalanced oxidative-antioxidant status and subsequent oxidative cell damage. In figure (1-6) schematic show effect oxidative stress on the binding ACE2 with COV-2 in thiol group the onset of severe lung injury in SARS-CoV infected patients depends on activation of the oxidative stress machinery that is coupled with innate immunity and activates transcription factors**(Forcados *et al.*, 2021)** .

In addition, it has been associated with the activation of mitochondrial cell death pathways (intrinsic and extrinsic signaling), apoptosis induced by human CoV (HCoV) infection has been studied by immunopathologic techniques, in which hallmarks of apoptosis were observed in SARS-CoV-19 infected lung, spleen, and thyroid tissues. Also, activation of apoptosis induced by SARS-CoV,that suggested that SARS-CoV replicates in VeroE6 cells (The Vero cell line is an immortalized cell line established from kidney epithelial cells of the African green monkey. A variety of Vero sublines have been developed and can be classified into four major cell lineages. In this study, we determined the whole-genome sequence of Vero E6 (VERO C1008), which is one of the most widely used cell lines for the proliferation and isolation of severe acute respiratory syndrome coronaviruses (SARS-CoVs),**(Konishi *et al.*, 2022)** and **(Ogando *et al.*, 2020)** inducing a weak Akt signaling pathway activation, which cannot prevent apoptosis induced by SARS-CoV infection Activation of the PI3K/Akt signaling pathway by a

variety of viruses is thought to be involved in the establishment of latent and chronic infections by allowing virus infected cells to escape from apoptosis **(Fung and Liu, 2019)**. Activation of the PI3K/Akt signaling pathway may lead to a delay in apoptosis of host cells, and the virus life cycle might be completed before apoptosis of host cells takes place. Thus, cellular apoptosis facilitates the spread of the virus in the organism Oxidative stress - NF-kB - toll-like receptor (mainly TL4) signaling pathways, triggered by viral pathogens like SARS-CoV, may further amplify the host inflammatory response, ultimately leading to acute cylung injury**(Delgado-roche *et al* , 2020)**. Activated neutrophils and mononuclear phagotic cells are to a large extent responsible for the massive release of ROS into the lung tissue . In addition, the massive TNF-α release during the cytokine storm could exacerbate ROS production via a positive feedback loop by activating NADPH oxidases, and TNF-α induced ROS production could contribute to the extension of COVID-19 effects to distant tissues . The importance of oxidative stress in COVID-19 is reinforced by the role of ROS production in associated co-morbidities **(Deflora Silvio, *et al* , 2021).**

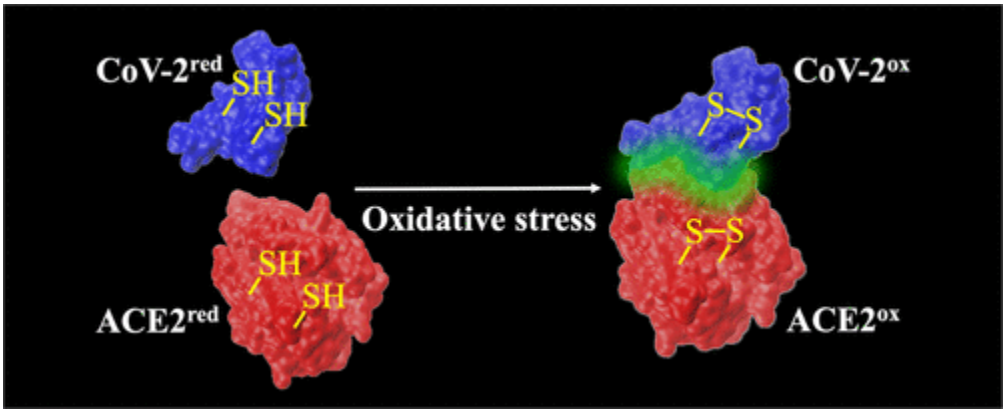


Fig (1-6):- Schematic show effect oxidative stress on the binding ACE2 with COV-2 in thiol group**.(Hati *et al* , 2020)**

1.3 The antioxidants and SARS-CoV 2

Antioxidants as any molecule that inhibits the oxidation of another molecule. A chemical reaction involving the loss of electrons and increase in the oxidative state is termed as "oxidation." Oxidation results in the formation of free radicals that are unstable atoms and molecules deficit in electrons**(Santos-Sánchez, N. F. et al., 2019)** . They have unpaired electrons and are extremely reactive and are capable of initiating chain reactions that destabilize other molecules and generate free radicals. These free radicals are also termed as reactive oxygen species or ROS and create a homeostatic imbalance that generates oxidative stress and causes cell death and tissue injury **(Mehta *et al* , 2015)**. The scientist , Guttering and Halliwell classified the antioxidants into three categories: primary, secondary, and tertiary antioxidants. Primary antioxidants are involved in the prevention of oxidant formation; secondary antioxidants are known to be scavengers of ROS, and tertiary antioxidants repair the oxidized molecules through sources like dietary or consecutive antioxidants. Antioxidants may also be classified as enzymatic or non-enzymatic antioxidants can also Classification as the following :- Hydrophobic antioxidants , Endogenous antioxidants, Exogenous antioxidants ,the Antioxidant Defense mechanism Free radicals are constantly being generated in the body through various mechanisms and are also being removed by endogenous antioxidant defensive mechanisms that act either by scavenging free radicals, by decomposing peroxides, or by binding with pro-oxidant metal ions**(Patekar *et al.*, 2013).**

Vitamin C can influence chemotaxis, as well as phagocytosis. Given its antioxidant (ROS scavenging) ability, vitamin C exerts protective effect from the impairment suffered upon oxidative burst in neutrophils

and phagocytes , and lowering of pro-inflammatory cytokines production . Vitamin B1 exerts anti-inflammatory effect in macrophages, lowers oxidative stress and alleviates pro-inflammatory cytokine release , its antioxidant power exerted in neutrophils, it protects –SH groups present at the cell's surface**(Magdalena *et al.*, 2020)**. Vitamin B1 impairment may lead to unappropriate antibody response, and eventually more severe disease form , Thiamine also improves oxygen levels So, high-dose administration at early COVID-19 stages can lower hypoxia and hospitalization duration. Folic (pteroyl-L-glutamic) acid involved in the adaptive immune response , used as dietary supplement is converted to folate in the body. folic acid supplementation significantly lowers oxidative stress markers: an increase of serum glutathione concentrations and of total antioxidant capacity, alongside a decrease of malonyldialdehyde concentration have been report**(Pisoschi *et al.*, 2022).**

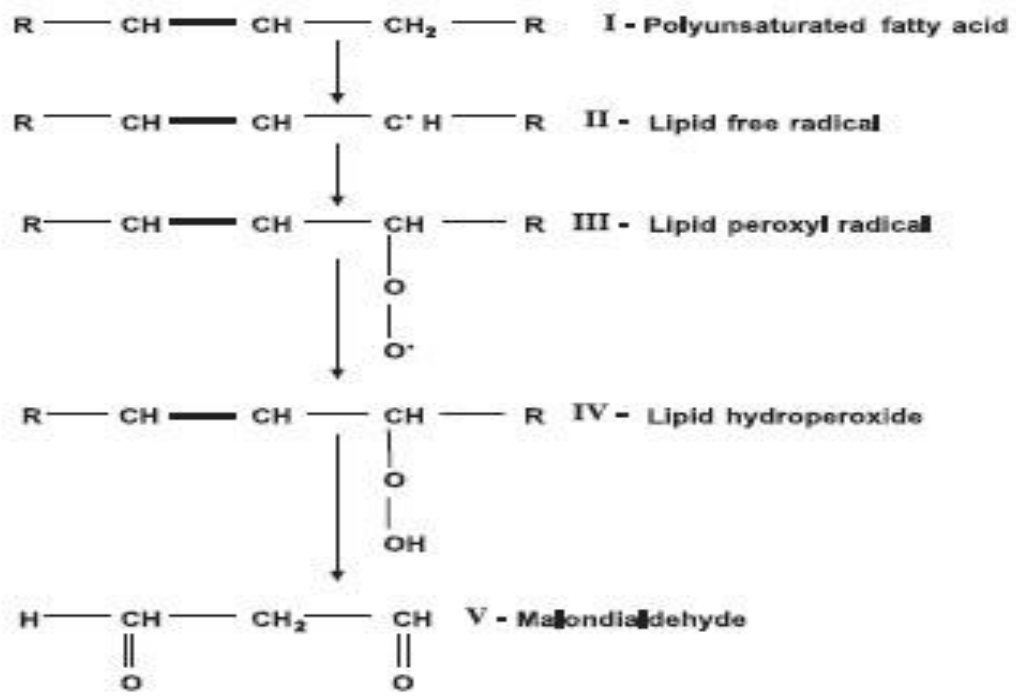
1.4.1 Lipid Peroxidation

Lipid peroxidation or reaction of oxygen with unsaturated lipids produces a wide variety of oxidation products. The main primary products of lipid peroxidation are lipid hydroperoxides. Secondary products during lipid peroxidation, malondialdehyde (MDA). MDA appears to be the most mutagenic product of lipid peroxidation , Malondialdehyde (MDA) is an end-product generated by decomposition of arachidonic acid and larger PUFAs through enzymatic or no enzymatic processes MDA Production by Enzymatic Processes.: MDA can be generated in vivo as a side product by enzymatic processes during the biosynthesis of thromboxane A_2 ($TXA_{2)}$ is a biologically active metabolite of arachidonic acid. Production of MDA by Non enzymatic Processes. A mixture of lipid hydroperoxides is formed

during lipid peroxidation process, undergo cleavage to produce MDA **(Ayala,et al , 2014), (Tsermpini *et al.*, 2022).**

1.4.2 Malondialdehyde (MDA) and SARS-CoV 2

In patients admitted in ICU find high serum level of MDA. The MDA is an important indicator of oxidative stress. There is a significant correlation between oxidative stress markers and respiratory viral infection particularly RNA viruses) In vitro and In vivo studies indicated that some viruses could change redox balance of cell**(Tsermpini *et al.*, 2022)**. In the beginning of oxidative stress by virus infection (such as respiratory syncytial virus) is necessary for activation of innate immunity by cytokines production, It is described the function of macrophage respiratory burst in reaction to Covid-19 infection, which can lead to ROS production). Over production of ROS/RNS have role in lung tissue injury and dysfunction of epithelial barrier. Induced by acute respiratory viral infections) **(Mehri *et al.*, 2021)**,the increase lipid peroxidation, during infection establishing an oxidative stress cycle, and ultimately, increasing the risk of suffering severe COVID-19 illness forms **(Martín-Fernández *et al.*, 2021)**.



Fig(1-7):- schematic steps of MDA formation from polyunsaturated fatty acids.**(Antonio Ayala, *et al*, 2014)**

1.5 Cytokines

1.5.1 General Characteristics of Cytokine

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. (Greek) Cyto = cell Kinein = to move> 200 cytokines ,the cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). **(Hegazi and Abdel-rahman, 2015)**

..Cytokines may be classified into three main functional categories based on their principal biologic actions**(Djuichou Nguemnang *et al.*, 2019):-**

"Cytokines acting as mediators and regulators of innate immune .These cytokines act mainly on endothelial cells and leucocytes to stimulate early inflammatory reactions to microbes, and some functions to control these responses. Examples of such cytokines, tumor necrosis factor(TNF) , IL1 , chemokines , IL12 ,type1 IFNs(α – β) , IL10 , IL6 , IL15 , IL18 , the principles cell sours $CD^{+}4T$ (TH1) diffrentional **,(Gary Kaiser,2022).**

. "Cytokines acting as mediators and regulators of adaptive immunity regulate the growth and differentiation of various lymphocytes , activate and regulate specialized effector cells like mononuclear phagocytes, neutrophils and eosinophils to eliminate antigens in the effector phase of adaptive immune responses. For examples , (IL2 , IL4 , IL5 , interferon - γ(INF- γ) , transforming grouth factor_ β(TGF_ β) , lymfotoxine(LT) , IL-13 , the principale cell sources $CD4^{+}T$ (TH2) , the principale cell target and biological effects to IL13 (Bcell :isotype switching to IgE), (Epithelial cell : increased mucuse production), (Macrophages : inhibition**),, (Brightling, *et al* , 2014)**" Cytokines acting as stimulators of hematopoiesis: Cytokines stimulating haemotopoiesis are produced by bone marrow stromal cells, leucocytes, These cause stimulation of growth and differentiation of immature leucocytes ,,**(Liu *et al.*, 2021)** . ,,

1.5.2 Interleukins

Interleukin (cytokines made by one leukocyte and acting on other leukocytes), Interleukins (ILs) are a group of secreted proteins with diverse structures and functions. These proteins bind to receptors and are involved in the connection between leukocytes**(Justiz Vaillant AA.*et al* ,2022)** They are

intimately related with activation and suppression of the immune system and cell division. The interleukins are synthesized mostly by helper CD4+ T lymphocytes, monocytes, macrophages and endothelial cells. Interleukins are named as IL plus a number. Previously, different names were used to refer to the same IL. For instance, IL-1 was called lymphocyte-activating factor, mitogenic protein or T cell replacing factor III. In order to standardize the nomenclature, in 1979, during the Second International Lymphokine Workshop, the term interleukin was introduced**(Liu *et al.*, 2021)**.

After that, the interleukins started being named consecutively according to the date of their discovery . There have been identified 40 interleukins so far and some of them are further divided into subtypes (IL-1α, IL-1β). These ILs are grouped in families based on sequence homology and receptor chain similarities or functional properties**(Behzadi *et al.*, 2022)**.

1.5.3 Interleukin 13

The interleukin – 13 (IL-13) has a mass of 13 kDa and folds into 4 alpha helical bundles, A, B, C, and D. In Figure (1- 8) Structure of Interleukin (13) and Receptor that IL-13 is produced by several immune cells and has many diverse functions on a wide variety of cell types relevant to the pathogenesis of allergic disorders in Figure (1- 9) schematic representation of the cellular sources of IL-13 **(Rael and Lockey, 2011)** . IL-13 can be produced by activated ILC2 , Th2 cells , mast cells , macrophages, basophils , eosinophils, and B cells. promoting B cell proliferation and inducing class switching to IgE and IgG4 ,IL-13 promotes survival, activation, and recruitment of eosinophils, IL-13 stimulates eosinophil trafficking from the peripheral blood to the site of inflammation by inducing the production of IL-5 and eosinophil chemokines**(Marone *et al.*, 2019)**.

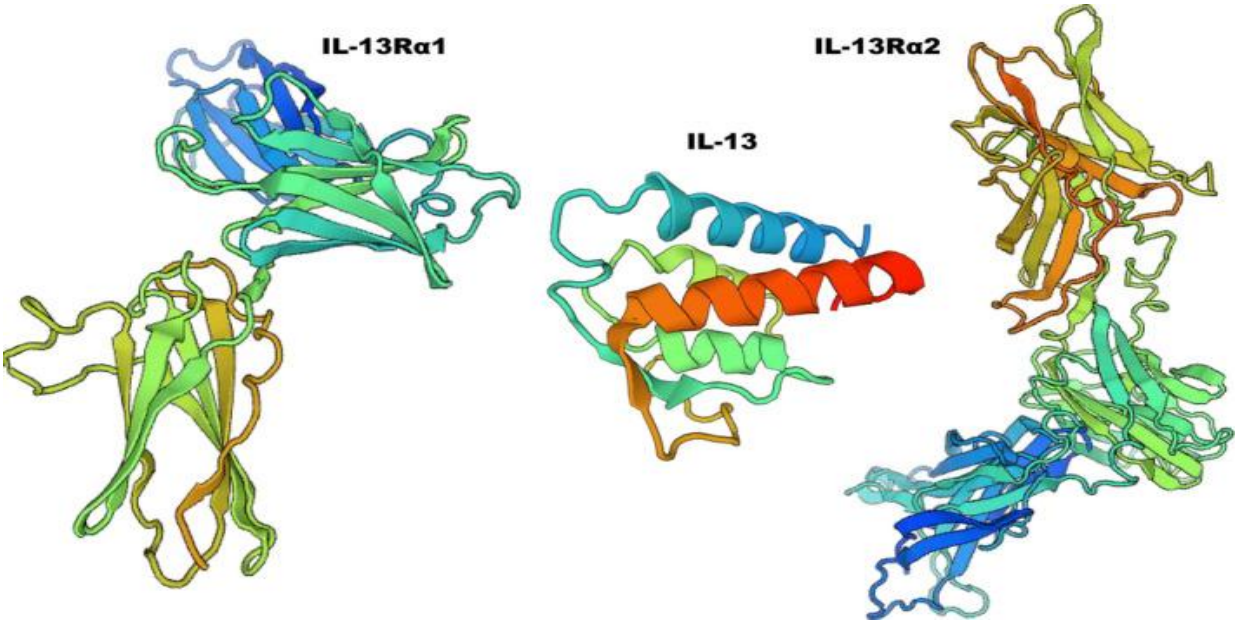
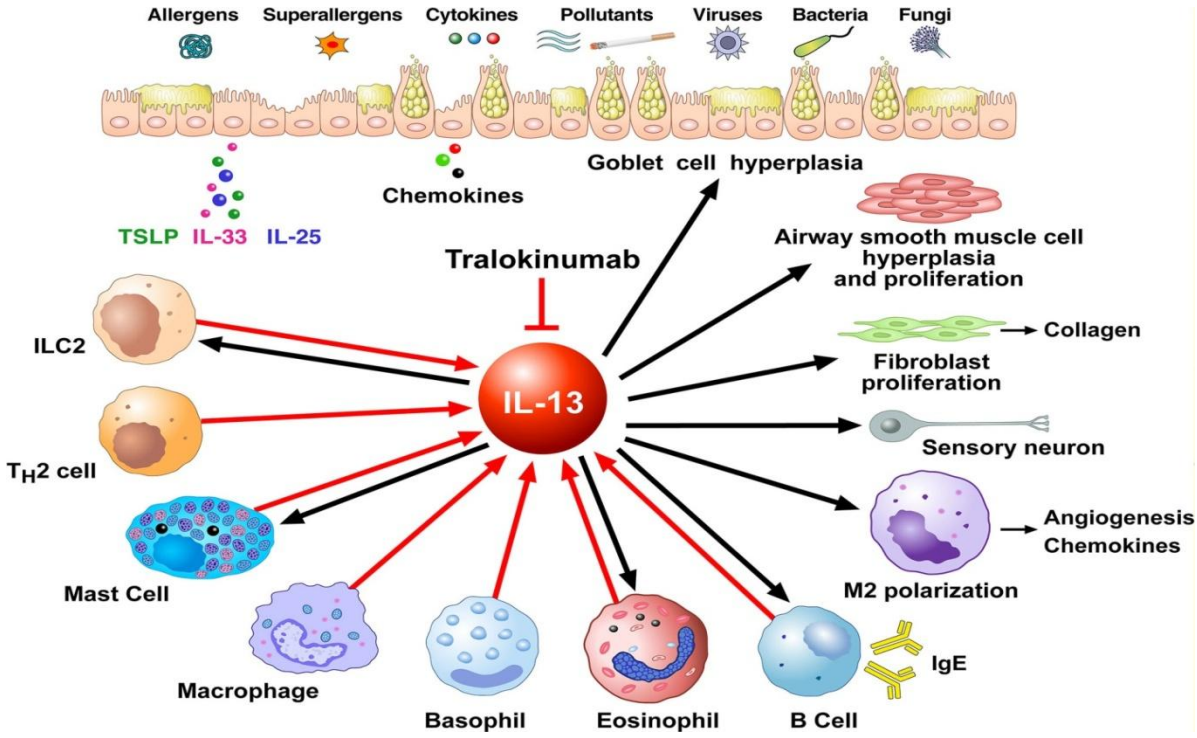


Fig (1- 8):- Structure of Interleukin (13) and Receptor **(Qian *et al.*, 2021)**



Fig(1- 9) Schematic Representation of the Cellular Sources of IL-13 .

Different stimuli (allergens, super allergens, pollutants, viral and bacterial products, activate epithelial cells which release several cytokines. These mediators activate a variety of immune cells (ILC2, Th2 cells, mast cells, macrophages, basophils, eosinophils, B cells) which produce several cytokines including IL-13. IL-13 modulates the functions of IL-13+ ILC2, mast cells, macrophages, eosinophils, and B cells.**(Donlan *et al.*, 2020)** .This cytokine induces goblet cell hyperplasia and mucus production, airway smooth muscle cell hyperplasia and proliferation, fibroblast activation and collagen deposition, macrophage polarization (M2) and B cell activation and immunoglobulin E production and It induces the pathogenesis of glycoprotein hypersecretion , IL-13 also inhibits tumor immunosur veillance, which leads to carcinogenesis **(Jain *et al.*, 2022)**These effects of IL-13 are mediated by the engagement of type II IL-13 receptor (IL-13Rα1/IL-4Rα expressed on these cells **(Marone *et al.*, 2019)**.

IL-13, one of the powerful cytokines with broad functions, is widely expressed in most tissues, such as heart, lung, liver and skin. IL-13 is recognized to be engaged in regulating cell mediated immunity, modulating cell proliferation, growth and apoptosis and taking part in the genesis and development of a variety of diseases, including allergic asthma, chronic obstructive pulmonary disease, schistosomiasis, hepatic fibrosis and cancers and relationship between IL-13 and cardiovascular diseases**(Qian *et al.*, 2021)**. Goblet cell hyperplasia and mucus overproduction are features of asthma and chronic obstructive pulmonary disease and can lead to airway plugging, pathologic feature of fatal asthma. Animal models demonstrate that IL-13 induces goblet cell hyperplasia and mucus hypersecretion. Human bronchial epithelial cells (HBEs), stimulated by IL-13, can also undergo

changes from a fluid absorptive state to a hyper secretory state independent of goblet cell density changes **(Marone *et al.*, 2019)** .

1.5.4 IL-13 and SARS-CoV-2 severity

The type 2 cytokine, IL-13, is associated with severe COVID-19. neutralization of IL-13 in mice infected with SARS-CoV-2 protects from death, in part by blocking hyaluronan synthesis and excessive deposition. Overall, this work opens a new avenue in the study of COVID-19 by demonstrating a causal role for type 2 immune responses and downstream hyaluronan accumulation in respiratory failure, and offers potential avenues for immunotherapy of this disease. Considering the extreme heterogeneity in immune responses to COVID-19 it is unlikely that IL-13 blockade will work in all patients**(Kudryavtsev *et al.*, 2022)**. The goblet cells following IL-13 blockade, the biological significance of their contribution was likely minimal given the low magnitude of their induction compared to other models of type 2 immunity in the lung The identification of *Has1* as the most down regulated gene following IL-13 neutralization in infected mouse lungs, along with down regulation of *Has2* and *Cd44,* two other genes involved in the HA pathway, enabled the discovery of a novel route by which IL-13 impacts pathology via upregulation of hyaluronan synthesis**(Pandey, *et al* , 2021**). The IL-13 neutralization not only decreased *Has1* gene expression but lowered hyaluronan deposition in the lung. The identification of *Has1* as the most down regulated gene following IL-13 neutralization in infected mouse lungs, along with down regulation *of* Has2 *and* Cd44, two other genes involved in the HA pathway, enabled the discovery of a novel route by which IL-13 impacts pathology via up regulation of hyaluronan synthesis. IL-13 neutralization not only

decreased *Has1* gene expression but lowered hyaluronan deposition in the lung. Downstream of hyaluronan production, neutralization of the hyaluronan receptor improved survival in infected mice . it may contribute to inflammation in the lung by providing a matrix for inflammatory cells to migrate over and adhere to, as well as via signaling through its receptor CD44. Additionally, excessive build-up of hyaluronan, which binds a large amount of water, could contribute to severely impaired oxygen uptake, which is a significant component of disease in hospitalized patients. Because increases in hyaluronan have been observed in patients with COVID-19, this study provides a potential mechanistic link between the association of IL-13 with severe disease and increased hyaluronan seen in other studies . Understanding the relationship between IL-13 and HA may be widely relevant to respiratory diseases beyond COVID-19 **(Donlan *et al.*, 2021)**.

