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Study the immunological status for COVID-19 patients

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ORIGINAL STUDY

Study the Immunological Status for COVID-19 Patients

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Abstract

Introduction: **In the second half of 2019 a sort of sever pneumonia with unknown etiology was developed that extended to all over the word with rapid spread named 2019 Novel Coronavirus. Viral infection ability to produce an extensive immune reaction in the host which associated with increase concentrations of pro-inflammatory cytokines/chemokines. They study aimed to evaluate the immunological state of