1.6 Sars-cov2 with Antibody IGM and IGG

Immunoglobulins were initially called neutralizing substances, and they were discovered in 1890 by two immunologists, Emil von Behring and Kitasato Shibasaburo. Immunoglobulins are special types of glycoproteins that play an important role in maintaining the body's immune system. Also called antibodies, immunoglobulins are highly specific, and they are secreted in massive amounts by plasma cells in response to pathogenic antigens. Functions of Immunoglobulins protect us against: Bacteria ,Chemical substances ,Viruses , Parasites , Allergens , Synthetic substances , Cancerous cells , Fungu. Plasma cells produce specific antibodies against a specific antigen **(Mix et al , 2006)**

For instance, antibodies released by plasma cells against the COVID-19 virus will only bind to the COVID-19 virus and not any other

virus or bacteria. This specificity of immunoglobulin makes the body's immune system stronger and more active against multiple pathogenic invasions. Immunoglobulin (Ig) primarily constitute 20% of blood plasma. The primary function of immunoglobulin is to elicit humoral immunity by binding to the foreign antigen. The antibody-mediated humoral immune response kills the invading microbes and prevents infections from spreading to other regions of the body **(Sebina *et al* , 2018).**

This type of immune response is highly specific and complex. There are five different classes of immunoglobulins (IgG, IgM, IgA, IgD, and IgE) based on their functions, chemical structure, biological features, distribution, and target specificity. Any genetic abnormality during antibody processing, or any variation in the normal immunoglobulin levels in the body increases the risks of developing various immunological diseases such as primary immune deficiency diseases or

Autoimmune diseases (a condition in which immune cells attack the healthy cells/tissues of the body) **(Aryal, 2018).** Immunoglobulin G (IgG) is the most common and abundant antibody present in the body. Blood plasma consists of 75-80% of IgG antibodies. Of all antibodies, IgG has the longest lifespan of about 23 days. IgG antibodies remember the pathogens that have previously entered the body and caused an infection**(Vashti *et al.*, 2015)**. The function of IgG is to enhance the phagocytosis of pathogens, neutralize bacterial or viral toxins, and trigger the activation of the complement system. IgG has four isotypes: IgG1, IgG2, IgG3, IgG4 **(Aryal, 2018)** .

Immunoglobulin M (IgM) is the first antibody that interacts with new bacteria that enters the body, and it initiates a primary immune response. IgM is also called a natural antibody because it serves as the first line of

defense of the immune system and provides short-term protection**(Sebina *et al* , 2018)**. IgM has a gigantic pentamer structure above all other antibodies and consists of 10 antigen-binding sites, making them more effective than IgG in killing bacteria or viruses. The life span of the IgM antibody in our body is about five days and it makes up 5-10% of the antibodies in blood plasma. IgM also causes agglutination (formation of clumps) of bacteria when binding to its surface epitope. The IgM antibody is known as a potent agglutinin and is also found on the surface of naïve B-cells and red blood cells in its monomeric form**(Keyt *et al.*, 2020)**.

Antibody responses against enveloped viruses, such as SARS-CoV-2, are usually comprised of immunoglobulin (Ig) M, IgG3, IgG1 and IgA antibodies to glycoproteins of the virus envelope and to nucleoproteins (NP, internal to the envelope). IgG (IgG3 and IgG1) antibodies against virus envelope glycoproteins possess various functional characteristics that confer the most efficacious systemic antibody response against viruses **(Vashti *et al.*, 2015)**, these functional characteristics result in virus neutralization, by binding of antibody regions to viral antigens and impairment of virus binding to cell receptors, and activation of antiviral effector cells, by binding of antibody regions to receptors on NK cells, to induce antibody-dependent cellular cytotoxicity of virus-infected cells **(French *et al.*, 2017)**.

By day 14 after symptom onset, the serum of 95–100% of patients with COVID-19 contains IgM and/or IgG antibodies to the SP of the SARS-CoV-2 envelope, including antibodies to the receptor-binding domain (RBD) of the SP, which strongly correlate with antibodies that neutralize viral replication in cell cultures**(Zhao J, *et al*, 2020)** .

SARS-CoV-2 SP at an average time of day 14 or later after symptom onset were independently associated with a worse clinical classification.

This association was not observed for either IgM antibodies to the SARSCoV-2 SP, IgG antibodies to SARS-CoV-2 were higher in patients with critical disease severity**(Li; *et al.*, 2015)** .IgG antibodies to SARSCoV-2 SP might enhance the infection of immune cells and/or the immunopathogenesis of COVID-19. Antibody-dependent enhancement (ADE) of virus uptake by macrophages is an undesirable action of IgG antibodies affect macrophage function associated with acute lung injury characterized by macrophage activation towards a proinflammatory to increased production of pro-inflammatory cytokines and chemokines**(Jaume *et al.*, 2011)** this show in Figure (1 -10) Schematic the Antibodies Responses. SP antibodies were associated with the occurrence of pulmonary immunopathology, characterized by a Th2 response, following virus challenge**(Liu *et al.*, 2019)**. The higher serum SARS-CoV-2 SP antibody levels have been associated with worse clinical outcomes in COVID-19 patients**(Zhao J, *et al* , 2020)**. Antibody is dependent on germinal centre function, and antibody glycosylation are adversely affected by older age, these characteristics of IgG antibody function might be age-related risk factors for COVID-19**(Shankwitz *et al.*, 2020).**

The serum SARS-CoV-2 antibodies have variable neutralization activity, but also the possibility that some individuals might have antibodies that could enhance disease pathogenesis**(Xun *et al.*, 2020)**.

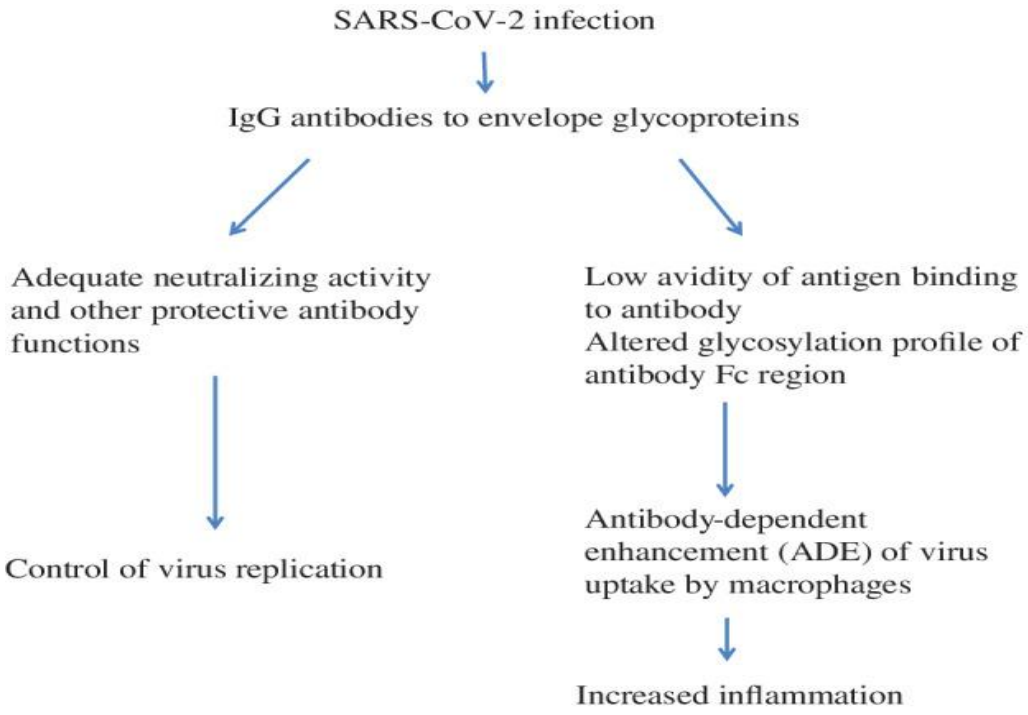


Fig (1 -10):- Schematic the Antibodies Responses **(French *et al* , 2020)**

1.7 Vaccination

A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen. To achieve this, the vaccine must contain antigens that are either derived from the pathogen or produced synthetically to represent components of the pathogen**(Alan R. Shaw, 2019)**.

The essential component of most vaccines is one or more protein antigens that induce immune responses that provide protection. Protection conferred by a vaccine is measured in clinical trials that relate immune responses to the vaccine antigen to clinical end points (such as prevention of infection, a reduction in disease severity or a decreased rate of hospitalization) **(Pollard *et al* , 2021).**

1.7.1 Vaccines Induce Antibodies

The adaptive immune response is mediated by B cells that produce antibodies (humoral immunity) and by T cells (cellular immunity). All vaccines in routine use, except BCG (which is believed to induce T cell responses that prevent severe disease and innate immune responses that may inhibit infection), are thought to mainly confer protection through the induction of antibodies **(Pollard *et al* , 2021).**

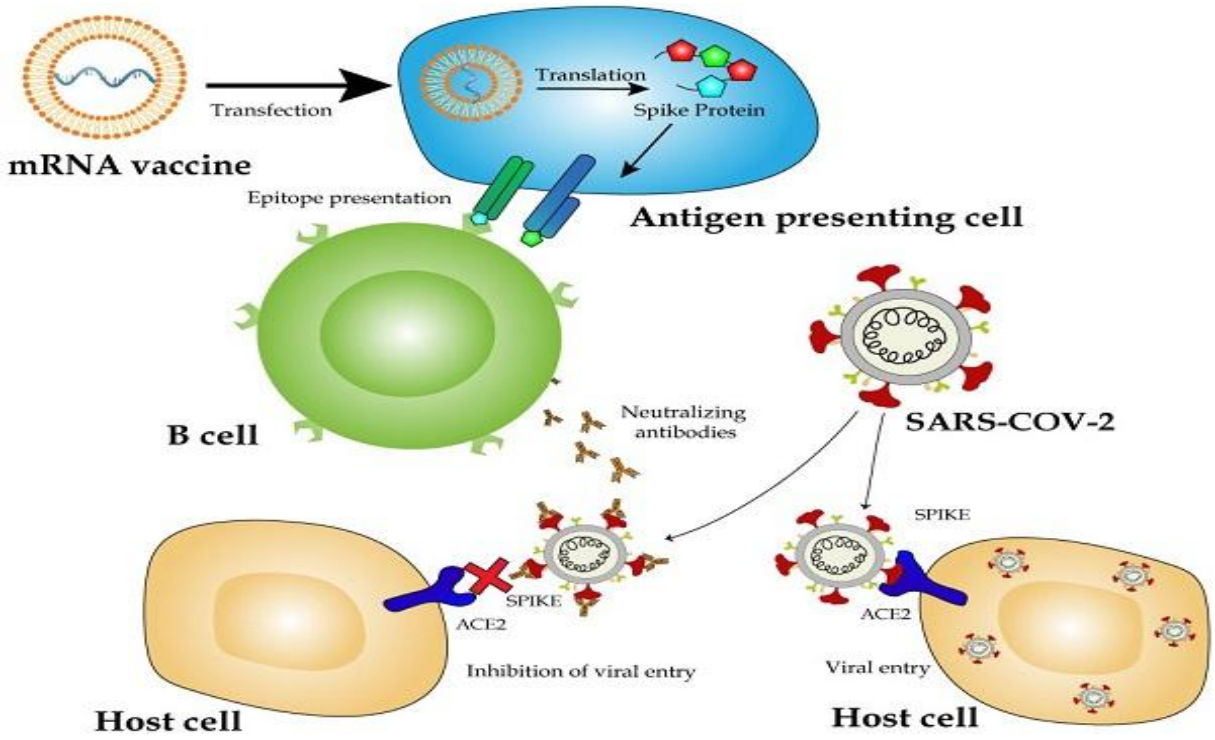


Fig (1 - 11):- schematic of Mechansem to mRNA Vaccine **(Park *et al.*, 2021)**

The immune response following immunization with a conventional protein antigen.In figure (1 - 11) schematic of Mechansem to mRNA Vaccine , the vaccine is injected into muscle and the protein antigen is taken up by dendritic cells, which are activated through pattern recognition receptors (PRRs) by danger signals in the adjuvant, and then trafficked to the draining lymph node. Here, the presentation of peptides of the vaccine protein antigen by MHC molecules on the dendritic cell activates T cells

through their T cell receptor (TCR) **(Heine, *et al* , 2021)**. In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the T cells drive B cell development in the lymph node. Here, the T cell-dependent B cell development results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes. The production of short-lived plasma cells, which actively secrete antibodies specific for the vaccine protein, produces a rapid rise in serum antibody levels over the next 2 weeks. Memory B cells are also produced, which mediate immune memory. Long-lived plasma cells that can continue to produce antibodies for decades travel to reside in bone marrow niches. CD8+ memory T cells can proliferate rapidly when they encounter a pathogen, and CD8+ effector T cells are important for the elimination of infected cells**(Pollard *et al* , 2021).**

1.7.2 Type of covid -19 vaccine:-

There are four types of vaccines in clinical trials: whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA), each of which protects people, but by producing immunity in a slightly different way . In figure (1-12) type of vaccines, activity and side effect the type vaccine is Pfizer/BioNTech , AstraZeneca , Janssen, The Moderna , The Sinopharm COVID-19 vaccine , The Sinovac **(Tregoning *et al.*, 2020).**

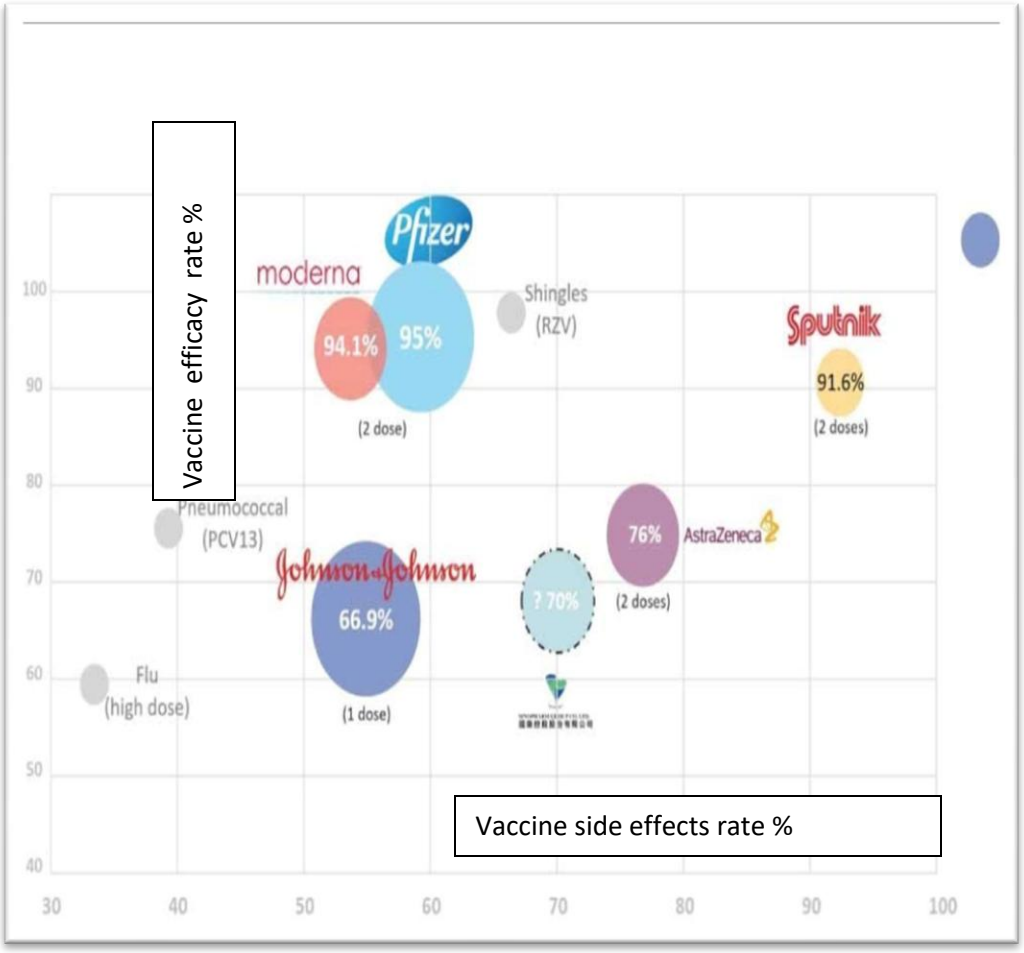


Fig (1-12):- Type of vaccines, Activity and Side Effect

1.7.3 Design Strategies for SARS-CoV-2 mRNA Vaccines

The conceptualization of mRNA vaccines might seem quite simple at first, due to the straightforward modus operandi of mRNA vaccines. Upon delivery of an mRNA vaccine encoding a target antigen, cells will take up the mRNA and translate it into protein in situ. The individual's immune system will then mount a robust adaptive immune response against the target protein. Nevertheless, the actual design process of mRNA vaccines requires important considerations of mRNA modifications to reduce reactogenicity and optimize protein expression; proper selection of the target antigen; and optimal formulation allowing for an efficient delivery**(Bettini *et al* , 2021)**.

1.7.4 . Antigen Selection

In selecting the antigen for an mRNA vaccine, it is essential to choose a target that is both immunogenic and capable of eliciting a protective immune response. Of the multiple epitopes on SARS-CoV-2, the spike (S) glycoprotein is the target commonly selected for COVID-19 vaccine development , since it is the major SARS-CoV-2 surface protein and mediates viral entry by binding to the angiotensin-converting enzyme 2 (ACE2) receptor in host cells**(Bettini *et al* , 2021)**. SARS-CoV-2 S is a class I viral fusion glycoprotein, consisting of a receptor binding subunit (S1) and a fusion subunit (S2) that are joined by a furin cleavage site unique to this coronavirus . S is cleaved post-translationally at this furin site. However, the S1 and S2 subunits stay associated until S is bound to the ACE2 receptor via the receptor binding domain (RBD), leading to irreversible conformational changes and membrane fusion. Information gleaned from previous work with similar fusion glycoproteins has shown how important it is to use prefusion stabilized proteins that preserve neutralization-sensitive epitopes for the development of effective vaccines**(Hsieh1 *et al.*, 2020)**.

To stabilize the S protein, a few different strategies have been adopted . A mutation where amino acids 986 and 987 are replaced with prolines (S-2P), stabilizing the transmembrane-anchored S glycoprotein in the perfusion conformation but still allowing for cleavage of the S1 and S2 subunits is the approach used in the licensed vaccines BNT162b2 **(Bettini *et al* , 2021)** .

1.7.5. Delivery of mRNA

Although mRNA can be directly injected for immunization, this method of delivery is rather inefficient. Indeed, mRNA molecules must be able to penetrate a cell's lipid membrane in order to reach the machinery required to translate the transcripts into proteins. Thus, delivery methods facilitating the cytosolic localization of mRNA vaccines are important for achieving efficient protein translation. as LNPs are able to efficiently deliver mRNA in vivo . When injected intramuscularly, mRNA-LNPs can be internalized and quickly translated by antigen-presenting cells at both the injection site and in draining lymph nodes, thus promoting the initiation of adaptive immune responses **(Shi *et al.*, 2020).** LNPs can protect mRNA from degradation by nucleases. Although the precise composition of the LNPs used by many vaccine developers is proprietary information, it is known that LNPs contain a combination of ionizable cationic lipids, cholesterol, phospholipid and PEGs that self-assemble into ~100 nm nanoparticles encapsulating the mRNA **(Bettini *et al* , 2021)** .

Table (1-1):- Common Side Effect to COVID-19 Vaccine (Vasireddy *et al.*, 2021)

COVID-19 vaccine	Common side effects	Other adverse effects
Pfizer-BioNTech	Fever, cough, fatigue, headache, shortness of breath, chills, muscle pain, sore throat, diarrhea, or vomiting, local injection site redness or swelling.	Lymphadenopathy, Bell's paroxysmal ventricular arrhythmia, leg paresthesia and shoulder

1.7.6 Mechanism of Action

Unlike traditional vaccines, a synthetically created RNA sequence of virus fragments encoding the S protein is injected. The mRNA fragment is placed in the lipid nanoparticle (LNP) vehicle which prevents degradation by the host until it is taken by the cell . The mRNA strand does not enter the nucleus of the cell. Thus, these vaccines do not affect the genetic makeup of the cells**(Shi *et al.,* 2020)**. The intracellular lipases degrade the LNP and expose the mRNA. The dendritic cells take up these fragments by phagocytosis. Then, ribosomes read the mRNA and produce viral antigens which are further broken down by proteasomes. These viral antigens are taken up by major histocompatibility complex (MHC) class I and II molecules further activating the dendritic cells. These activated cells present T and B cells (CD8+ cytotoxic T cells or CD4+ helper T cells) in the lymph nodes resulting in stimulation of cellular and humoral immunity **(Vasireddy *et al.,* 2021)**.

1.7.7 Ingredients the mRNA vaccine

The mRNA vaccine is a Comirnaty concentrate from Pfizer and BioNTech. One dose (0.3 mL) contained 30 micrograms of the COVID-19 mRNA vaccine. The active substance of the preparation is the mRNA that encodes the spike protein of the virus and acts as an antigen. The vaccine also contains four types of fats in the form of lipid nanoparticles: (4-hydroxybutyl)azanediyl, bis(hexane-6,1-diyl), bis(hexyl-2-decanoate), (ALC-0315),2-((polyethylene glycol)-2000)-N, N-ditetradecylacetamide (ALC-0159), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol and other substances such as potassium chloride, potassium

dihydrogen phosphate, sodium chloride, disodium phosphate dehydrate, saccharose, and water for injections **(Tretyn *et al.*, 2021)**.

1.7.8 Explanation of Ingredients

The mRNA technology to build antibodies against COVID-19.- Lipids: Nanolipids, or tiny fat molecules, protect the mRNA and provide a "greasy" exterior that helps the mRNA slide inside cells also**(Tenchov *et al.*, 2021)** very effective at improving the surface properties of the liposomes by preventing access to their surface through steric hindrance, inert polymers, typically poly(ethylene glycol) (PEG), making them invisible to phagocytes.- Nanolipid components in the Pfzer-BioNTech vaccine include: (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), (polyethylene glycol)-2000 , N,N-ditetradecyl acetamide, 1,2-distearoyl-sn-glycero-3- phosphocholine, and cholesterol.**(Shi *et al.*, 2020),(connecticue department of public health,2021)**. Salts: Helping to balance the acidity in your body, the following salts are included in the Pfzer vaccine: potassium chloride, monobasic potassium phosphate, sodium chloride, and dibasic sodium phosphate dihydrate - Sugar: Basic table sugar, also known as sucrose, can also be found in the Pfzer vaccine. This ingredient helps the molecules maintain their shape during freezing**(DPH, 2021)**. .

1.7.9 Lipid Nanoparticle Basics

The Liposomes, is The Earliest Generation of Lipid Nanoparticles . The term "liposome" was coined in the 1960s, shortly after it was found that closed lipid bilayer vesicles form spontaneously in water. The term "lipid nanoparticle" came into use much later, in the early 1990s, with the beginning of the era of nanoscience and nanotechnology. Since liposomes are made of lipids and in most cases are nanosized, they are rightfully

considered as the earliest generation of lipid nanoparticles **(Tenchov *et al.*, 2021)**.

Potential of liposomes as drug and vaccines delivery systems was recognized almost immediately after their discovery. Since LNPs are mainly composed of natural lipids, they have been considered pharmacologically inactive and minimally toxic. **(Shi *et al.*, 2020)**However, in some cases, LNPs are not immunologically inert while LNP constituents are unnatural compounds which may be toxic to human cells.

For example,while lipids offer great promise as carriers for the delivery of fragile compounds such as nucleic acids, some lipids cause cytotoxicity, lipids reduce mitosis in cells, form vacuoles the cytoplasms of cells, and cause detrimental effects on key cellular proteins , PEG–lipid conjugates may also cause undesired toxicity, while LNPs containing PEG–lipid conjugates are known to interact with immune cells to generate undesired antibodies against some PEGylated lipids (**Tenchov *et al.*, 2021**)**.**

1.8 Aim of Study :-

This study was planned for addressing the basic overview of the virus' profile that may provide the scientific community with evidence-based insights into COVID-19 and the vaccine Pfizer to understand the change in immunity system in the body of human to help in discover a drug for treatment and develop the vaccine more activity and more specific depending on the age and sex without side effect specific aims include:

* to estimation of the level of anti –Covid -19 immunoglobulin to better understand the extent to which responses antibody are associated with vaccine-mediated protection

***** .to investigate MDA levels in patients with COVID-19 and healthy groups

* to determine the Interleukin -13 (IL-13) levels change in patients with COVID-19 healthy groups

***** to explore highlight the importance of redox-sensitive pathways based targets , the prominent role of oxidative mechanisms in the pathogenesis of COVID-19 as well as anti oxidative strategies in the prevention and therapy of COVID-19 infection and effectiveness of the vaccine Pfizer.

Chapter Two Materials and MethodS

2.0 Materials and methods

2.1 .1. Materials

The Materials of ELISA kits were used In the present study listed in table (2-1) , as manufacturer , and country .

Table (2-1): The Bio Materials Kits

Materials of kit	Cat.No	Manufacturer	Country
Human Total antioxidant capacity(TAOC)ELISAkit	E2199Hu	BT laboratory	China
Human-Immunoglobulin-G IGG ELISA-Kit	E0186Hu	BT laboratory	China
Human Immunoglobulin M ELISA Kit	E0187Hu	BT laboratory	Chine
Human-Interleukin-13IL-13ELISA-Kit	E0098Hu	BT laboratory	Chine
Human Malondialchehyche ELISA Kit	E1371Hu	BT laboratory	Chine

2.1.2 Instruments and Tools

The tools use in the study with Manufacturer , country , mentioned in Table(2-2).

Table (2 - 2): The Instruments and Tools .

No.	Tools	Manufacturer	country
1	Centrifuge	Kubota	German
2	Cool box	Unisef	Russia
3	ELISA advice	Biotek	USA

2.2 Subjects

This study Sample have been collection was worked during the period from October 2021 to November 2021 in AL - Mahaweel Hospital .

2.3 Study design:

The patient of covid 19 the blood samples were taken from them after confirming that they were infected with thevirus by taking a swab and examining it with a device(PCR)(polymerase chain reaction).

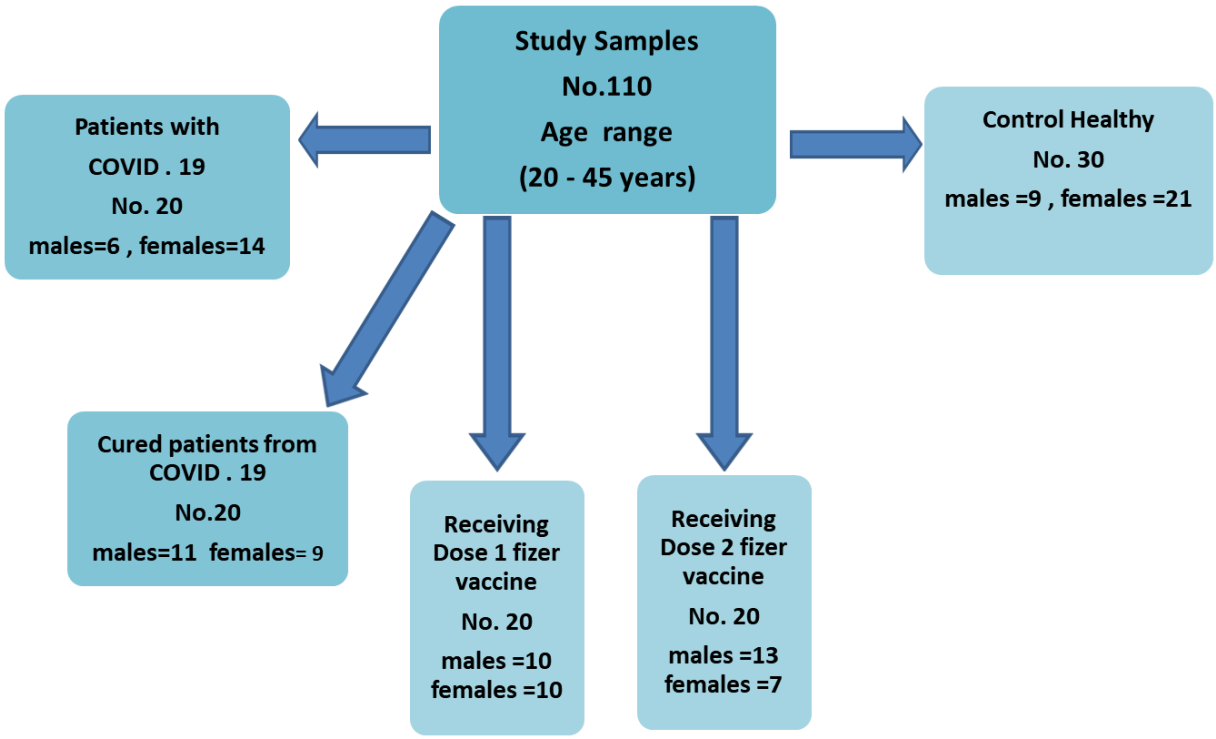


Fig (2- 1) :- Schematic of subjects groups in study

2.4 Exclusion criteria :-

The study excluded patients with other chronic diseases, smoker , systematic immune diseas e , gestational diabetes also thyroid gland disease.

2. 5 Blood sample collection:

About 5 milliliters of venous blood were drawn from each the patients ,control group , cured patients , receiving Dose 1 fizer vaccine and receiving Dose 2fizer vaccine .By 5 ml syringes , the blood were place in gel tubes and then left at room temperature for a period of 20 minutes for coagulation , then centrifuged (at 3000 X g) for 20 minutes for serum separation. The sera were divided into five Eppendorf tubes and stored at (-20C^{o}) until the time of biochemical estimation .

2.6 Determination of certain studied parameters by ELISA technique

By using the principle and manual procedure provided by Bio –Assay company , the assessment of (IL- 13 , IgG , IgM , Total antioxidant and MDA were done according to specific standard curve for each one .

2.7. Assay Principle

This sandwich kit is for the accurate quantitative detection of human (Interleukin 13- MDA- TAC –IGM – IGg) is an Enzyme-Linked Immunosorbent Assay (ELISA) in serum .

2.7.1 Wash Buffer

Diluted 20ml of Wash Buffer Concentrate 25x into distilled water to yield 500 ml of 1x Wash Buffer. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved .

2.7.2 Assay Procedure

1- All reagents, standard solutions and samples as instructed. all reagents wear brought to room temperature before use. The assay is performed at room temperature.

2- The number of strips required for the assay were Determined. the strips were inserted in the frames for use. The unused strips were stored at 2-8C˚.

3- A volume of 50µl standard was added to standard well. Note: antibody dose not add to standard well because the standard solution contains biotinylated antibody.

4- A volume of 40 µl of sample was added to sample wells and then added 10µl from anti-(IL-13 – MDA – TAC – IgM) anti-body was add to sample wells, then 50µl streptavidin-HRP was added to sample wells and standard wells (Not blank control well).They were mixed well. The plate was covered with a sealer. It was incubated 60 minutes at 37C˚.

5- The sealer was removed and the plate had been washed 5 times with wash buffer. The wells wear soaked with at least 0.35 ml wash buffer for 30 seconds to 1 minute for each wash. For automated washing, all wells wear aspirated and washed 5 times with wash buffer, overfilled wells with wash buffer. the plate was bloted onto paper towels .

6- A volume of 50µl substrate solution was added to each well and then 50µl substrate solution B was add to each well. The plate were incubated covered with a new sealer for 10 minutes at 37C˚in the dark.

7- A volume of 50µl from stop solution was added to each well, the blue color changed into yellow immediately.

8- The optical density (OD value) of each well was immediately used Amicroplate reader set to 450 nm within 10 minuets after adding the stop solution.

2.7.3 Calculation

Construct a standard curve by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and draw a best fit curve through the points on the graph.

2.8. Determination of Human Interleukin-13 ELISA

As like describe in 2.7.2, the mesurment is done by same principle and methods , with the following stadanrd curve listed in Figure (2- 2).

2.8. 1.Reagent Preparation Interleukin 13

Standard Reconstitute the 120µl of the standard (128ng/L) with 120µl of standard diluent to generate a 64ng/L standard stock solution. the standard was allowed to sit for 15 mins with gentle agitation prior to making dilutions. The standard points was prepared by serially diluting the standard stock solution (64ng/L) 1:1 with standard diluent to produce 32ng/L, 16ng/L, 8ng/L and 4ng/L solutions. Standard diluent serves as the zero standard(0 ng/L).standard(0 ng/L).

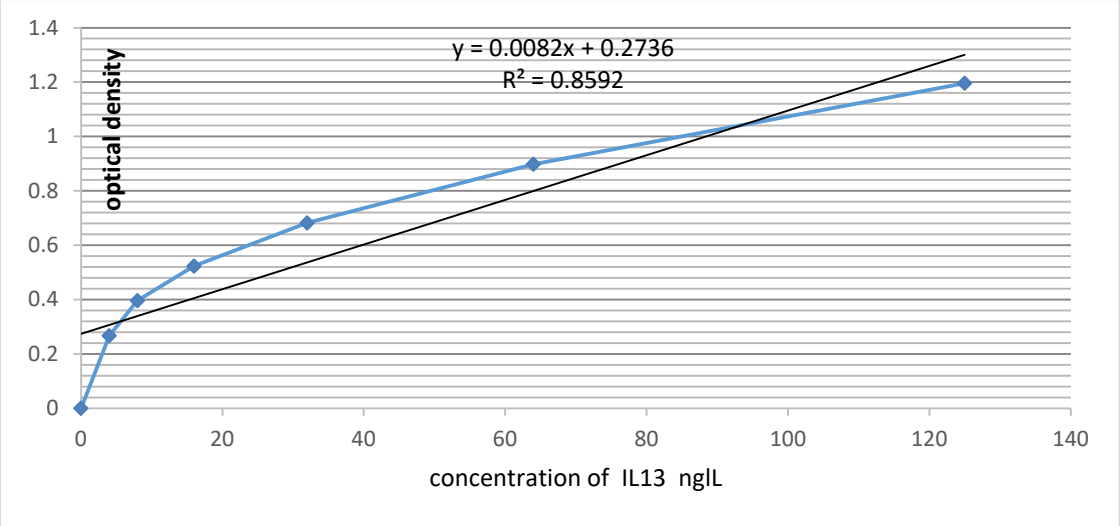


Figure (2-2):- Standard curve used in Interleukin IL-13 measurment

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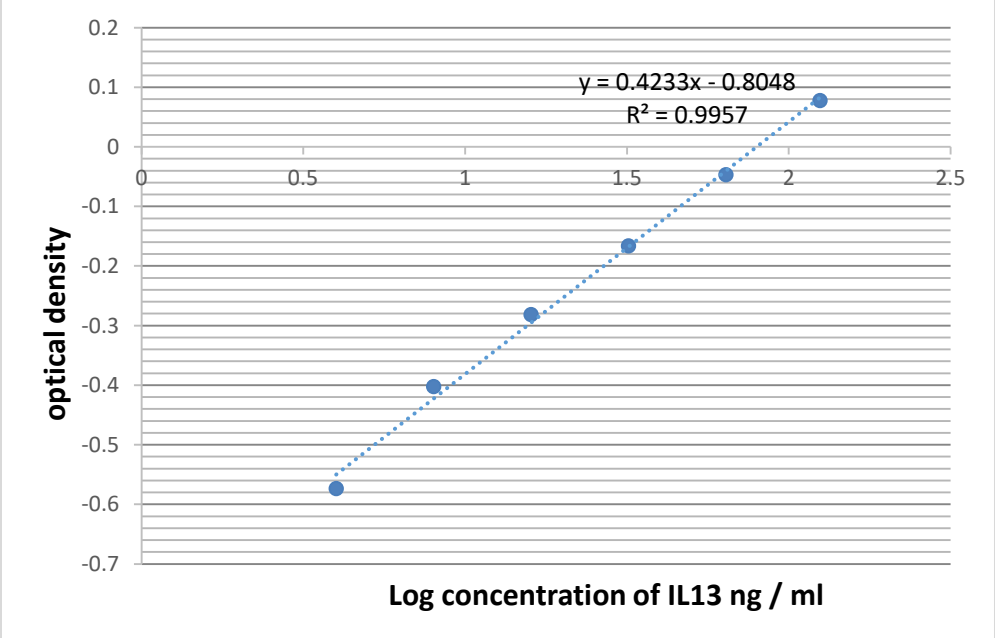


Figure (2-3):- log – log calibration optical density and concentration of Interleukin IL-13.

2.9. Determination of Human Immunoglobulin M ELISA

As like describe in 2.7.2, the mesurment is done by same principle and methods , with the following stadanrd curve listed in figure (2- 4).

2.9.1. Reagent Preparation Immunoglobulin M

Standard Reconstitute the 120µl of the standard (12.8mg/ml) with 120µl of standard diluent to generate a 6.4mg/ml standard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare standard points by serially diluting the standard stock solution (6.4mg/ml) 1:1 with standard diluent to produce 3.2mg/ml, 1.6mg/ml, 0.8mg/ml and 0.4mg/ml solutions. Standard diluent serves as the zero standard(0 mg/ml).

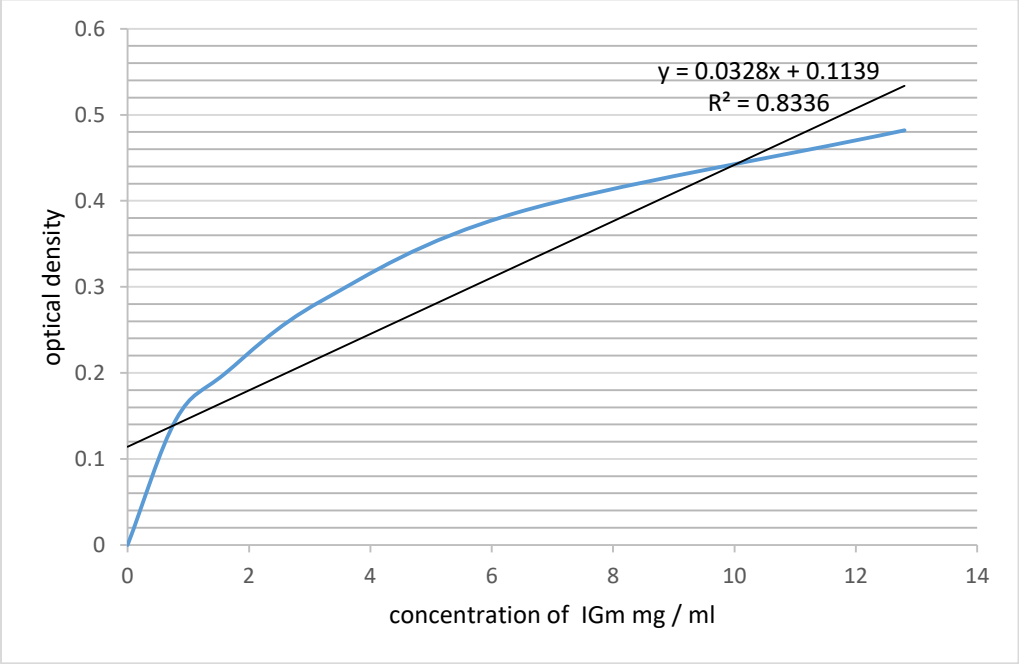


Figure (2-4) Standard curve used for Determination of Human Immunoglobulin M .

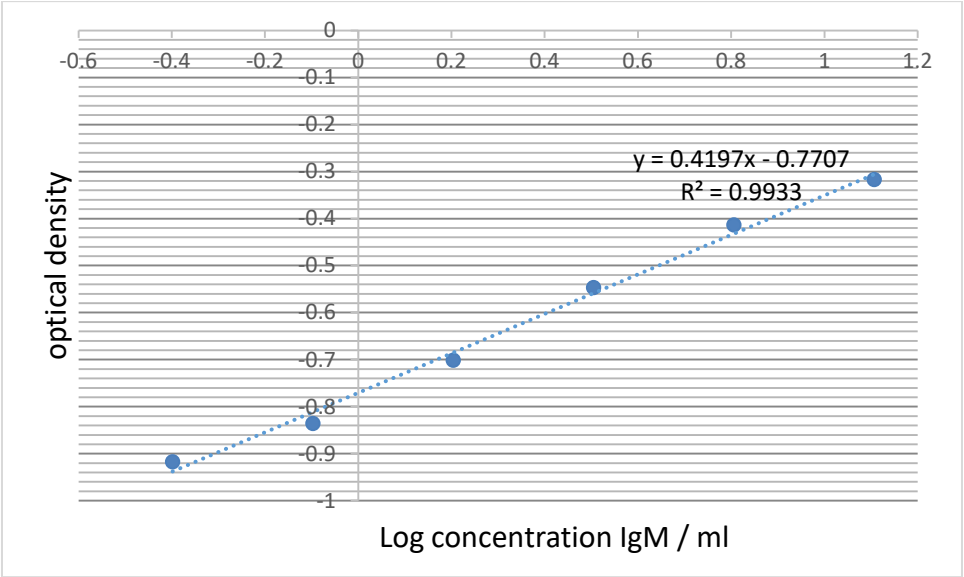


Figure (2-5):- log – log calibration optical density and concentration of Immunoglobulin M .

2.10. Determination of Human Total Antioxidant Capacity ELISA

As like describe in 2.7.2, the mesurment is done by same principle and methods , with the following stadanrd curve listed in figure (2-6).

2.10.1 Reagent Preparation Total Antioxidant

Standard Reconstitute the 120µl of the standard (96U/ml) with 120µl of standard diluent to generate a 48U/ml standard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare standard points by serially diluting the standard stock solution (48U/ml) 1:1 with standard diluent to produce 24U/ml, 12U/ml, 6U/ml and 3U/ml solutions. Standard diluent serves as the zero standard(0 U/ml).

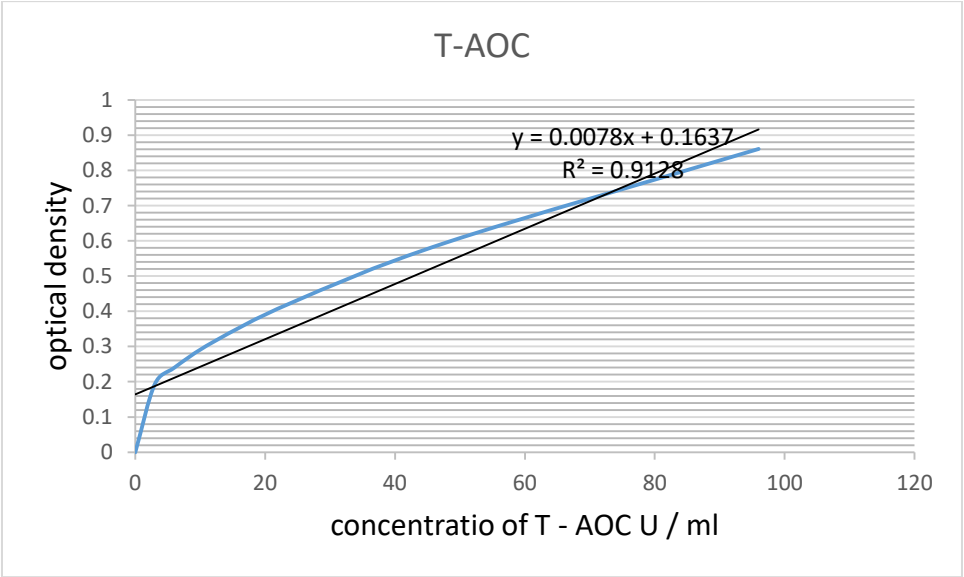


Figure (2-6) Standard curve used for Determination of Human Total Antioxidant Capacity

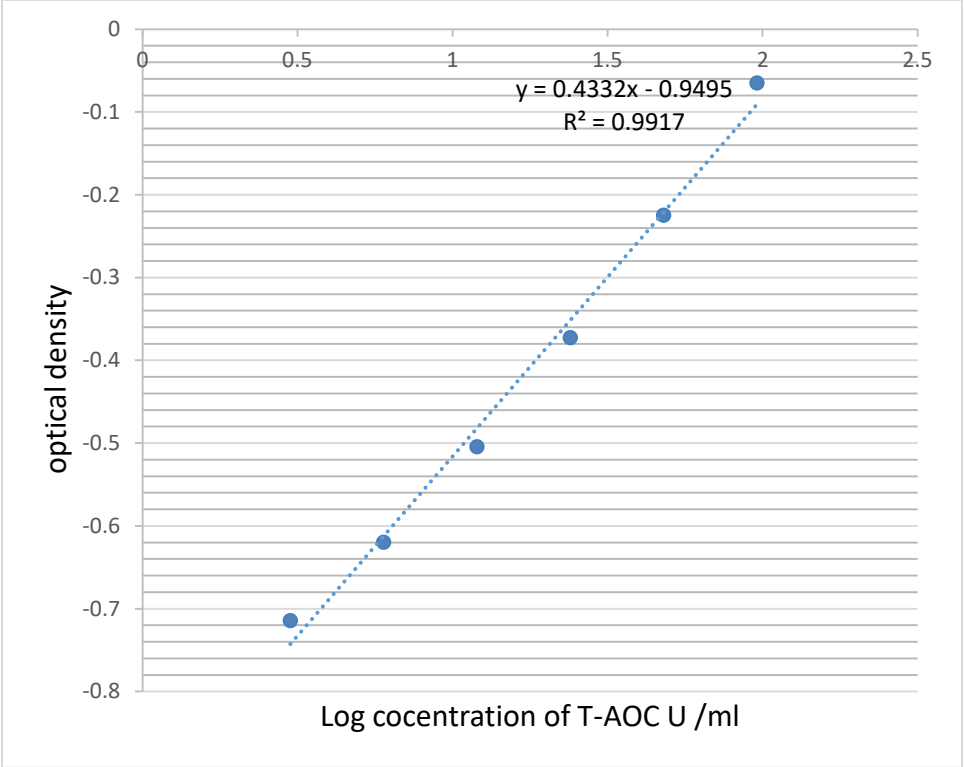


Figure (2-7):- log – log calibration optical density and concentration of T-AOC.

2.11. Determination of Human Malondialdehyde ELISA

As like describe in 2.7.2, the mesurment is done by same principle and methods , with the following stadanrd curve listed in figure (2 - 8).

2.11.1.Reagent Preparation Malondialdehyde

Standard Reconstitute the 120µl of the standard (80nmol/ml) with 120µl of standard diluents to generate a 40nmol/ml standard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare standard points by serially diluting the standard stock solution (40nmol/ml) 1:1 with standard diluent to produce 20nmol/ml, 10nmol/ml, 5nmol/ml and 2.5nmol/ml solutions. Standard diluent serves as the zero standard(0 nmol/ml).

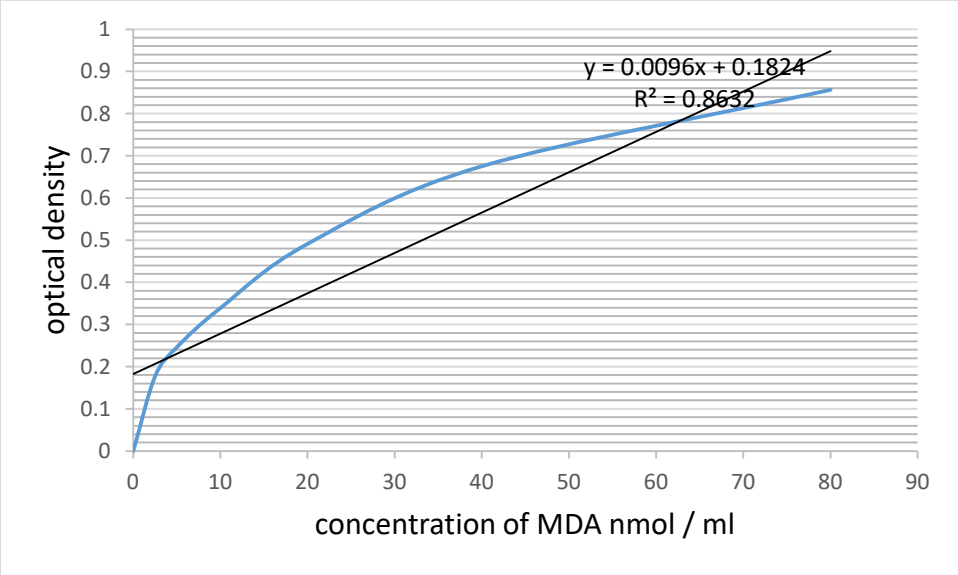


Figure (2-8) Standard curve used for Determination of Human Malondialdehyde.

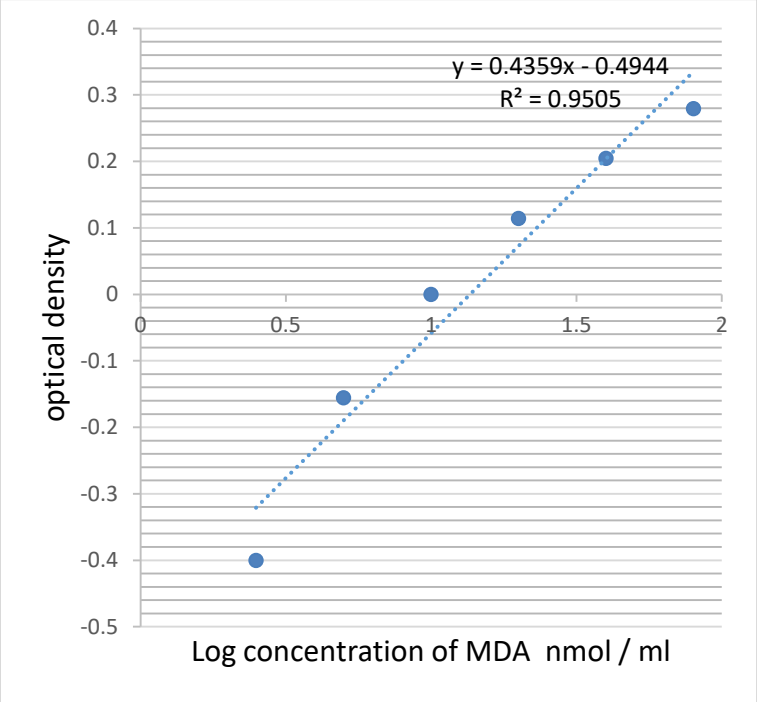


Figure (2-9):- log – log calibration optical density and concentration of Human Malondialchehyche.

2.12. Determination of Human Immunoglobulin G ELISA

2.12.1 Reagent Preparation Immunoglobulin G

Standard Reconstitute the 120µl of the standard (80mg/ml) with 120µl of standard diluent to generate a 40mg/ml standard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare standard points by serially diluting the standard stock solution (40mg/ml) 1:1 with standard diluent to produce 20mg/ml, 10mg/ml, 5mg/ml and 2.5mg/ml solutions. Standard diluent serves as the zero standard(0 mg/ml).

2.12.2 Assay Procedure

1- All reagents, standard solutions and samples as instructed. All reagents were brought to room temperature before use. The assay is performed at room temperature.

2- The number of strips required for the assay were Determined. The strips were Inserted in the frames for use. The unused strips were stored at 2-8C˚.

3-The substrate solution A , substrate solution B and stop solution was added only as blank control .

4- A volume of 50µl diluted standard was added to standard well , 50µl sample (sample recommended dilution :2-5 time when necessary) was added to sample well , and 50µl biotinylated antigen to each well will mixed ,the plate was covered with sealer and was incubated for 60 minutes at 37C˚.

5- The sealer was removed and the liquid in the well ,wash 5 times with 300 µl wash buffer manually . the plate was inverted and decant the contents each time , hit 4-5 times on absorbent material to complete remove liquid .

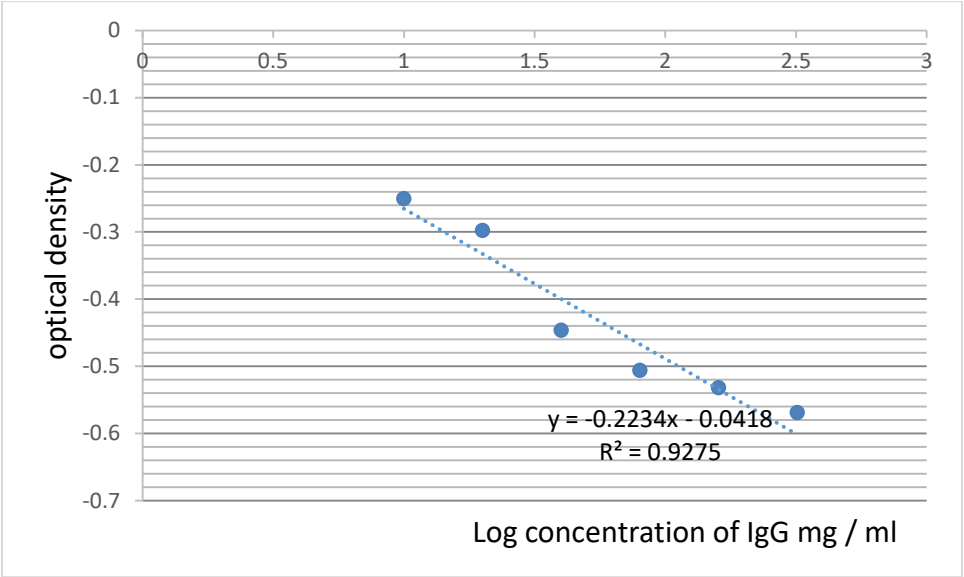
6- Avolume of 50 µl avidine-HRP was added to the standard well and sample well, the plate was covered with a sealer and incubated for 60 minutes at 37 C˚.

7- The sealer was removed and washed as described above.

8- A volume of 50 µl substrate solution A was add to each well and then 50 µl substrate solution B was added to each well . the plate incubated was covered with a new sealer for 10 minutes at 37 C˚.

9- A 50µl from Stop Solution was add to each well, the blue color was changed into yellow immediately.

10- The optical density (OD value) of each well was immediately used a microplate reader set to 450 nm within 10 minuets after adding the stop solution.



Figure(2-10):- log – log calibration optical density and concentration of Human Immunoglobulin G

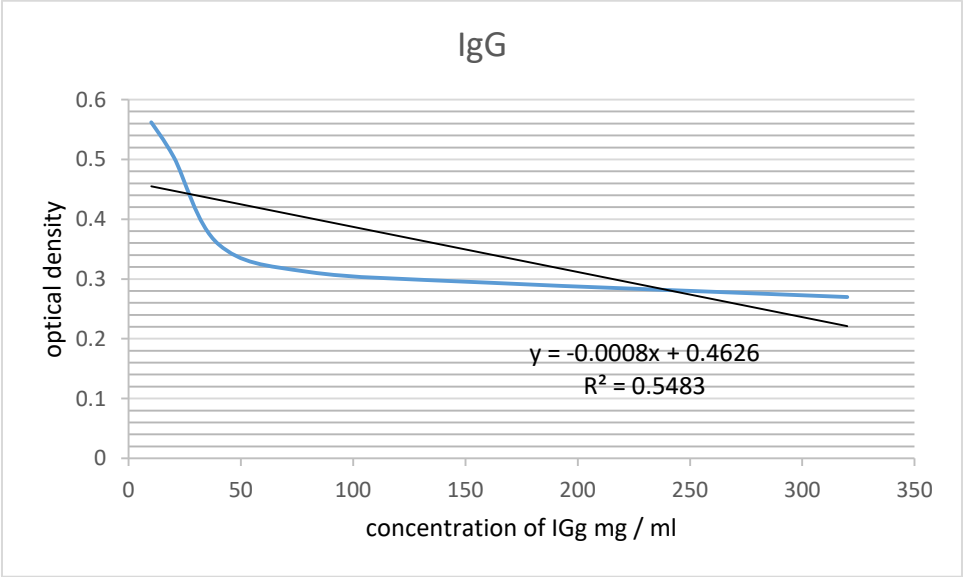


Figure (2-11) Standard curve used for Human Immunoglobulin G

2.13 Statistical analysis :

The results were subjected to statistical analysis and analyzed using By using SPSS program , the statistical analysis of all studied parameters in patients and control , were done by ANOVA test , Chi Square , Corelation , T-Test and Regresion modele as well as scattered graph in correlation figures at two level (< 0,05 and < 0,01) **(Mustafa Ebaid · 2021)** .

Chapter Three

Results And Discussion

3. Results and Discussion

3.1. Demographic distribution of all studied groups.

This study carried out a sample of (110) subjects divided into healthy populate as acontrol (30), patient (20) , cured patient, persons have received one dose (20) and persons have received two doses (20) according to the following Table **(3-1) :-**

Table (3 - 1):- Percentage of current study Groups and Control.

Study Groups	Frequency	Percent%	P.Value
Cured patients	20	18.2	0.020
Receiving Dose	20	18.2	
Receiving Dose 2	20	18.2	
Covid -19 patients	20	18.2	
Control	30	27.2	
Total	110	100.0	

3.1.1 Age and Sex distribution

In Tables (3- 2) and (3 - 3)the current study the age to participants from (20 – 45) and distribution of sex.

Table (3 - 2) :- Age distribution in all studied groups and control.

Age Range	No.	Mean±S.D	P. Value of F-Test
Cured patients	20	31.18±6.24	0.244
Receiving Dose	20	25.31±7.11	
Receiving Dose 2	20	31.20±7.30	
Covid -19 patients	20	33.63±8.76	
Control	30	29.13±7.77	
Total	110	29.72±7.70	

Table (3- 3) :- Sex Distribution in recent study groups and control.

SEX		Frequency	Percent%	P.Value
Cured	**Male**	11	10	0.016
	Female	9	8.2	
Dose 1	**Male**	10	9.1	0.126
	Female	10	9.1	
Dose 2	**Male**	13	11.8	0.002
	Female	7	6.3	
Patients	**Male**	6	5.4	0.002
	Female	14	12.7	
Healthy	**Male**	9	8.2	0.006
	Female	21	19.0	
Total		110	100.0	

3. 2Measurement of Levels Human Total Antioxidant Capacity

Table (3- 4) TAC level in group study

TAC level	No.	Mean ± S.D	P. Value of F-Test
Cured patients	20	22.10 ±10.39	0.033
Receiving Dose1	20	31.19 ±16.76	
Receiving Dose 2	20	25.16 ±16.25	
Covid -19 patients	20	17.00 ± 1.74	
Control	30	23.97 ±2.90	
Total	110	23.25 ± 11.48	

The present study shows (Table 3- 4) that in all group patients with control group there are significant when the P. value<0.05.

In group Covid -19 patients(17.00 ±1.74) decrease in average compared with group control(23.97 ±2.90) in group Cured patients shows mean(22.10 ±10.39) increases , in group Receiving Dose1 shows mean(31.19 ±16.76) high increases , in group Receiving Dose 2 shows mean(25.16 ±16.25) increases .

The results of the study were in(Table (3-4)and Figure (3-1) in group of Covid -19 patients have shows that levels mean(17.00 U/mL) of antioxidants were low among COVID-19 patients because Antioxidants have the capability to counteract the action of oxidants by scavenaging reactive oxygen species (ROS) and by inhibiting oxidant generating enzymes. in response to the invasion of pathogens, the host organism activates leukocytes, which, as a result of an increased activity of pro-oxidative enzymes, generate large amounts of ROS ,. ROS modify both the host organism's resistance and susceptibility to infections since, due to their

non-specific nature and unique reactivity in larger amounts, ROS become harmful to both the pathogen and the host. Overproduction of ROS promotes the degradation of pathogens, and thus protects the body against their effects; however, it is known that their elevated level may enhance cytotoxicity and damage the host's molecules/cells and organs, while their reduced level may favor the survival and spread of pathogens. The consequences are similar in both situations, but reduced ROS levels usually lead to increased host mortality **.** These result consistent with many other studies **(Novaes, *et al* ,2019) , (Pisoschi *et al.*, 2022) , (Lingappan, 2018), (Griffiths, 2017), (Ivanov , *et al* , 2017) , (Pohanka , 2013)**.

The generated ROS modulate the signal transduction cascade and enhance the immune functions of lymphocytes. Moreover, infections are usually accompanied by inflammation and a decrease in the effectiveness of endogenous antioxidant defense mechanisms, which ultimately promotes the development of oxidative stress observed in viral diseases**)**. On the other hand, under oxidative stress conditions, oxidative modifications of the basic components of cells/biological fluids, such as DNA, lipids, and proteins occur, which may alter their functionality, including the promotion of inflammation, which is a significant consequence of the host's immune response. These result consistent with many other studies **(Ebrahimi, *et al* ,2021**) , **(Karkhanei, *et al* ,2021), (Belikov,*et al* , 2015) , (Komaravelli, *et al* 2014)** , **(Shastri *et al* ,2018)**.

Consequently, the disruption of host redox homeostasis by pathogens leads to a modification of both cellular metabolism and intra- and extracellular signaling .Overproduction of ROS and deprivation of antioxidant systems. The antioxidants a central protective role against oxidants is played by reduced glutathione, which is depleted in SARS-CoV-

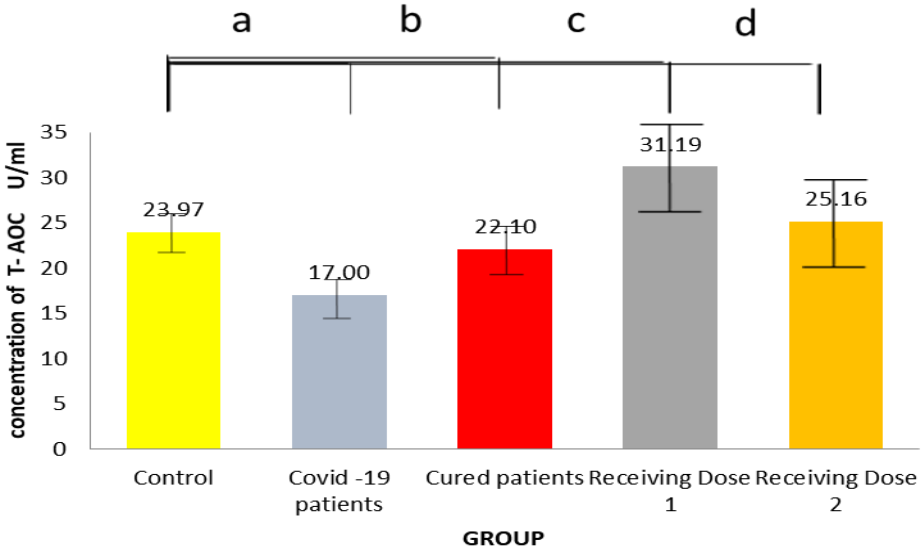
2 infection. N-acetyl cysteine, a precursor of GSH, is of particular interest as an anti-COVID-19 agent. GSH and NAC hamper binding of the S1 subunit of SARS-CoV-2 spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptor . Apoor nutrient status being associated with oxidative stress, inflammation, and impairment of the immune system . The systemic (OSS) source of oxidative stress was strongly altered in critically ill COVID-19 patients as evidenced by increased lipid peroxidation but also by deficits in some antioxidants (vitamin C, glutathione, thiol proteins) and trace elements (selenium ,zinc).These results consistent with many other studies **(Pincemail *et al.*, 2021) , (Deflora Silvio,et al , 2021) .**

The results were in(Table (3-4)and Figure (3-1) study in group of Cured patients shows mean (22.10 U/ml) increase of antioxidant then patients because the death the viruses in the body that not need to large of antioxidant because the antioxidants a central protective role against oxidants is played by reduced glutathione (GSH), which is depleted in SARS-CoV-2 infection. N-acetylcysteine (NAC), a precursor of GSH, is of particular interest as an anti-COVID-19 agent. GSH and NAC hamper binding of the S1 subunit of SARS-CoV-2 spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptor, and in ill covid increase lipid perodoxation and in time therapy the patient- have the antioxidant as drug and the body not need alarge amount of antioxidant to activated the immunity system than infection lead to increase the antioxidant then patient and control. This results are consistent with other study **(Forcados *et al.*, 2021)**.

The current study that in(Table (3-4) and Figure (3-1) in group receiving dose 1 high significant when shows mean (31.19 U/mL) in the group of receiving dose 1 the level of total antioxidant increase in mean

compare the infection in corona virus because the difference between mechanism of inter the virus real and of COVID-19 Vaccine .When real virus corona inter show stimulated by a vigorous but deregulated innate immune response, along with a worse adaptive response but in vaccine receiving dose 1 the body active or strong and the level of antioxidant high the immune response toward one type spike protein and the symptoms less then real infection corona virus. The results were in agreement with other studies **(Martínez-Flores *et al.*, 2021) , (Bettini, *et al* 2021)**.

In this study that Table (3-4) and Figure (3-1) in group receiving dose 2 Show mean (25.16) not significant .The group receiving dose 2 showed the level of total antioxidant less than group receiving dose 1 because the body use the amount of antioxidant in first dose to activated the immunity system toward one spike protein and in time (21 day) the body take the second dose to activated the immunity that not work in dose one to activated towered other protein. When the human infected in real virus this process needed to antioxidant to balance the high free radical that product from mechanism response immunity to produce the antibody and symptoms of severe infection compared to the vaccine , which differs in the mechanism , as well as the symptoms are less . These results are consistent with other study **(Stanford Medicine News, 2021).**



Fig(3-1): Comparison of TAOC Means Among all Study Groups.

The current study in the Table**(3- 5)** patients with covid 19 group male(16.12±2.31) , female(17.33±1.53) shows significantly when P- value < 0.05 and receiving dose 1 Pfizer vaccine group the male (26.17±13.12) , female (36.21±19.29) there is not significantly differences when P- value > 0.05 and control group male (20.95±2.72) , female (20.97±3.04) significantly when P- value < 0.05.In cured patients group male (23.32±12.14) , female (20.53±8.26) not significantly differences when P-value > 0.05 . In group receiving dose 2 statistically significantly when P-value < 0.05.

The Table**(3- 5)** patients with covid 19 group the mean male(16.12) U /ml , female(17.33) U /ml and receiving dose 1 Pfizer vaccine group the mean male ((26.17) U /ml , female (36.21) the relationship between antioxidants and sex shows the female have level of antioxidants increase than the level in male because the presence of estrogen could explain the sex differences in various in antioxidant or mechanisms are involved. Estrogen may also act as an antioxidant, in women special in pre-menopausal women in this study limited the age (20- 45) in other study discussed the relationship between

sex and oxidative stress. Showed that *in vivo* biomarkers of oxidative stress were higher in young men than in women of the same age. Similarly, it was observed that ROS production was higher in the vascular cells from males than in the cells from females. In addition, clinical and experimental data suggested a greater antioxidant potential in females over males **.**And the body in start to enter the viruses the level of antioxidants in female more due to subject to the rule the correlation between gender and oxidative stress have demonstrated that sex differences may be of great value in stress response; indeed male cells are often more sensitive to oxidative stress-induced cell death . These results are consistent with many other studies **(Kander, *et al*, 2017) , (Deflora Silvio, et al , 2021) .**

This point justifies why men with COVID-19 are more prone to worse outcomes and death.in study and other epidemiological data confirm a more severe disease in males found an exclusive use of IL-6 inhibitors only in few males. An enzymatic system involved in this different sex predisposition could be represented by angiotensin converting enzyme 2 (ACE2), which allows penetration of SARS-CoV-2 into cells and is down-regulated by the virus .ACE2 is counter regulatory to the activity of angiotensin II, leading to angiotensin-(1–7) formation, which exerts vasodilatory, anti-inflammatory, antifibrotic, and antigrowth effects. Sex hormones can effect the immune and inflammatory modulation during infection, with estrogens promoting both innate and adaptive immunity and testosterone having a suppressive effect on immune function**.** Biochemical profile at presentation. platelets counts, coagulation, liver and renal function, suggests a tendency to a lower inflammatory status and organs impairment in females . The mechanisms proposed include the generation of NO, promotion of endothelial repair and regeneration, anti-inflammatory and antioxidant effects. All female

population confirmed to be less fragile in this field(1) the mechanism of cell entry of the virus; (2) the immune and inflammatory modulation during infection; (3) the endothelium and vascular function . Thses result are consistent with other studies **(Taneja, 2018)** ,**(Raimondi *et al.*, 2021)**.

In Table (3-5) cured patients COVID-19 the mean male (23.32) U /ml , female (20.53) U /ml and receiving dose 2 fizer vaccine groups the mean male (27.50) U /ml , female (20.50) U /ml the relationship between antioxidants and sex in this groups. The females have level of antioxidants lower than the level in males because the response of immunity in adult female produce higher levels of T helper 1 (T_H1)-type cytokines and long time after infection or second dose than males produce higher levels of T helper 2 (T_H2)-type cytokines an . Regardless of age, females tend to show greater antibody responses than males, higher basal immunoglobulin levels and higher B cell numbers. Global analysis of B cell gene-expression signatures reveal that the majority of genes differentially expressed between the sexes are significantly up regulated in B cells from females compared with males because this role make female more oxidative stress and consume antioxidants to balance it. During their reproductive years, females have a more vigorous cellular and humeral immune response than males and a greater ability to reject tumors and homografts. Evidence suggests that physiological levels of estrogen affect humeral and cell-mediated immune responses, while the male hormone, testosterone, does the opposite. These results are consistent with other studies **(Klein *et al*, 2016)** .

Ironically, this enhanced baseline immune function is associated with a higher prevalence of autoimmune disorders in females of reproductive age . Antioxidant enzyme activity levels, NADPH-oxidase level and angiotensin II may also play an important role. It is very likely that multiple

mechanisms are responsible for the sex differences .these results agreement with others studies **(Pellegrini *et al.*, 2011) (Kander,*et al*, 2017)**.

Table 3 – 5 : Comparison of TAC and SEX at all studied groups and control.

TAC and SEX		N	Mean± SD	P. Value
Cured	**Male**	11	23.32±12.14	0.098
	Female	9	20.53±8.26	
Dose 1	**Male**	10	26.17±13.12	0.538
	Female	10	36.21±19.29	
Dose 2	**Male**	13	27.50±18.63	0.026
	Female	7	20.50±10.13	
Patients	**Male**	6	16.12±2.31	0.019
	Female	14	17.33±1.53	
Healthy	**Male**	9	20.95±2.72	0.009
	Female	21	20.97±3.04	
Total		110	23.25±11.48	

3.3 Measurement of levels Human Malondialdehyde

Table(3-6); MDA level in all study

M DA level	No.	Mean ± S.D	P.Value of F-Test
Cured patients	20	15.80 ±3.20	0.017
Receiving Dose1	20	15.23± 2.09	
Receiving Dose 2	20	14.73 ±1.83	
Covid -19 patients	20	19.60 ±9.48	
Control	30	14.29 ±5.81	
Total	110	16.84 ±5.27	

This result of study in Table (3-6) shows in all group patients and control group significant when the (P.value<0.05).In group Covid-19 patients shows the average(19.60 ±9.48) increase compared with group control (14.29 ±5.81) ,in cured group (15.80 ±3.20) the average shows increase , in group Receiving Dose1(15.23± 2.09) the average shows increase , in group Receiving Dose 2(14.73 ±1.83) the average shows equal approximately.

The Table(3-6) and Figure (3-2) shows the (oxidative stress increases in Covid-19 patients. MDA serum levels as an indicator of lipid, peroxidation were nearly higher in case groups in comparison to control group.This study supplies proof that Covid-19 patients showed high serum level of oxidative stress and inflammatory markers and low serum level of antioxidants,in comparison with control group. All results presented high serum level of MDA in case groups. MDA is an important indicator of oxidative stress. There is a significant correlation between oxidative stress markers and respiratory viral infection particularly RNA viruses .*In vitro* and *In vivo* studies indicated that some viruses could change redox balance of cell. The beginning of oxidative stress by virus infection is necessary for activation of innate immunity By cytokines production . Besides, oxidative stress induced by several viruses involved in facilitation of virus replication inside the cell. It is described the function of macrophage respiratory burst in reaction to Covid-19 infection, which can lead to ROS production . Over production of ROS/RNS have role in lung tissue injury and dysfunction of epithelial barrier induced by acute respiratory viral infections . NADPH oxidase 2(NOX2) has important role in ROS production, arterial dysfunction, and thrombosis (induced by platelet activation).These results

are consistent with other studies **(Cherian DA, 2019) (Forcados *et al.*, 2021)** .

It is indicated NOX2 over activation in COVID19 patients Viruses can suppress antioxidant systems including super oxide dismutase, glutathione S-transferase, catalase, glutathione peroxidase in human alveolar type 2-like epithelial cells and small airway epithelial cells**.**Reduced oxygen transport to the tissues, disseminated intravascular coagulopathy and sepsis are shown inCOVID-19 patients (Hypoxia can produce reactive species such as superoxide and H2O2 which can up regulate the expression of inflammatory cytokines. In turn, inflammatory cytokines can increase oxidative stress markers via activation of macrophages, neutrophils, and endothelium cells . These interactions between oxidative stress and inflammatory cytokines can lead to several organ failures in COVID-19 patients who proceed to worsening the condition.(Cytokine storm) in covid-19 patients is well established. Cytokine storm has prominent role in development of acute respiratory distress syndrome and various organ dysfunctions . ROS as an inflammatory some activator has function in inflammation induced by COVID-19 virus and following blood dissemination. As well, it is suggested that adaptive immune response to oxidative stress may be associated with systemic injury**.**These results agreement with other studies **(Elmarakby *et al*, 2012)**, **(Mehri *et al.*, 2020) , (Mehri *et al.*, 2021)**.

In cured group when compared with group control statistical analysis Show mean (15.80)nmol/ml in MAD compared infection in patient corona 19(19.60) nmol/ml . Studies that are agreement with our conclusion are MDA Production by Processes during lipid per oxidation. That in many process undergo cleavage to produce MDA. These process

swill low rang because the end the virus corona in the body , will not needed in replication himself and the immunity system will not needed to high energy to release the antibody agents viruses because this the free radical will low that refer to low of process of oxidative stress to produce MDA because increase the antioxidant These results agreement with other studies **(Martineau, *et al*, 2020) , (Lage *et al.*, 2022)** .

In receiving dose1(people who received the first dose) when compared with group control statistical analysis show mean (15.23) nmol/ml and in receiving dose2 (those who received the second dose) Show mean (14.73)) nmol/ml the level of MDA decrease in receving vaccines because the process of production of MDA these processes will low rang because the viruses inter to body not real only spike protein, because the vaccine's spike protein does not bind to ACE2 because replace site of binding . These results agreement with other study **(Hati *et al* , 2020)**.

After injection and enhancing its uptake into cells surrounding the injection site by endocytosis. Thus, formulation in LNPs enables expression of the S protein, and elicitation of both antibody and cellular immune responses and the immunity system will not activated than real viruses infection ,because all these the processes that undergo cleavage to produce free radical and MDA low these refer to low oxidative stress. The difference between two group Receiving vaccine the level of MDA height in first then two due to that upon administration of vaccine antigen to a naïve individual, antibodies to the antigen become detectable at about 10-14 days; IgM comes up first, followed by IgG. The scenario is called the primary response. Memory B cells become established along with the specific IgG. Upon re-exposed to the same antigen in the same host,

production of the antibodies to the antigen is very rapid and robust, normally within 1 - 3 days after the injection. IgG is the first dominant antibody isotype, followed by IgM. Result refer to COVID-19 may be elevated production of ROS rely on inhibition of ACE2 and impaired antioxidation enzymic, while vaccination increase from activity of antioxidation enzymic.

This phenomenon is called the secondary response. These results agreement with other study **(Siegrist, 2018) , (Pfizer Medical Information, 2020) , (Göker *et al.*, 2022)** .

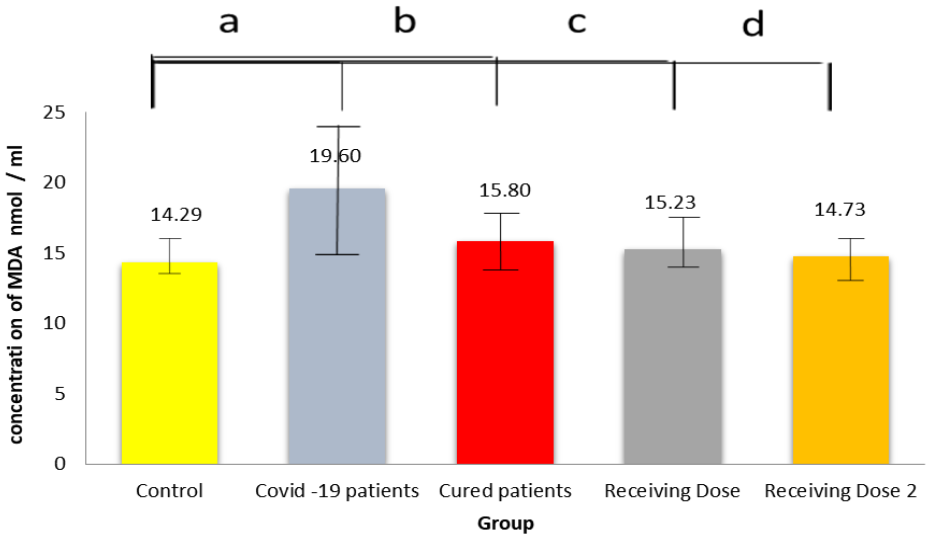


Figure (3-2) : Comparison of Human Malondialdehyde parameter mean between all study groups.

In Table **(3-7)** shows in group Patients COVID-19 male(16.89±1.56), female(20.62±1.11) significant when (P.value< 0.05),in Cured group male (16.08±3.49) , female(15.44±3.02) not significant when (P.value>0.05),in group receiving dose1 male (14.83±1.93), female(15.63±2.29) not significant when (P.value>0.05), in group receiving dose2 male (14.51±2.20) , female(15.17±0.70) significant

when(P.value=0.05), in healthy group male (14.09±1.02), female(12.09±1.41) significant when (P.value< 0.05).

The comparison of MAD and sex to male and female mean between groups. when the rang of age constant between (20- 45). This study show in cured Patients COVID-19 and healthy groups the mean of MDA level in male more than mean MDA female .The steady state concentrations of MDA are independent of age in men. In contrast, in women the concentrations of MDA depend on age in a complex fashion. In our opinion the age-dependency of the levels of biomarkers in women (only) is due to menopause. Menopause is associated with substantial biochemical alterations, including a significant decline in plasma concentrations of sex hormones, and an increase in the concentrations of gonadotropinsns and other hormones**(Honour, 2018)** .

Estrogen has antioxidant effects at high concentrations by inhibiting DNA oxidation .The impact of estrogen on human antioxidative capacity is clear that estrogens upregulate mitochondrial antioxidant defense. (MDA concentration of women increases at the age of around 50 years. Notably, the average MDA concentration in women aged 50-75 years remains significantly lower than that observed in men of the same age , while in groups (Receiving Dose1, Receiving Dose2 and Patients COVID-19) the level of MDA in female more than male because the response immunity in Adult female produce higher levels of T helper 1 (T_H1)-type cytokines than males., Regardless of age, females tend to show greater antibody responses than males, higher basal immunoglobulin levels and higher B cell numbers. Global analysis of B cell gene-expression signatures reveal that the majority of genes differentially expressed between the sexes are significantly up

regulated in B cells from females compared with males. These results agreement with other studies **(Klein *et al* , 2016), (Pinchuk *et al.*, 2019),** .

Antioxidant enzyme activity levels, NADPH-oxidase level and angiotensin II may also play an important role. It is very likely that multiple mechanisms are responsible for the sex differences. role sex plays cardiovascular diseases . effects can be observed in COVID-19 mRNA vaccination as well. The cardiac involvement cases have been detected among individuals roughly between 12 and 39 years of age. Seventy-nine percent were in males, with the majority in individuals <30 years of age with a median age of 24-19, 67% of cases were after the second dose. Possible mechanism for mRNA vaccine-induced myocarditis is autoantibody generation lead to increase oxidative stress. These results agreement with other studies**(Kander, *et al*, 2017), (Chang *et al.*, 2021)** .

Another mechanism can be the trigger effect of the preexisting deregulated pathways in certain individuals with predisposition,resulting in a polyclonal B-cell expansion, immune complex formation **(Dursun *et al.*, 2022) .**

Table (3-7) Comparison of MDA and sex to male and female mean between groups .

MDA and SEX		N	Mean± SD	P. Value
Cured	**Male**	11	16.08±3.49	0.198
	Female	9	15.44±3.02	
Dose 1	**Male**	10	14.83±1.93	0.338
	Female	10	15.63±2.29	
Dose 2	**Male**	13	14.51±2.20	0.056
	Female	7	15.17±0.70	
Patients	**Male**	6	16.89±1.56	0.029
	Female	14	20.62±1.11	
Healthy	**Male**	9	14.09±1.02	0.018
	Female	21	12.09±1.41	
Total		110	23.25±11.48	

3.4 Measurement of levels Human Immunoglobulin M and G

Table (3-8) ; IgM level in all study

IgM level	No.	Mean	P. Value of F-Test
Cured patients	20	2.82±0.43	0.540 S
Receiving Dose1	20	3.28±0.72	
Receiving Dose 2	20	2.82±0.28	
Covid -19 patients	20	3.35±0.28	
Control	30	2.33±0.23	
Total	110	3.25±0.52	

Table (3- 9); IgG level in all study

IgG level	No.	Mean ± S.D	P. Value of F-Test
Cured patients	20	47.28±7.28	4.95
Receiving Dose	20	42.29 ±4.29	
Receiving Dose 2	20	42.05 ±6.24	
Covid -19 patients	20	46.94±9.94	
Control	30	40.86±5.54	
Total	110	43.93±6.70	

This study compared Human Immunoglobulin M (Igm)in Table **(3-8)** in all group not significant when P.value >0.05 ,and G (IgG) Test in Table **(3-9)** in all group not significant when P.value >0.05.This study compared Human Immunoglobulin M (Igm)in Table (3-8) and Figure (3-3)shows in group Covid -19 patients(3.35±0.28)the average increase , in group Cured patients(2.82±0.43) the average increase ,in group Receiving Dose1(3.28±0.72) the average increase , in group Receiving Dose2(2.82±0.28) the average increase compared with Control group (2.33±0.23).

And G (IgG) Test in Table (3-9) and Figure(3-4) shows in group Covid -19 patients(46.94±9.94) the average increase , in group Cured patients(47.28±7.28) the average increase , in group Receiving Dose1(42.29 ±4.29) the average increase , in group Receiving Dose2(42.05 ±6.24) the average increase compared with Control group (40.86±5.54).

In group of Covid -19 patients corona virus can provide insight into the antibody responses that occur during SARS-CoV-2 infection. The spike subunit of SARS CoV-2 binds the human angiotensin-converting enzyme 2

(ACE2) receptor to infect and enter host cells. Viral cell entry additionally requires priming of the spike protein by cellular serine proteases such as TMPRSS. ACE2 is expressed along the entire human respiratory system and in brain endothelium and vascular smooth muscle cells. adaptive immune response may be initiated, lymphocytic cells called B-cells, which characteristically mature in the bone marrow. These results are consistent with other studies **(Kirtipal *et al.*, 2022)**.

During a primary innate immune response, naïve B-cells will recognize foreign antigens in the body. the secretion of antibodies by plasma cells into the extracellular environment may contribute to immunity All antibody-mediated immune responses are dependent on the ability of an antibody to bind specific antigens to recognize a foreign pathogen. Antibodies,. IgM antibodies are produced early in the adaptive immune response and are great at activation of innate immune responses . From study, it has been demonstrated that after 2 weeks post-disease onset the average sero conversion rate is between 90-100% for IgM-IgG antibodies produced against the SARS-CoV-2 S and N proteins. These results are consistent with other studies **(Teslow, 2021) .**

All data here show that IgM was generated in COVID-19 patients in 1 week after symptom onset, then reached its peak level in 2–3 weeks, after which the level decreased. Mean while, IgG levels increased quickly beginning a little later compared with IgM and were maintained at a high level for 2 months. Therefore,

The detectable levels of IgM and IgG antibodies. In study show the detection of IgM antibody indicates a recent exposure to SARS-CoV-2 and the detection of IgG antibody in the absence of detectable IgM antibody indicates prior virus exposure. The positive rates of IgM and/or IgG

detection were not significantly different among the mild, severe and critical groups. However, quantitative analyses of antibody levels over the disease course revealed that SARS-CoV-2-specific IgM levels were higher and neutralising IgG levels were lower in patients in the critical group, as compared with the other groups, which might be because of high disease activity and/or a compromised immune response in these patients**(Cheng *et al.*, 2021)**.

In response to SARS-CoV-2 infection, humans produce specific antibodies, CD4+ Tcells, which activate high-affinity antibodies produced by B cells, and CD8+ T cells, which destroy infected cells]. SARS-CoV-2-specific antibodies are directed against the spike protein (S) and nucleocapsid (N). Special roles are played by neutralizing antibodies against the S1 subunit on the receptor-binding domain (RBD) that binds to angiotensin-converting enzyme 2 (ACE2) sites, thereby facilitating endocytosis, viral entry into host cells. After infection, antibodies can be detected in patients after 3 days when symptoms occur, and sero conversion in most of them appears within 7–14 days. In the acute phase of the disease, IgM antibodies develop and peak at 14 to 35 days and then begin to decline over the next 21 to 35 days. IgG antibodies peak at around 21 to 49 days after infection and, together with neutralizing antibodies, may persist for up to four months**(Tretyn *et al.*, 2021)**.

The current study show the Cured patients(IgM) and (IgG) show the mean of IgM low then patients infected COVID-19 and the mean of IgG is increase than patients infected COVID-19 becouse the IgM antibodies are produced by host immune cells during the early stages of a viral infection. IgG is often the most abundant antibody in the blood and plays a more prominent role in the later stages of infection and in establishing long-term

immune memory . In study suggested The IgM antibody against SARS-CoV-2 of the recovered subjects was all positive during 5–7 weeks, while during 8–11 weeks, 16.7% of the patients were negative for the Igm. And the number of negative samples for IgM increased gradually during the followed weeks . the IgG titers did not decline significantly over time in either mild or severe patients .

These data suggested the IgG antibody against SARS-CoV-2 could be stable till 34–42 weeks in the recovered patients. In study reported that 100% of cases had detectable levels of IgA, IgM, and IgG on day 32 after onset of symptoms**(Hou *et al.*, 2020)**. Their findings also revealed IgM and IgG levels to be significantly higher in severe COVID-19 cases than in patients with mild or moderate disease , suggesting that serological tests require high sensitivity to detect lower levels of antibodies in mild cases. Studies on the persistence of antibodies in blood suggest that high levels of IgG are detectable for at least 49 days after the onset of symptoms, while IgM levels declined rapidly on day 35 post infection .**(Ghaffari, *et al* , 2020).**

In study show the Cured patients whom happened “cytokine storm,” the level of antibodies (IGg) not great level to explaine this depended on other study the pattern differed. Instead of high levels of IgG antibodies, patients showed increased levels of another type of antibody, called immunoglobulin A (IgA). These IgA antibodies apparently were interacting with immune cells called neutrophils, which in turn led to the release of cytokines. That’s notable because

The release of too many cytokines can cause what’s known as a “cytokine storm,” a severe symptom of COVID-19 that’s associated with

respiratory distress syndrome, multiple organ failure, and other life-threatening co complications, developed IgA (5–7 days post symptoms), with an average of IgA level much higher than IgG two and three weeks later**(Anka *et al.,* 2021)**. Importantly, IgA anti-SARS-CoV-2 were also detected in saliva and could remain for three months or longer after symptoms .High IgG and IgA levels were correlated with COVID-19 severity while in the normal infection they saw high levels of immunoglobulin G (IgG) antibodies, which normally help to control an acute infection.

This high levels of IgG may activate scavenging immune cells, called macrophages, to drive inflammation and more severe illness. In study suggested There was no age difference between females and males in our cohort. females had lower anti-RBD and -S IgG titers than males. These results are consistent with other studies**(Saad, *et al* 2021), (Gazumyan *et al.,* 2020), (Wei *et al.,* 2021)** .

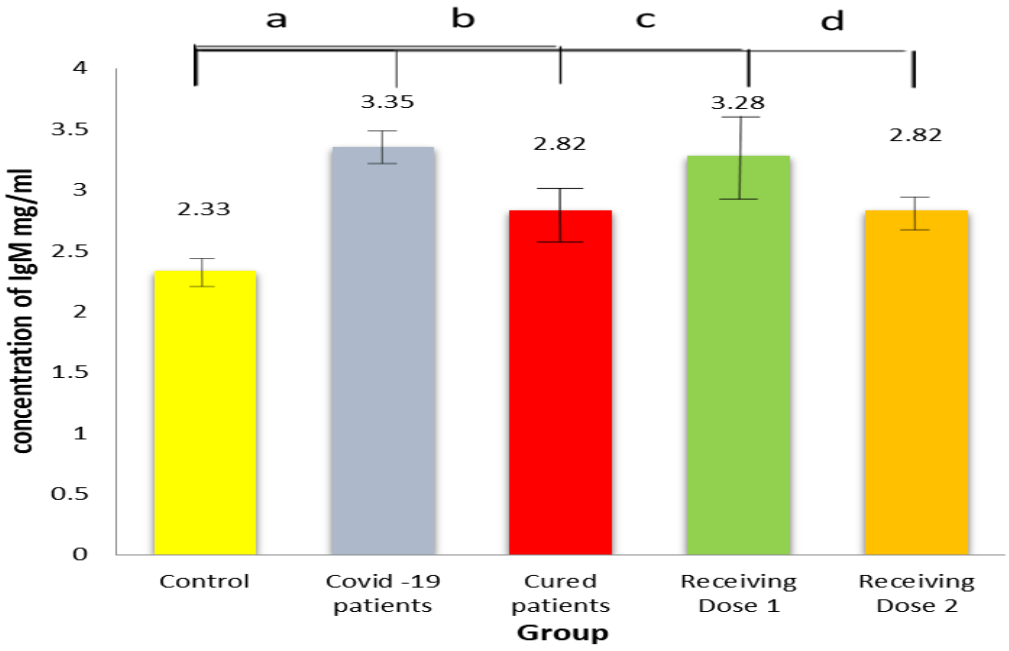
In group receiving dose1when compared with control group , (IgG) and in group receiving dose2 (IgM) and show (IgG) that show the meam of IgM in group Receiving Dose1 is high level than group receiving dose2 becouse the Receiving 1st mRNA vaccine dose the response immunity produce in the first step the IgM in first week then produce

IgG increased further, peaking approximately 7 days later, and remaining elevated

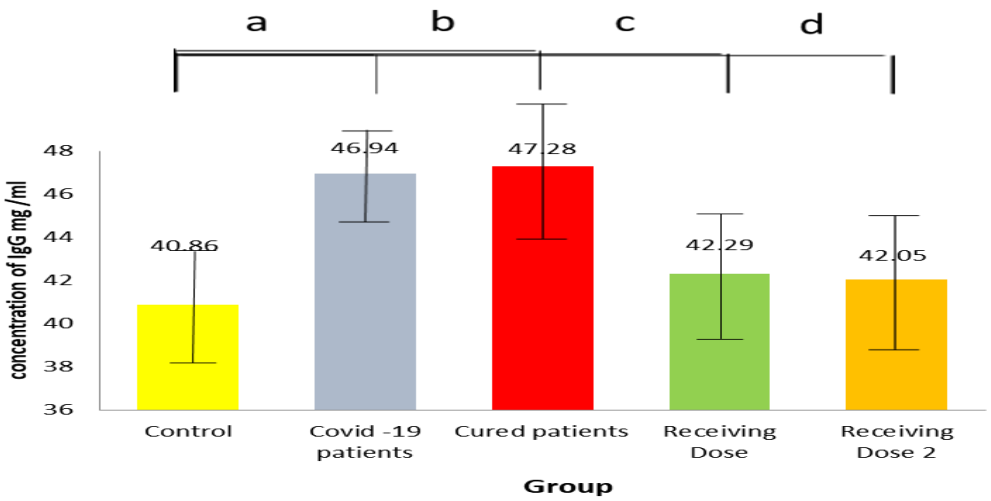
to one year because this we observe low level to IgM in group receiving dose2(is that upon administration of vaccine antigen to a naïve individual, antibodies to the antigen become detectable at about 10-14 days; IgM comes up first, followed by IgG. The scenario is called the primary response). and the mean to IgG in group Receiving Dose1 stay high then group Receiving

Dose2 becouse in this phase convert to B cell memory become established along with the specific IgG. Upon re-exposed to the same antigen in the same host, production of the antibodies to the antigen is very rapid and robust, normally within 1 - 3 days after the injection. IgG is the first dominant antibody isotype, followed by IgM. This phenomenon is called the secondary response .**(Pang *et al.*, 2021).**

In study show serum levels of SARS-CoV-2 spike-specific IgG rose exponentially and reached a plateau approximately 18–21 days. After the 2nd vaccine dose, SARS-CoV-2 spike-specific serum IgG increased further, peaking approximately 7 days later, and remaining elevated (58% of peak values) during the additional >100 day follow-up period**(Wisnewski, *et al*, 2021)** .



Figure(3-3): Comparison of IgM means among all study groups.



Figure(3-4): Comparison of IgG means among all study group.

In Table (3-10) observe comparsion of IgG and sex to male and female mean between groups .when the rang of age constant between (20-45). In group covid patients male(3.44±0.11), Female(3.32±0.33) low significant when (P.value =0.05),in group Cured male(2.90±0.49), Female(2.72±0.34)not significant when (P.value>0.05), in group Dose 1 male(3.01±0.26) , Female(3.55±0.94) not significant when (P.value>0.05), in group Dose 2 male(2.81±0.25), Female(2.86±0.35) not significant when (P.value>0.05), when compare Healthy group male(2.53±0.21), Female(2.67±0.24).

In this study show the data in Table(3-11)of male to IGg and femal , In group covid patients male(48.23±15.06), Female**(**46.46±8.69) low significant when (P.Value=0.05),in group Cured male(47.11±8.97), Female**(**47.50±5.00)not significant when(P.Value>0.05), in group Dose 1 male (42.93±3.52), Female**(**41.66±5.11) not significant when(P.Value>0.05), in group Dose 2 male (42.29±4.84), Female**(**41.59±9.12) not significant when(P.Value>0.05).

Results obtained from patients mahaweel hospital infected with SARS-CoV-2 revealed that there are no significant differences in immune responses between men and females.In study in Erbil,Iraq that show was no significant differences between men and females infected with COVID-19 , and this vital outcome clarified that a different therapeutic approach for male and female is not necessary. Furthermore, SARS-CoV- 2 IgG and IgM antibody concentrations in our population are pretty similar in both males and females**(Elia *et al.*, 2020)** .

In this study we observe the Table(3-10): comparsion of IgM and sex to male and female compersition with mean in group vaccine influenza vaccine induced higher levels of IgM in female compared to male while in Table(3-10) : comparsion of IgG and sex to male and female mean tin group vaccine influenza vaccine induced small low of IgG in female compared to male. the females typically develop higher antibody responses and experience more adverse events following vaccination than males. This enhanced immune reactogenicity among females is thought to render females more resistant to infectious diseases, but conversely also contribute to higher incidence of autoimmunity among women. Dissection of mechanisms which underlie sex differences in vaccine-induced immunity has implicated hormonal, genetic, and microbiota differences across males and females. women are more resistant to bacterial and viral infections, linked to overall higher antibody levels as well as greater T cell activation**(Fischinger *et al.*, 2019)** .

However, as a consequence of this enhanced immune activation, women tend to experience more adverse reactions following vaccination and have a higher incidence of autoimmune disease and the men are more susceptible to infectious diseases due to the hormone-dependent expression

of cell receptors involved in viral entry. estrogen alters the expression of the CC chemokine receptors C-C motif chemokine receptor (CCR1) involved in HIV infection .Furthermore, high levels of testosterone have been associated with low neutralizing antibody titers against influenza in men**(Raza *et al.*, 2021)**.

Studies pointed to significantly elevated The measles-mumps-rubella vaccine-specific immunoglobulin G (IgG) titers among girls compared to boys 14 years after vaccination, another study showed that 2–4 weeks after vaccination (peak immunogenicity), boys had higher antibody responses, but this difference waned 10weeks post-vaccination. This indicates that differences between the sexes are already evident before puberty, suggesting other influences than pubertal sex hormones on immune tuning. In adults, as mentioned above, women experience more adverse reactions following immunization compared to men, vaccine often leads to strong adverse reactions such as local inflammation, fever, pain, headache, and fatigue due to enhanced inflammatory cytokine and chemokine secretion **(Sahebi *et al.*, 2022)**.

In a second study comparing, adult females develop higher magnitude immune responses, with respect to antibody levels, and experience more severe adverse events following immunization, due to enhanced immune activation, compared to their male counterparts, thereby experiencing better protection in contrast to men, a mouse study with whole-virus trivalent inactivated influenza vaccine induced higher levels of IgM in female compared to male **(Fischinger *et al.*, 2019).**

Beyond the direct influence of sex hormones, gene expression off of the X and Y chromosomes has also been shown to drive immunologic

differences in vaccine-induced immunity across the sexes**(Youness, *et al*, 2021)**.

The X chromosome expresses ten times more genes than the Y chromosome, and many genes on the X chromosome are known to influence immunity, many of the genes involved in modulating pathogen- and vaccine-specific immunity are located on the X chromosome or can be modulated in a sex-dependent manner due to estrogen response elements (EREs) in their promoters. Finally, another factor that has been linked to altered vaccine and natural-infection humoral profiles is the microbiome**(Flanagan KL, et ,al 2017).**

The immune system occupies a critical position between aging and disease . Thus, aging has been associated with (a) decreased total lymphocyte count; (b)decreased T-cell subsets [CD3, CD4, CD8]; a decrease in both the number and percentage of T-cell subsets in elderly humans**(Knight, 2000)**.

Table (3-10) : comparsion of IgM and sex to male and female mean between groups.

IgM and sex		N	Mean± SD	P. Value
Cured	**Male**	11	2.90±0.49	0.209
	Female	9	2.72±0.34	
Dose 1	**Male**	10	3.01±0.26	0.198
	Female	10	3.55±0.94	
Dose 2	**Male**	13	2.81±0.25	0.342
	Female	7	2.86±0.35	
Patients	**Male**	6	3.44±0.11	0.059
	Female	14	3.32±0.33	
Healthy	**Male**	9	2.53±0.21	0.038
	Female	21	2.67±0.24	
Total		110	23.25±11.48	

Table (3-11): comparsion of IgG and SEX to male and female mean between groups.

IgG and SEX	N		Mean±	P.Value
Cured	**Male**	11	47.11±8.97	0.189
	Female	9	47.50±5.00	
Dose 1	**Male**	10	42.93±3.52	0.108
	Female	10	41.66±5.11	
Dose 2	**Male**	13	42.29±4.84	0.242
	Female	7	41.59±9.12	
Patients	**Male**	6	48.23±15.06	0.059
	Female	14	46.46±8.69	
Healthy	**Male**	9	40.23±6.13	0.338
	Female	21	40.52±5.41	
Total		110	43.93±6.70	

3. 5 Measurement of levels Human Interleukin 13

Table(3-12): IL-13 level in all study

IL-13 level	No.	Mean	P.Value of F-Test
Cured patients	20	21.81±8.54	2.230
Receiving Dose	20	29.61±15.80	
Receiving Dose 2	20	102.98±26.64	
Covid -19 patients	20	19.58±8.20	
Control	30	19.39±3.10	
Total	110	35.96±33.58	

This study compared Human Interleukin -13 (IL-13) Test means among the study groups (control, patients with covid, cured patients by covid , receiving dose1 fizer vaccine receiving dose 2 fizer vaccine) .In Table (3-12) and figure (3-5) When compared Human Interleukin 13 means among five study groups showed not significant difference when (P.value>0.05).In group Covid -19 patients(19.58±8.20) increase, In group Cured patients(21.81±8.54) increase, In group Receiving Dose1(29.61±15.80) increase, In group Receiving Dose 2(102.98±26.64) high increase , compared with Control group (19.39±3.10).

In current study the result in group Covid -19 patients show Low level mean of IL-13 compar with group (cured patients , receiving dose 1, receiving dose 2) because the patients (‘‘mild’’ is a COVID-19) with a SARS-CoV-2 infection, that temporal delay in innate immune responses is enough to result in asymptomatic infection because the T cell and antibody responses occur relatively quickly and control the infection. The presence of T cells and antibodies is associated with successful resolution of average

cases of COVID-19, the virus is particularly effective at avoiding or delaying triggering intracellular innate immune responses associated with type I and type III IFNs in humans the adaptive immune responses are not primed until the innate immune alarms occur duto this the Adaptive immune responses are slow due to the intrinsic requirement of selecting and expanding virus-specific cells**(Ramanathan *et al.*, 2020)** from the large pools of naive B cells and T cells specific for different molecular structures and sequences the Adaptive immune responses take time to generate sufficient cells to control a viral infection, 6–10 days after priming because this the level of IL-13 low comper another group while in severe COVID-19(requiring hospitalization) the long time enough to response the Adaptive immune and the level of IL-13 will increase compare (‘‘mild’’ a SARS-CoV-2 infection) **(Or Caspi, *et al* , 2020)** .

In response to stress-generating internal processes (disease infection),host cells secrete cytokines with a highly important role in cell metabolism reprogramming as a defensive response. The key point in SARS-CoV-2 infection could be the depletion of antiviral defenses related to innate immune response as well as an elevated production of inflammatory cytokines. observed a directly proportional association between IL-13 levels and the viral load of SARS-CoV-2**(Jeyanathan *et al.*, 2020)** .

The type 2 cytokine, IL-13, is associated with severe COVID-19.the IL-13 impacts pathology via upregulation of hyaluronan synthesis , excessive build-up of hyaluronan, which binds a large amount of water, could contribute to severely impaired oxygen uptake, which is a significant component of disease in hospitalized patients. In SARS-CoV-2 infected mice, IL-13 neutralization reduced death and disease severity without

affecting viral load, demonstrating an immunopathogenic role for this cytokin**e(Donlan *et al.*, 2021)**.

In study suggested the severe SARS-CoV-2 seems to promote lung damage through different mechanisms, such as the scarce participation Th1/Th17 response and the higher participation of the Th2. That mean patients in the ICU showed low TCD4+ and TCD8+ lymphocyte scores serological levels. Besides, these patients present high levels of PD-1 (programmed cell death protein 1) that appear to functionally deplete T cells, indicating that the immune system would be tilting abnormally towards Th2 response. IL-13 are closely linked to the remodeling tissue process, it is suggested that asthmatic patients have a lower risk of developing the severe form of COVID-19 because they have increased levels of interleukins Th2 **(Vaz de Paula *et al.*, 2020).**

In cured group increase the level of IL13 becouse the long time from infection this long time lead to complet the adepative immunity and proudused the interluken 13 .The IL13 the potent immunoregulatory role by including promoting B- cell proliferation. IL-13 is produced for much longer periods than IL-4 following T-cell activation suggesting an important role for IL-13 in the regulation of enhanced IgE synthesis in allergic individuals. People who have recovered from milder cases of COVID-19 seem to have TH2 cell responses have been associated with enhancement of lung disease following infection in hosts parenterally vaccinated with inactivated SARS-CoV viral vaccines .These results are consistent with other studies **(Lin, *et al* , 2018), (Jeyanathan *et al.*, 2020)**

In group receiving dose1 ,and receiving dose 2 show the mean increase compared with group Cured patients and Covid -19 patients because the mRNA vaccine tend to activation tended to have a Th2-biased

response, as indicated by the production of IL-4, IL-5 and IL-13. vaccines against human corona viruses have faced challenges, with several preclinical studies demonstrating disease enhancement in vaccinated animals after viral challenge.

This was characterized by eosinophilic infiltrates resulting in immunopathology, after the induction of a T helper cell type 2 (Th2)-biased response. challenge of mice given any of the vaccines led to occurrence of Th2-type immunopathology suggesting hypersensitivity to SARS-CoV components was induced. In study show vaccinated controls showed an elevated level of Th2-type cytokines compared to the healthy control group, the patient with myopericarditis after COVID-19 vaccination showed a slightly increased level of Th17-type cytokines, These findings indicate that Th2- or Th17-dependent immune activation unlikely contributed to myopericarditis after COVID-19 vaccination**(Tseng *et al.*, 2012), (Ewer *et al.*, 2021),(Won *et al.*, 2022).**

In study refers the SARS-CoV-2 adjuvants (nanopartical ,poly ethelen glygol)could lead to immune responsesTH2 **(Atalis *et al.*, 2022)** . In a study by Corbett et al., the authors reported that mice immunized with mRNA-1273 had predominant Th1 response (especially at the highest mRNA vaccine dose), measured by the production of Th1 cytokines IFN, TNF, and IL-2 by total CD4 T cells upon in vitro restimulation with SARS-CoV-2 peptide pools. By contrast, mice immunized with the prefusion stabilized recombinant S-2P protein in alum tended to have a Th2-biased response, as indicated by the production of IL-4, IL-5 and IL-13**(Bettini *et al*, 2021).**

Overall, SARS-CoV-1 based vaccines are protective, but some of them, including whole virus, virus like DNA-based vaccines can prompt a Th2 response after vaccination with eosinophilic infiltrate in the lungs,

suggesting that these vaccines generate hypersensitivity reactions. These immunopathologies have been associated with protein N from SARS-CoV-2

Vaccine-enhanced disease was also observed in early development of inactivated vaccines against respiratory syncytial virus, wherein pathology was associated predominantly a Th2-biased response**(Ewer *et al.*, 2021).**

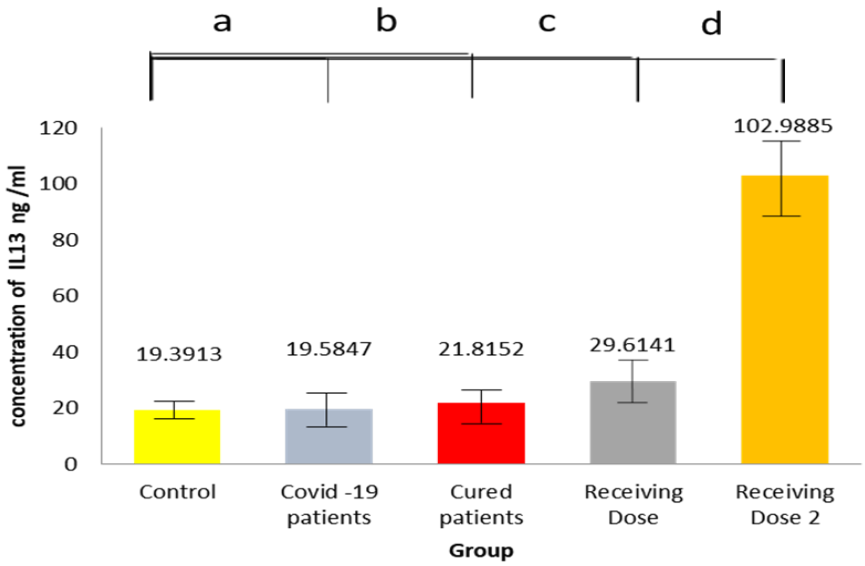


Fig (3-5) : Comparison of Human Interleukin 13 (IL-13) means among all study groups.

In Table (3-13): comparsion of Human Interleukin 13 (IL13) parameter mean between groups .we observe comparsion o f (IL13) and sex to male and female mean between groups.when the rang of age constant between (20- 45).in group Patients covid 19 male(25.48±15.94), female(17.37±1.78)significant when the (P . Value<0.05),in group Cured male(26.18±9.32), female(16.19±1.20) significant when the (P . Value<0.05), in group Dose 1 male(25.67±16.22), female(33.55±15.38), not significant when the (P . Value>0.05), in group Dose 2 male(104.82±18.90) ,

female(99.31±40.68)low significant when the (P . Value=0.05) , when the group of Healthy male(19.95±4.18), female(19.15±2.60).

In group covid 19 patient the mean of IL-13 to male more than femal because in mild infection the Females tend to have stronger Th1-mediated immune responses and are more prone to develop autoimmune diseasess including multiple sclerosis (MS), rheumatoid arthritis, systemic lupus erythematosus, and thyroiditis. Than the male response to Th2 .IL-13 it has inhibit the production of inflammatory cytokines .

Its role in experimental autoimmune encephalomyelitis (EAE) has been of an anti inflammatory cytokine and has been shown to be capable of suppressing EAE in Lewis male rats , the gender susceptibility is the possibility that IL-13 and estrogen (E2) have opposite effects on macrophages with IL-13 up-regulating and E2 down-regulating the expression Due to the pivotal role of macrophages in the effector phase of EAE **(Sinha *et al.*, 2008)**

In group cured patient covid 19 the level of IL13 to male more than femal because the long time after infection give time to the adaptive response to make the Thelper 2 and the response of male to Th2 . In study suggested Th1 and Th2 are an important pair of regulatory cells. However, they are mutually inhibiting cells because the interferon IFN-γ secreted by Th1 cells can inhibit the differentiation and function of Th2 cells, whereas interleukin-4 (IL- 4) from Th2 cells can also inhibit the differentiation and function of Th1 cells. .because the immunity response in femal Th1, Th1 cells can inhibit the differentiation and function of Th2 cells this explain the level of IL13 to male more than femal **(MaQ, *et al*, 2021)** .

In study demonstrate a gender-biased expulsion, which occurs in a delayed manner at 26 days and is characterised by a dramatic increase in IL-13 production and concurrent decrease in the pro-inflammatory cytokines TNF-α and IL-6 in the presence of high levels of IFN-γ. The delayed immune response in resistant female IL-4KO animals was accounted for by a late increase in IL-13 derived from both CD4+ T cells while male WT mice also demonstrated increased IL-13+ NK cell numbers in the draining lymph node upon infection**(Hepworth *et al* , 2009)**.

In group Received dose 1 the level mean of IL13 to male low than female the female have level of antioxidants increase than the level in male because the presence of estrogen could explain the gender differences in various in antioxidant or mechanisms are involved. Estrogen may also act as an antioxidant, in wamen special in pre-menopausal women in this study we take the age (20- 45) **(Deflora Silvio, *et al* , 2021)** .

Successful innate immunity activation results which provides all the requisites for the accelerated development of adaptive immunity and the enter of vaccine different of real virus .all this give the time to response immunity toward Th2 . in study explained Women are known to inherently mount a stronger innate and adaptive immune response to viral infection. Faster viral clearance and a lower viral load have also been reported in women. This enhanced immune response makes women more vulnerable to inflammatory and autoimmune diseases**(Primorac *et al.*, 2022)** ,**(Raza *et al.*, 2021).**

The endosomal Toll-like receptor 7 (TLR7) is a significant factor involved in the recognition of viral antigens and mounting an effective antiviral immune response (Berghofer B, et al (2006)).Increased expression of the TLR-7 gene, which is located on the X chromosome, has been

reported in women due to the ability of the TLR-7 gene to escape X-chromosome inactivation. Higher TLR-7-driven IFN-α production by plasmacytoid dendritic cells (pDCs) in females as compared to males

Increased TLR-7 expression may lead to increased cytokine production and faster viral clearance in women. The pandemic has led to the identification of several polymorphisms in men**, (Meier A, et al (2009)) , (Souyris M, et al (2018)) .** Other genes may also be responsible for the sex-based disparity in immune response to SARS-CoV-2. These may include X-linked genes, including the ones coding for Interleukins, FOXP3, XIST, and TLR-8, which may be similarly upregulated in females due to biallelic expression, as well as Y-linked genes (SRY and SOX9), which would have greater expression in males, and thus may also possibly contribute to lower viral loads and lesser inflammation in females as compared to males.. ACE-2 The angiotensin-converting enzyme 2 (ACE-2) receptor has a major role in the disease pathogenesis of COVID-19, acting as the receptor for viral entry of SARSCoV- 2 into its target cells, primarily alveolar type 2 pneumocytes **(Hoffmann M, *et al* (2020))** However, the ACE-2 receptor also has an important role in organ protection, as it inactivates the active forms, Angiotensin I and II by conversion into Angiotensin 1–9, and 1–7 respectively, and thus reduces the chances of development of pulmonary oedema during COVID-19 **(Zhang H ,*et al* (2020)).**

This may explain the apparent paradoxical protective effect that increased ACE-2 expression may confer against severe COVID-19 clinical outcomes in women, despite acting as the very vessel for its pathogen. The position of the ACE-2 receptor gene on the X-chromosome, Xp22.2, is such that it escapes X-inactivation in women.Therefore, this leads to increased

ACE-2 receptor expression in female type 2 pneumocytes, plausibly allowing the ACE-2 receptors unbound by SARS-COV-2 Receptor binding domains, to catalytically cleave Angiotensin II and offer protection against pulmonary oedema. The absence of this biallelic expression in men may result in the lack of availability of sufficient free ACE-2 receptors to cleave Angiotensin II, and a resultant reduced protective effect**(Carrel L ,*et al* (2005))**..

In group Received dose2 the level mean of IL13 to male more than femal because long time frome Received dose1 (21 day) that in first of dose made or response the IL13 and second after response duto this level in male mor than femal. In study suggested that the number of doses may influence the Th1/Th2 balance, as the split virus vaccine initially elicited a mixed Th1/ Th2 response, whereas the second vaccine dose seemed to induce a Th2 dominant response both in the spleen and the lymph nodes**(Hauge *et al.*, 2007)**.

Table(3-13): comparsion IL-13 and SEX with all group study .

IL-13 and SEX		N	Mean± SD	P . Value
Cured	**Male**	11	26.18±9.32	0.002
	Female	9	16.19±1.20	
Dose 1	**Male**	10	25.67±16.22	0.09
	Female	10	33.55±15.38	
Dose 2	**Male**	13	104.82±18.90	0.058
	Female	7	99.31±40.68	
Patients	**Male**	6	25.48±15.94	0.032
	Female	14	17.37±1.78	
Healthy	**Male**	9	19.95±4.18	0.29
	Female	21	19.15±2.60	
Total		110	35.96±33.58	

3.6 Correlation Analysis

3.6.1 Correlation between TAC and age range levels among Covid -19 patients .

The result of figure**(3-6)** show that aging might reduce the TAC level , the adult age or old age revealed that low level of TAC , as well as low immune reactivity .

The figure **(3- 6)** show this result Oxidative stress theory (OST) is considered one of the famous theories that increase result progress in age , it is considered one of the contributors toward aging. Although ROS is known to damage cell machinery, new evidence suggests their role in signal transduction to regulate biological and physiological processes. **(Warraich, *et al,* 2020).** The well-known age-related increase in free radical formation and lipid peroxidation contributes, at least in part, to this phenomenon. The dysregulation of the immune response predisposes elderly persons to higher incidences of infectious, neoplastic, autoimmune, and inflammatory diseases **(Cunha *et al.,* 2020)** .

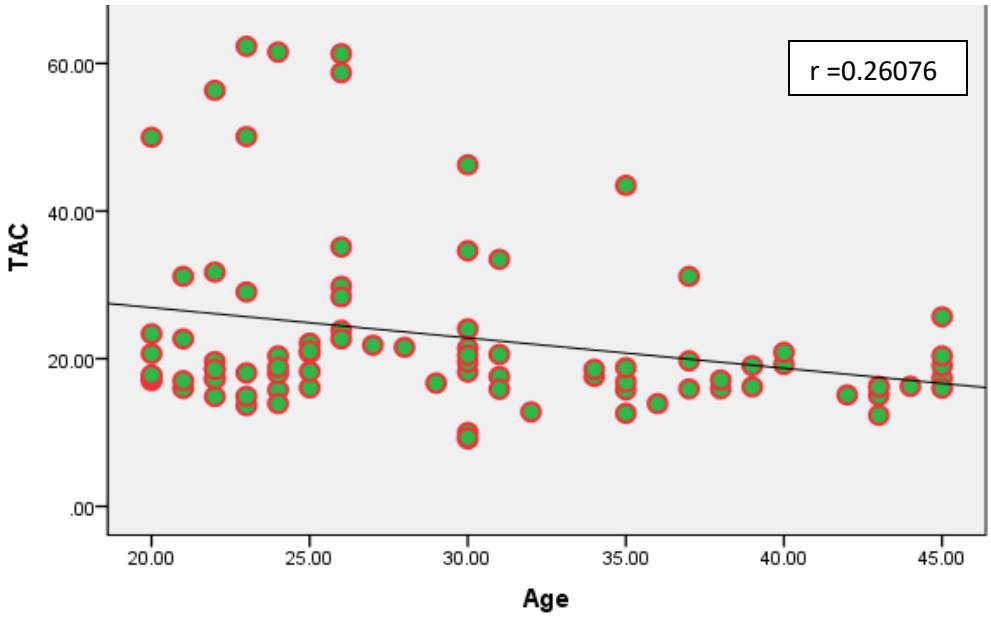


Fig (3 -6) Correlation between TAC and age range levels among Covid -19 patients .

3.6.2 Correlation between TAC level and IL-13 among Covi-19patients .

The result of figure **(3-7)** show that increase in TAC level might be associated with increase in IL-13 , and revealed a positive correlation between them . The TAC level are important supplement in which that aiding the immune activity at different types cellular or humeral . Increased in TAC might be associated with regulation of IL-13 production at different time of exposure to infection with Sars –Cov2 virus. In study **(Yarosz *et al*, 2018)**. Treatment with antioxidants causes these cells to produce IL-4 and shift toward an anti-inflammatory.

In study Vitamin D a fat-soluble vitamin, plays a vital role in both in immunomodulatory, antioxidant and antiviral responses VD also decreases theexpression levels of proinflammatory type 1 cytokines such as IL-12, IL-16, IL-8, TNF- a, IFN-g while increasing type 2 cytokines such as IL-4, IL-

5, balanced mitochondrial functions, prevents oxidative stress-related protein oxidation, lipid peroxidation and DNA damage **((Mrityunjaya *et al.*, 2020)** .

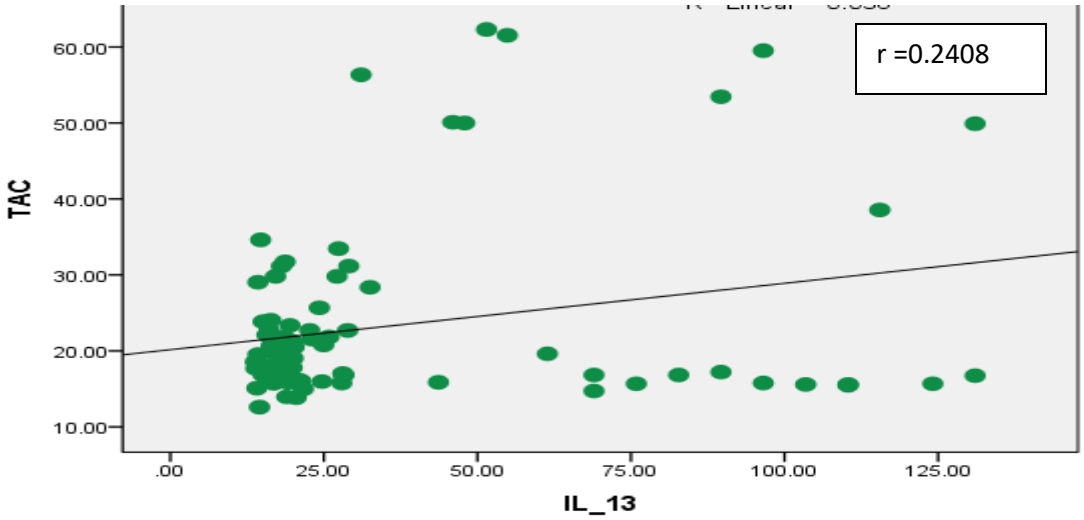


Fig (3-7) Correlation between TAC level and IL-13 among Covid -19 patients

3.6.3 Correlation between MDA and TAC levels among Covid -19 patients .

The result of figure(3 – 8) show that negative correlation between TAC and MDA , both of them are immune suplementation but TAC have more activity than MDA during the Sars-Cov 2 infection , as in figure**(3-8)** .During the process of lipid peroxidation, a wide range of pre-inflammatory products are produced which result in progression of the disease. One of these by-products is malondialdehyde (MDA),which is a common marker for oxidative stress. An increase in serum oxidative markers (MDA) paralleled by a decrease in the activity of antioxidants has been observed in patients (**(Zelber-Sagi *et al.*, 2020)**.

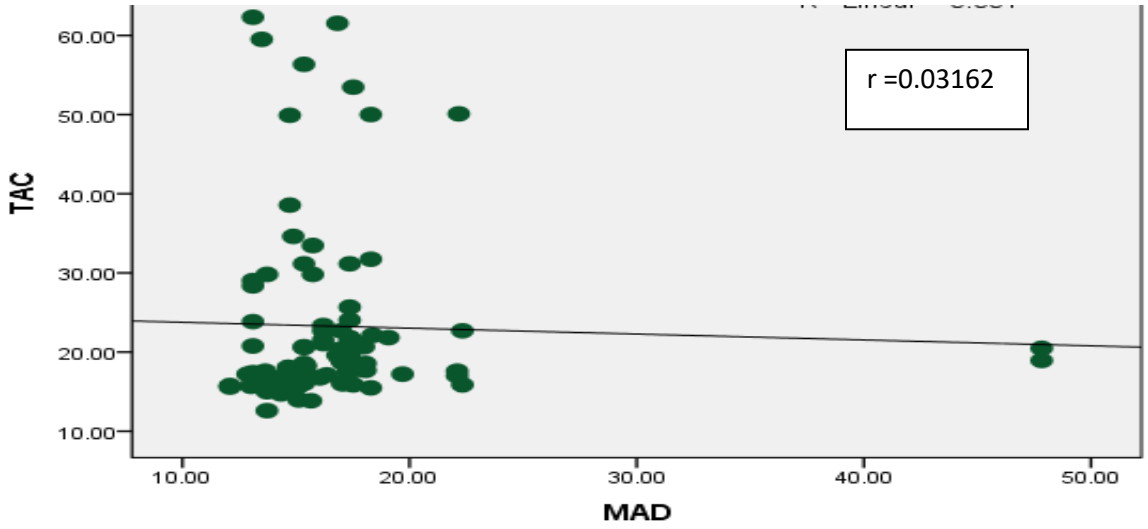


Figure (3-8) Correlation between MDA and TAC levels among Covid -19 patients .

3.6.4 Correlation between Ant-Sars-Cov2 –IgM and TAC level

The result of correlation between anti-Sars-Cov2 IgM and TAC among Covid -19 patients revealed that a direct or positive correlation, as in figure**(3- 9)** . This result might be show that , increased IgM level might be associated with increased in TAC The TAC activity might be regulate or induced the antibody produce at first few days after starting of infection.

Immune cells use ROS in order to keep up their functions and therefore need adequate levels of antioxidant defenses sequentially to avoid the harmful effect of an excessive production of ROS).

Immune cells contain high levels of antioxidant vitamins due to their high polyunsaturated fatty acids content and sensitive to external ROS, which are probably providing protection versus lipid peroxidation and immunosuppression, both of which are well known risks posed by high polyunsaturated fatty acids content **(Hajian, 2015). (Brambilla *et al.*, 2008)**.

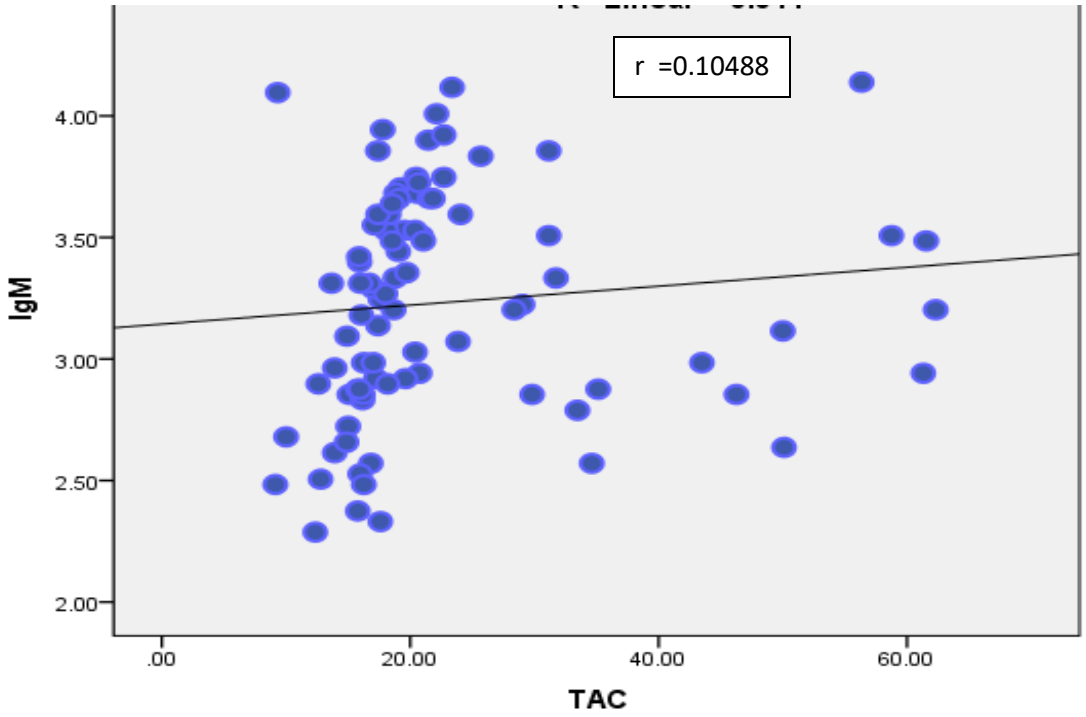


Figure (3-9) Correlation between Ant-Sars-Cov2 –IgM and TAC level

3.6.5 Correlation between Ant-Sars-Cov2 –IgG and TAC level of Covid -19 patients .

The result of correlation between anti-Sars-Cov2 IgG and TAC among Covid -19 patients revealed that a direct or positive correlation ,as in figure **(3- 10)** . This result might be show that , increased IgG level might be associated with increased in TAC .

The TAC activity might be regulate or induced the antibody production at time of starting infection. In study suggesting that intervention antioxidant drinks able to give the effect to the improvement of the subjects body immunity by improving the body oxidative stress level **(Siti Ika Fitrasyah, 2015)(Muhammad *et al.*, 2021) .**

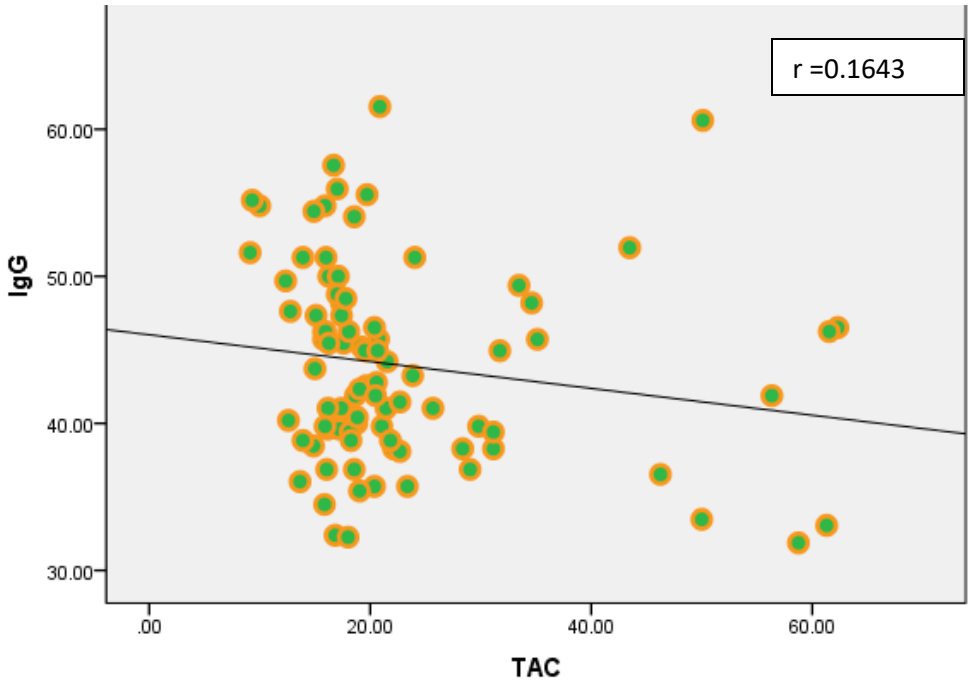


Figure (3- 10) Correlation between Ant-Sars-Cov2 –IgG and TAC level of Covid -19 patients .

3.6.6 Correlation between MDA and age range levels among Covid-19 patients .

The result of figure**(3-11)** show that increased of age might be reduce the MDA level , the adult age or old age revealed that low level of MDA , as well aslow immune reactivity in Covid -19 patients . In a SARS-CoV-2 infection, the virus is particularly effective at avoiding or delaying triggering intracellular innate immune responses associated with type I and type III IFNs in humans **(Or Caspi, *et al*, 2020).**

The figure (3-11) show this result because the progress in age progressive functional decline in the immune system of both sexes and low in metabolism in infection **(Klein *et al*, 2016).**

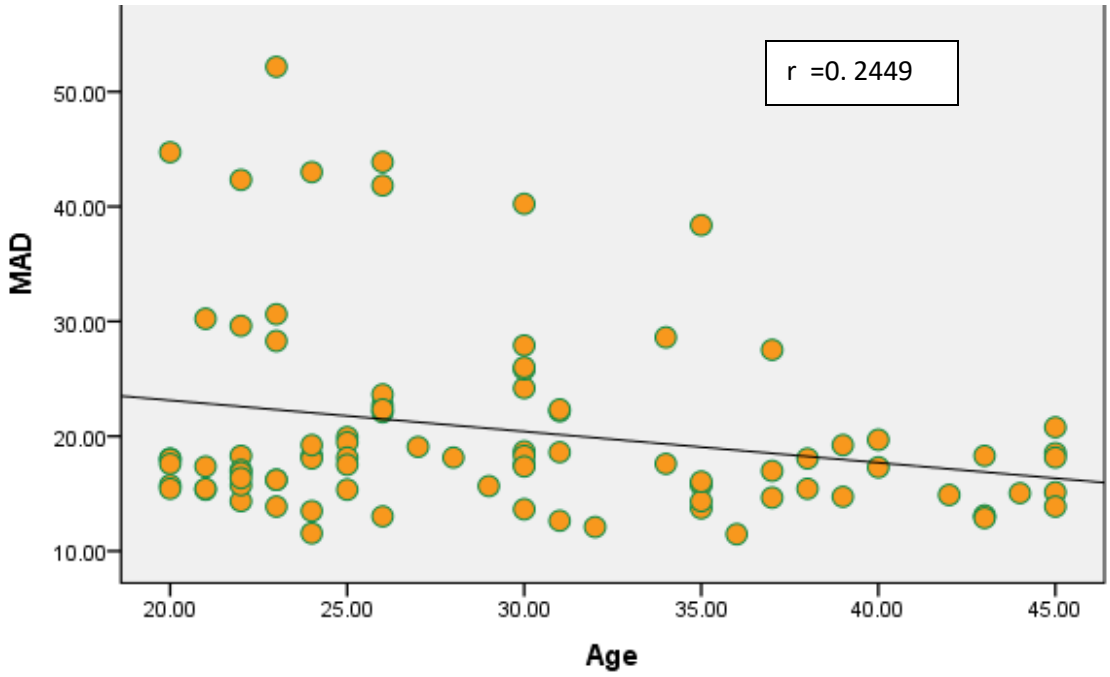


Figure (3 -11) Correlation between MDA and Age range levels among Covid -19 patients

3.6.7 Correlation between Ant-Sars-Cov2 –IgM and MDA level

The result of figure **(3 -12)** show there is a direct or positive correlation between anti-Sars-Cov2 IgM and MDA among Covid -19 patients, This result might show that increased IgM level might be associated with increased in MAD , as like as TAC , the MDA activity might be regulate or induced the IgM antibody produce at first few days after starting of infection.

Oxidant antioxidant balance is critical for immune cell function because it maintains cell membrane integrity and functionality, cellular proteins, and nucleic acids. Moreover, this balance is important in controlling signal transduction and gene expression. Immune cells are particularly sensitive to oxidative stress because of the high percent of

polyunsaturated fatty acids in their plasma membranes and a higher production of reactive oxygen species (ROS), which is part of their normal function . Moreover, membrane-related signaling and gene expression are critical in maintaining normal function of immune cells and their ability to defend against various foreign antigens**(Knight, 2000)**.

The increased production of disulfide-rich Ig might cause oxidative stress that could serve signaling roles in the differentiation and lifespan control of antibody-secreting cells. The early intracellular production of H2O2 facilitates B-cell proliferation and reveal a role for the pathway in the differentiation and function of IgM-secreting cells. Plasma cells acquire the ability to form and secrete IgM polymers **(Bertolotti *et al.*, 2016) ,(Suhail *et al.*, 2020).**

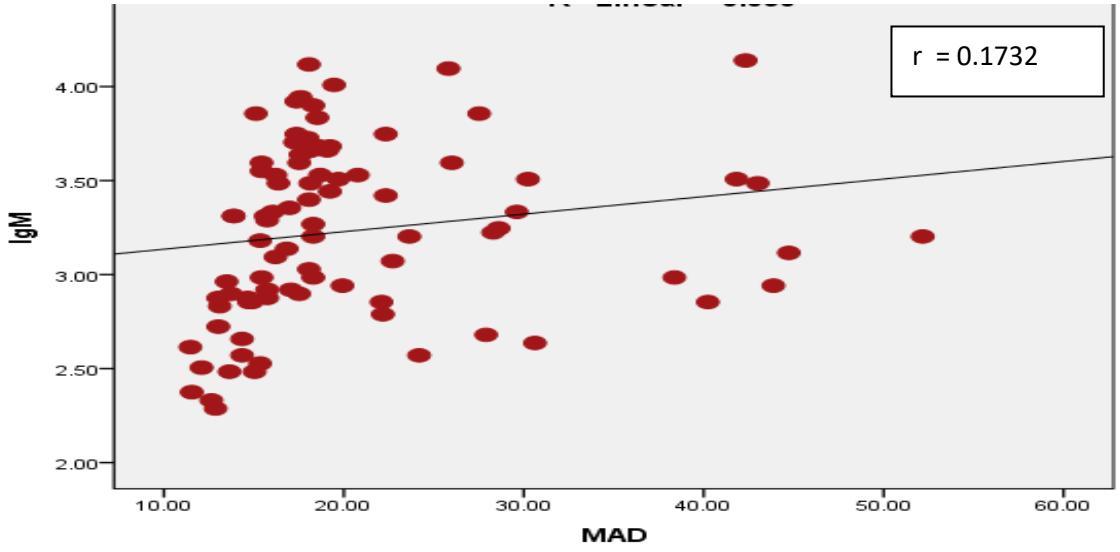


Figure (3 -12) Correlation between Ant-Sars-Cov2 –IgM and MAD level .

3.6.8 Correlation between Ant-Sars-Cov2 –IgG and MDA level of Covid -19 patients.

The result of figure **(3-13)** show that indirect or negative correlation between anti-Sars-Cov2 IgG and MDA among Covid -19 patients. This result might be show that , increased IgG level might be associated with decreased in MDA , because the IgG prolonged for long time after infection , the MDA activity might be regulate or induced the IgG antibody production at first few days after starting of infection and reduced in later time**(Papac-Milicevic, *et al*, 2016) (Marcotte *et al.*, 2022) .**

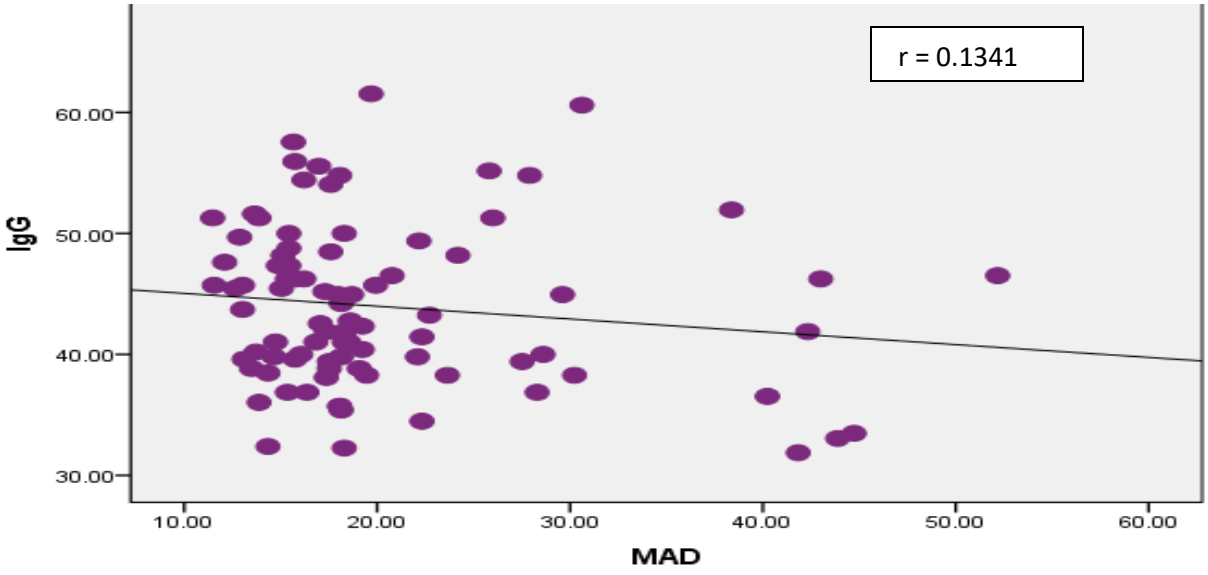


Figure (3 -13) Correlation between Ant-Sars-Cov2 –IgG and MDA level of Covid -19 patients.

3.6.9 Correlation between MDA and TAC levels among Covid -19 patients.

The result of figure **(3 -14)** show that negative correlation between TAC and MDA , both of them are immune suplementation but TAC have more activity than MDA during the Sars-Cov 2 infection , as in figure **(3 - 14)** . During excessive oxidative stress, Malondialdehyde (MDA) increases and total antioxidant capacity (TAC) decreases in body **(Khajehnasiri *et al.*, 2013)**

Oxidative stress has critical function in inflammatory processes; reactive oxygen species (ROS) and H2O2 can activate to trigger inflammatory cytokine production . It is postulated that oxidative stress is associated with pathogenesis of SARS-CoV-2 infection .

In covid-19, uncontrolled inflammatory responses cause low count of lymphocytes. Reduced oxygen transport to the tissues, coagulopathy and sepsis are shown in COVID-19 patients**(Lage *et al.*, 2022)**. Hypoxia can produce reactive species such as superoxide and H2O2 which can up regulate the expression of inflammatory cytokines . In turn, inflammatory cytokines can increase oxidative stress markers via activation of macrophages, neutrophils, and endothelium cells . This interaction between oxidative stress and inflammatory cytokines can lead to several organ failures in COVID-19 patients who proceed to worsening condition **(Mehri *et al.*, 2020)**.

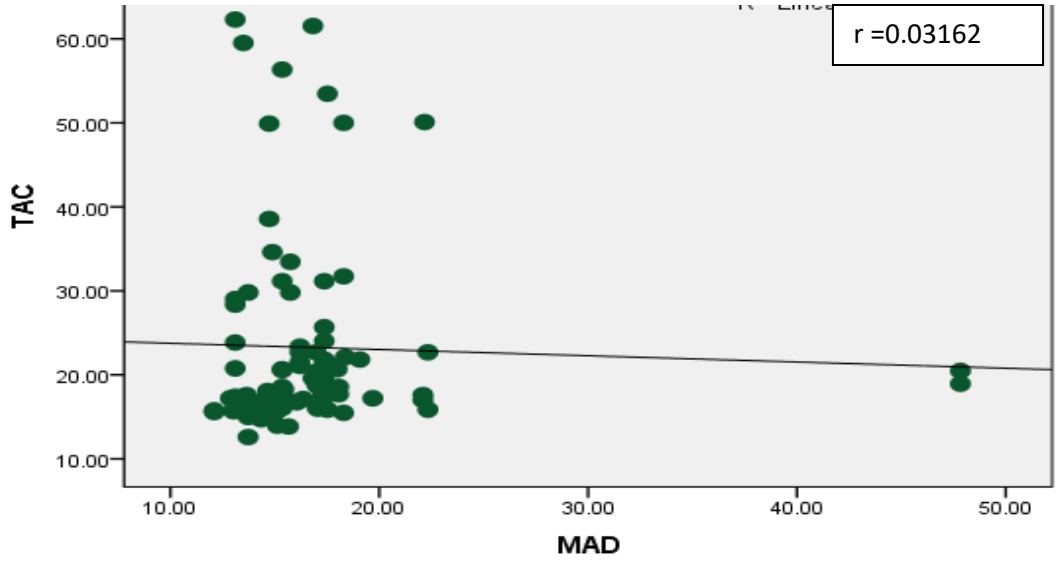


Figure (3 -14) Correlation between MDA and TAC levels among Covid -19 patients.

3.6.10 Correlation between MDA and IL-13 levels among Covid patients

The result of figure **(3-15)** show that increased MDA level might be reduce the IL-13 level , There is a negative correlation between them , IL-13 might be elevated during viral infection and with time may reduce after regulation of such infection ,the MDA was necessary to supplement the immune response during health or infection .

Subpopulations of T cells are characterized by the differential production of cytokines and cell distribution. They also show plasticity, that is, the ability to change from one lineage to another under certain inflammatory conditions that canbe affected by an oxidant microenvironment. In this respect, it has been proven that in an oxidative stress state, Th1 cells present an opposite response compared to Th2 cells .In

study suggest, clones of Th1 and Th2 were used to evaluate the proliferation and secretion capability of cytokines as a response to oxidative stress.

It was observed that low doses of H_2O_2 reduce the production of IFN-γ by activated Th1 cells, and increase IL-4, IL13 secretion by activated Th2 cells. Increase the oxidative stress the loss of redox balance induces alterations in the differentiation and number of $CD4^+$T cell subpopulations, leading to an increase in of the inflammatory response Th1 and Th17 response**(Solleiro-Villavicencio,*et al* 2018).**

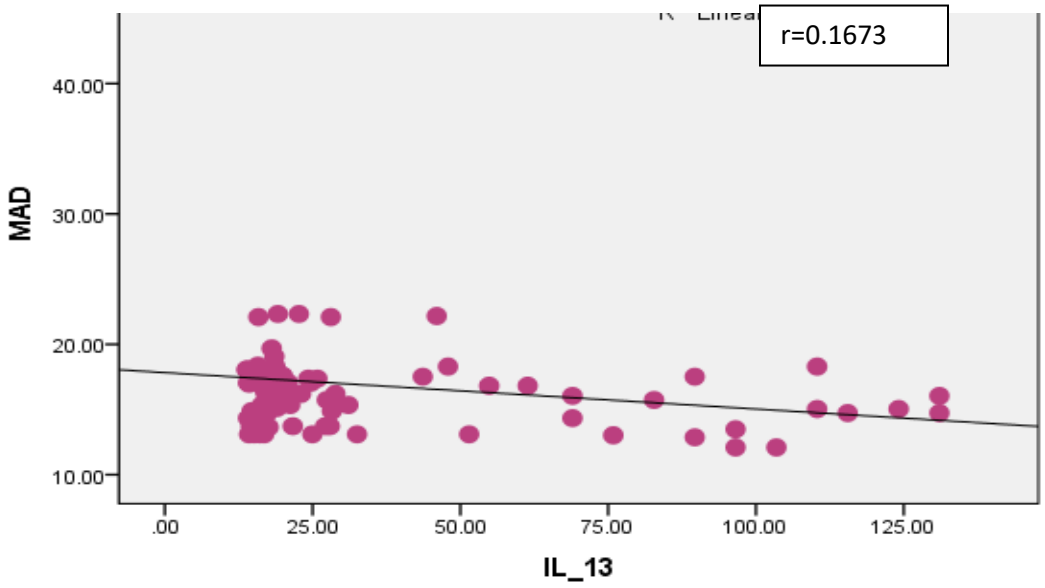


Figure (3 -15) Correlation between MDA and IL-13 levels among Covid -19 patients .

3.6 .11 Correlation between IgM and IgG Anti Sars cov2

The result of figure(3-16) show that , acute attack of viral infection might be accompanied by elevation in Anti – Sars –cov2 –IgM antibody rather than IgG , and there is a negative correlation between them as like as in figure (3 -16) .

In study suggested , the level of IgM antibody was higher in the group of deceased cases . The IgM level showed heterogeneity within the group of deceased cases, and some patients had very high IgM levels which might be in the active status of disease or very low IgM levels due to the long disease course . The increased IgM level in the deceased case group might be related to the higher disease severity in these patients**(Hou *et al.*, 2020) .**

The viral load in tissues affects the immune response, where the reaction was more effective and rapid at low doses of SARSCoV- 2 than high exposure SARS-CoV-2 enters the target cell along with the ACE2 receptor, which decreases the expression of ACE2 on the cell surface and increases the inflammation and tissues destruction . ACE2 plays an anti-inflammatory role by converting Angiotensin II into Ang (1–7) that reduces vaso-permeability, edema and neutrophils infiltration to the lungs. suggested that SARS-CoV-2 might up regulate ACE2 expression to enhance the infection further. in study suggested not all patients showed the same pattern of immunoglobulins production during infection that a high proportion of COVID-19 patients had developed IgG earlier than IgM in serum. This might be explained by the presence of IgG released from memory B cells due to previous exposure to other coronaviruses with similar epitopes, which gives the disease an antibody-dependent enhancement (ADE) characteristic . Sixteen percent of B-cells specific for SARS-CoV are able to recognize SARSCoV- 2**(Saad *et al,* 2021)** .

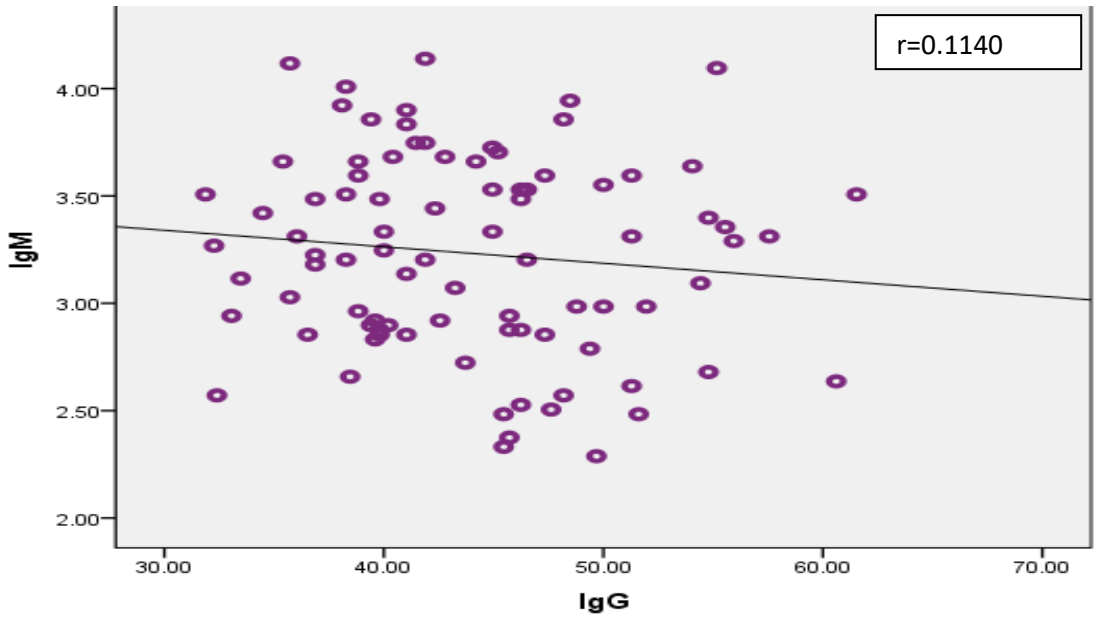


Figure (3-16) Correlation between Anti-Sars Cov2 –IgM and Anti –IgG antibodies.

3.6.12 Correlation between Anti Sars cov2 IgM and age

The result of correlation between anti-Sars-Cov2 IgM and age range of Covid -19 patients revealed that indirect or Negative correlation , as in figure (3 -1 7) , This result might be show that , increased the age might be associated with reduced the antibody production , The age have variable effect on the immunity status of patients and regulate or reduce the antibody produce in different immunological responses .

In this study show That was no evidence of differences age and gender in participants not infection befor vaccination because the range of age from (20 – 45) in tow group receiving dose and the Interval between doses A 3-week minimal interval between primary doses avoids competition between successive waves of primary responses. Immunological studies in man have revealed that both the cellular and the humoral immune responses decline with advancing age. When studying immunoglobulin levels in sera of aged people, one would accordingly expect a decrease. This was actually found only for IgG and IgM in the age groups between 30 and 60 years by in contrast, an increase in IgG and IgA during ageing, while IgM was hardly changed, **(Tretyn *et al.*, 2021)**.

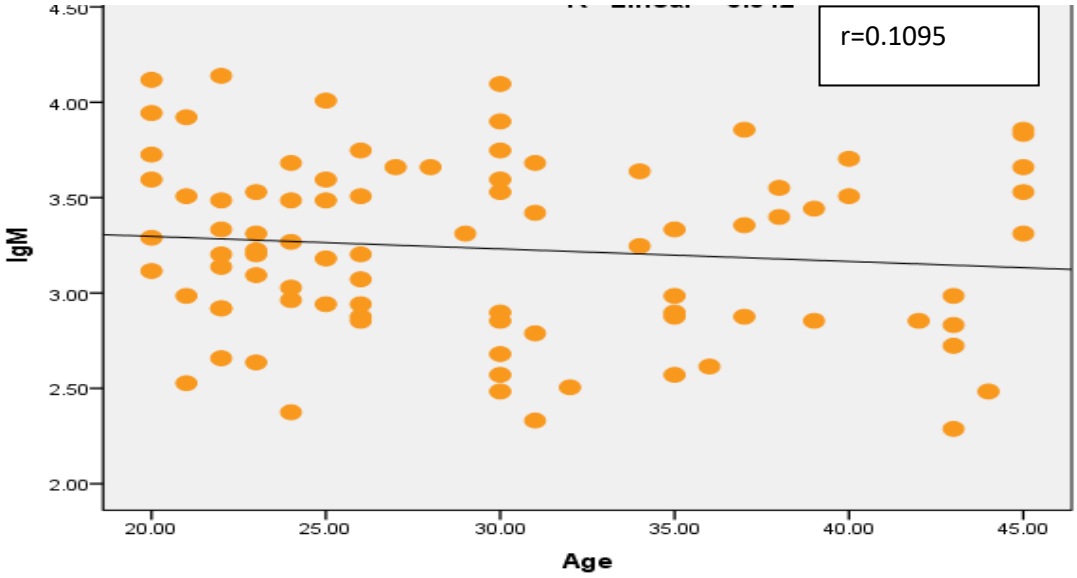


Figure (3 -17) Correlation between Ant-Sars-Cov2 –IgM and age range of Covid -19 patients .

3.6.13 Correlation between Anti Sars cov2 IgG and age

Similar rates of sero conversion were seen in males and females . The result of correlation between anti-Sars-Cov2 IgG and age range of Covid -19 patients revealed that direct or positive correlation , as in figure (3 -18) . The age have variable effect on the immunity status of patients and regulate or reduce the antibody produce in different immunological responses , IgG prolonged to more time than IgM , so increased age might be reduce the IgM rather than IgG.In other study from participants the general population of the United Kingdom In participants without evidence of prior infection, models of binary (positive versus negative) post-vaccine antibody responses showed that positive anti-spike IgG results increased over the 2–4 weeks after the first vaccination the estimated percentage of sero positive 95%, for 40 year olds. There was no evidence of differences in sero positivity rates 14–42 days after the first vaccine in those of younger ages(20 and 40 years) receiving one dose or two doses of pfizer, but greater rates of seroconversion were seen in older individuals (for example, 80 years) receiving two doses.

There was evidence of effect modification between age and sex, whereby at younger ages (30–55 years), similar rates of sero conversion were seen in males and females (for example, in 40 year olds, adjusted odds ratio (aOR) = 0.91, but at older ages (>60 years) males were less likely to seroconvert (for example, aOR = 0.65 for 70 year olds). There was no evidence of independent associations between antibody positivity and household size or working in social care or long-term care facilities**(Wei *et al.*, 2021)** .

The degree of protection depends on the strength of immunity at the moment when an individual is exposed. This level depends on several

factors: the initial immune response is lower in older adults and declines in all individuals from a peak in the early weeks after vaccination .in study shows that After the first vaccine dose, recently infected participants had higher titers of antibody to S proten, and the receptor-binding domain than did those with no history of infection**(Admin-, 2021)**.

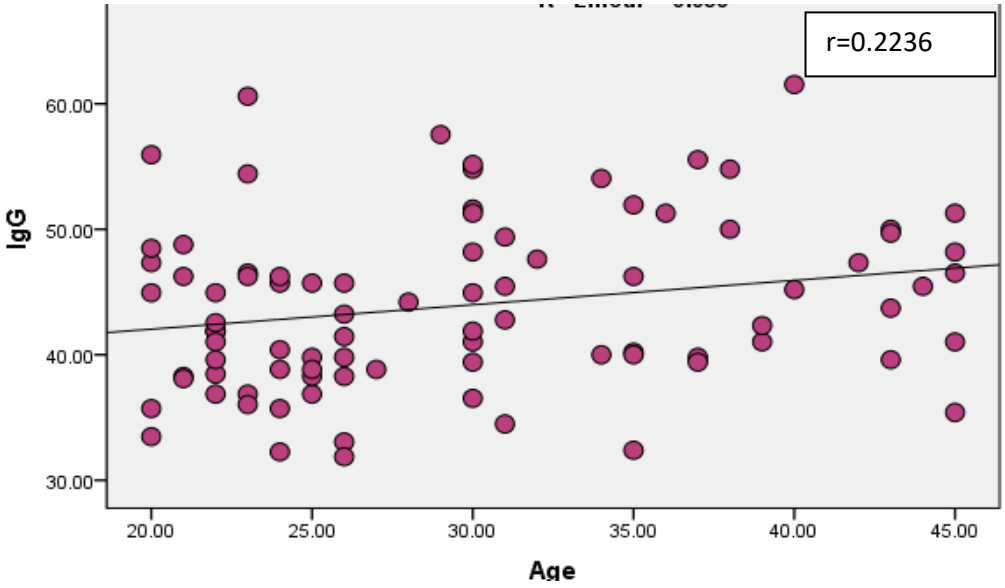


Fig (3 -18):- Show the IgG at younger ages (20- 45 years).

3.6.14 Correlation between IgM anti-Sars-Cov2 and IL-13.

The result of correlation between anti-Sars-Cov2 IgM and IL-13 among Covid -19 patients revealed that in direct or negative correlation ,as in figure (3 -19) , This result might be show that , increased IgM level might be associated with decreased IL-13 .

Immunoglobulin are produced by plasma cells as part of the body's adaptive humeral immune (third immunity) response against a foreign pathogen. While interleukin 13 forms the type that is secreted in the fourth

immunity it is the adaptive cellular immunity that come from T helper 2**(Paul *et al*, 2010)**.

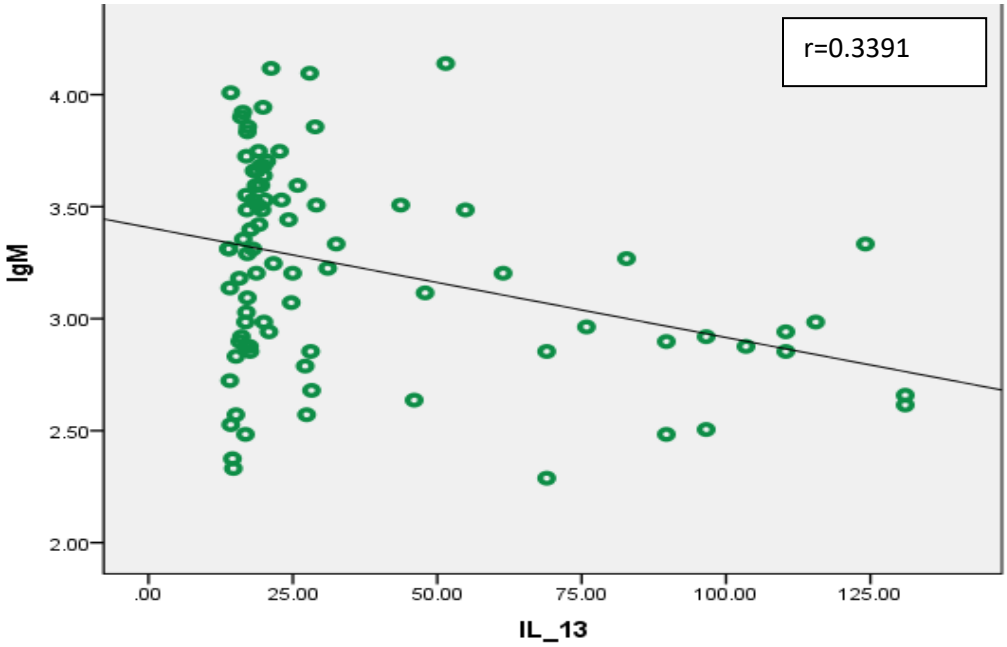


Figure (3 - 19) Correlation between Ant-Sars-Cov2 –IgM and IL-13 level .

3.6.15 Correlation between IgG anti-Sars-Cov2and IL-13

As like as anti-Sars-Cov2 IgM , the result of correlation between anti-Sars-Cov2 IgG and IL-13 among Covid -19 patients revealed that indirect or negative correlation ,as in Figure (3 - 20) , This result might be show that , increased IgG level might be associated with decreased IL-13 .

The spleen and the lymph nodes are important organs for the initiation of an immune response after vaccination and infection, the IgM class dominated the response in the spleen, peaking in numbers at 7 days after the first infection In the lymph nodes and few numbers IgG with a peak response observed at days 14 after this and depended on the number of doses from virus may influence to continuation response immunity to induce

a Th2 dominant response both in the spleen and lymph nodes. These results agreement with other study **(Lakna, 2018)**.

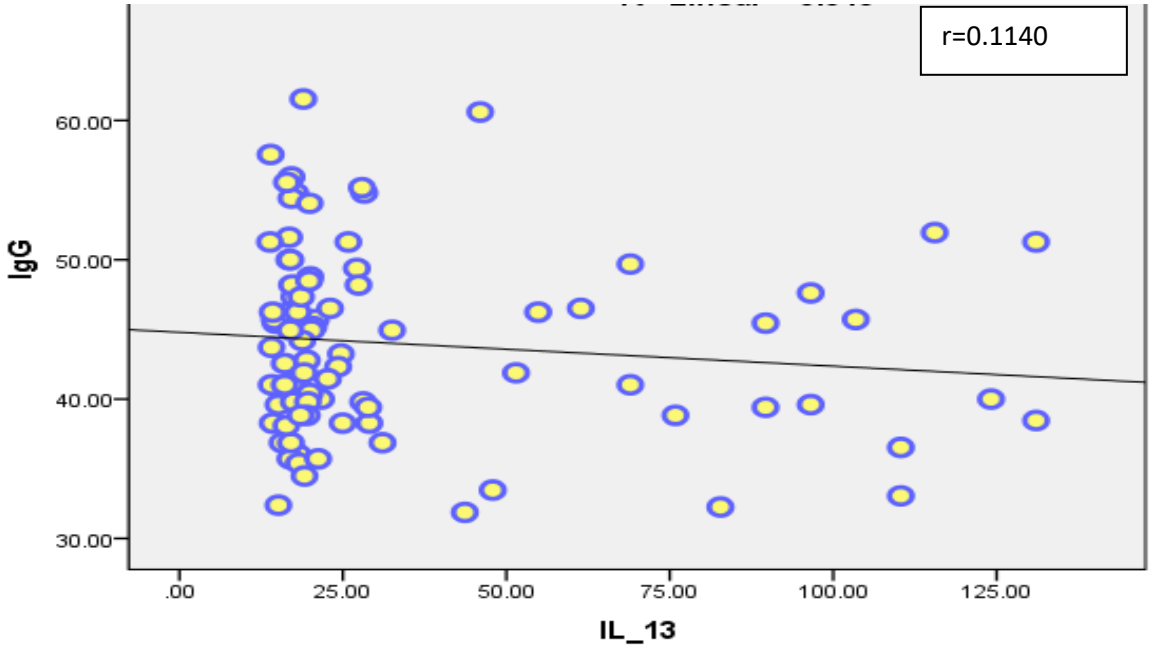


Figure (3 - 20) Correlation between Ant-Sars-Cov2 –IgG and IL-13 level of Covid -19 patients.

4.1 Conclusions

1- Quantitative assays of IgM and IgG could play an important role in the diagnosis and prognosis of COVID-19.

2- Sex-driven differences in immune programming points were appear cross infections and or vaccines . as well as immune modulators were observed across the sex are beginning to emerge.

3- The mRNA vaccine (Pfizer) have induced activity of IL-13 at covid -19 exposure, and limitation of lood prognosis .

4- The immune response were maintained by anti-Oxidants activity by increasing it levels at Covid -19 infection.

5- Increasing of patient ages leading to inhibition of antibody production especially (IgM) antibody against Sars-Cov 2 virus , in counter with IgG antibody enhancement .

6- The adaptive cellular mechanism was monitored by induction of IL-13 synthesis , as well as specific immunity as IgM and IgG antibody production against Sars-Cov 2 antibody.

7- Increase the IgM and IgG level that produce from humeral might be associated with decrease the IL13 because is secreted in the adaptive cellular immunity .

8- Increase the level of TAOC might be associated with increased in IL-13 this important supplement to help the immune activity at different types cellular or humeral against SARS-Cov 2.

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9- The increase of MDA level might be give a hint for diseased prognoses in regarding to IL13 level increased .

10- Increase of MDA level might be induced antibody production or immune activation against virus .

4 . 2. Recommendation

1- conducting more studies on vaccines mRNA and developing them by producing vaccines that are free from side effects and inflammation of epidemics in the future.

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2- Antioxidants have an important role in activating the immune system ,so we recommend studying that minerals and vitamins be more specific according to their effect on the mechanism in the stages of each disease .

3- We recommend further studies on cationic lipids with structures representative of natural lipids that are used to encapsulate mRNA vaccines to reduce their sid effects.

4-focusing on sex differences that have emerged as assign of a major mechanistic difference in protective immunity may pave the way for more effective next generation sex specific vaccine desgn and to aid drug discovery for treatment and vaccine development in a more active and more age specific manner.

5- The relationship between ROS and proinflammatory markers is the key for developing underlying mechanisms by which the pathogenic development of chronic diseases become understood.

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وفي مجموعة متلقين جرعة ثانية عند مقارنتها مع المجموعة الضابطة اظهر المعدل فرق غير معنوي. وفي الدراسة بين مرضى كوفيد 19 والمتلقين للجرعة الاولى لقاح فايزر العلاقة مع مضادات الأكسدة والجنس اظهر الذكور لا يمكن مقارنتهم بالإناث بشكل كبير. وفي مجموعة المتشافين من كورونا والذين تلقوا الجرعة الثانية من لقاح فايزر فأن العلاقة بين مضادات الأكسدة والجنس أظهرت ان الذكر له دلالة معنوية مقارنة بالإناث في الدراسة حيث ان مستوى مضادات الأكسدة لدى الإناث اقل عن مستوى الذكور وفي الدراسة (المالون داي الديهايد)) وفي اختبار مجموعه المرضى كوفيد ١٩ مقارنة بالتحليلات الاحصائية للمجوعة الضابطة اظهر المعدل عالية المعنوية .وفي مجموعة المتشافين من كورونا عند مقارنتها مع المجموعة الضابطة اظهر المعدل تغير معنوي .وفي مجموعة المتلقين للجرعة الاولى مع مقارنتها مع المجموعة الظابطة اظهر المعدل تغير غير معنوي .وفي قياس التحليل الاميونوكلوبيولين ج , الاميونوكلوبيولين م اظهرت مجموعة المرضى المصابين بكورونا عند مقارنتها مع مجموعة السيطرة ان التحليل الاحصائي ل (الاميونوكلوبيولين م) يظهر تغير معنوي و(الاميونوكلوبيولين ج)يظهر تغير معنوي عالي في مجموعة المتشافين من كورونا عند مقارنتها مع مجموعة السيطرة ان (الاميونوكلوبيولين م) اظهر تغير غير معنوي و (الاميونوكلوبيولين ج)اظهر تغيرغير معنوي . اظهر الاستنتاج من الدراسة الحالية ان سن البالغين او الشيخوخة كشفت المستوى المنخفض من مضادات الاكسدة الكلية وكذلك انخفاض التفاعل المناعي يظهر ان الزيادة في مستوى مضادات الاكسدة قد ترافق مع زيادة الانترليوكين 13وكشفت عن ارتباط ايجابي .بينهما هذا الارتباط يظهر علاقة سلبية بين مضادات الاكسدة والمالون داي الديهايد كلاهما هو تكامل مناعي ولكن مضادات الاكسدة له نشاط اكثر من المالون داي الديهايد اثناء عدوى السارس كوفيد 19 .قد تظهر النتيجة ان زيادة مستوى (الاميونوكلوبيولين م) قد يرتبط بزيادة في مضادات الاكسدة و قد يتم تنظيم نشاط مضادات الاكسدة تحريضة على انتاج الاجسام المضادة في الايام القليلة الاولى بعد بدء العدوى وقد يترافق مع زيادة مستوى (الاميونوكلوبيولين ج)مع زيادة مضادات الاكسدة .قد يتم تنظيم او تحفيز انتاج الجسام المضادة في وقت الاصابة بالعدوى وهناك علاقة سلبية بين ال الاميونوكلوبيولين ج , الاميونوكلوبيولين م .

الخلاصة

تعد جائحة مرض كورونا كوفيد 19 الناجم عن متلازمة الالتهاب التنفسي الوخيم الفيروسي وتعد من اخطر الجائحة التي واجهتها البشرية منذ قرن من الزمان على الرغم من انه لا يزال هناك الكثير مما يوجب فهمه فيما يتعلق بالاستجابة المناعية لسارس كوفيد 2 وقد تختلف المناعة الوقائية التي يسببها القاح عن المناعة الطبيعية بسبب التهرب المناعي للفيروس .أن تحسين فهم الاستجابة المناعية الطبيعية سيكون مفيدا في تطوير لقاح فعال واستراتيجيات علاجية ووصفنا ايجابيات وسلبيات منصة اللقاح(ام ار ان اي) تتناول الدراسة الحالية الاختبارات العملية ونتائج المصل التي تم جمعها الخاصة بمرضى مصابين بفيروس كورونا(عشرون (ذكور و اناث)) والمجموعة الضابطة(ثلاثون (ذكور و اناث))و مجموعة المتشافين (عشرون ((ذكور و اناث)) , ومجموعة الملقحين جرعة اولى فايز((عشرون ((ذكور واناث)) و ومجموعة الملقحين جرعة ثانية فايزر((عشرون ((ذكور و اناث)) . خلال الفترة من تشرين الاول ٢٠٢١الى كانون الاول ٢٠٢١.في مستشفى المحاويل والعمر لجميع الاشخاص ذكورا واناث من (عشرون – خمسة واربعون)عاما مع استبعاد المرضى الذين يعانون من امراض مزمنة اخرى والمدخنين وامراض المناعة المنتظمة والسكري والحوامل وامراض الغدة الدرقية . الهدف من الدراسة هو التخطيط لمعالجة النظرة العامة الاساسية لملف الفيروس الذي يزود المجتمع العلمي برؤى قائمة على الادلة حول كوفيد 19 ولقاح(فايزربايوتك) مع التطوير في نظام المناعة في جسم الانسان للمساعدة في اكتشاف دواء للعلاج و تطوير لقاح اكثر نشاطا وأكثر خصوصيتا.حسب العمر والجنس دون اثار جانبية ولإكمال العمل تم عمل الفحوصات التالية لجميع الفئات المدروسة (مرضى كوفيد 19والمتشافين من المرض والذين تلقوا جرعة اولى وجرعة ثانية من اللقاح ومجموعة السيطرة لتقيم نشاط معين ضد العدوى الفيروسية. اظهرت نتيجة الاختبار الكيميائي الحيوي السعة البشرية الكلية لمضادات الأكسدة في مجموعة (مرض كوفيد ١٩ مقارنة بالتحليل الإحصائي للمجموعة الظابطةاظهر المعدل فرق معنوي عالي .وفي مجموعة المتشافين من مرض كورونا مقارنة بالتحليل الإحصائي للمجوعة الضابطة اظهر المعدل فرق غير معنوي .وفي مجموعة المتلقين للجرعة الاولى عند مقارنتها مع المجموعة الظابطة اظهر المعدل تغير عالي.

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة بابل / كلية العلوم للبنات

قسم الكيمياء

ربط حالات الاجهاد التاكسدي , الانترليوكين 13 ,ومستويات الغلوبيولين المناعي في مرضى كوفيد 19 مع او بدون تطعيم في محافظة بابل

رسالة مقدمة الى

مجلس كلية العلوم للبنات / جامعة بابل

وهي جزء من متطلبات نيل درجة ماجستير علوم

في الكيمياء

من قبل

بشرى رحيم هادي الجبوري

(بكلوريوس علوم , كيمياء , بابل , 2001)

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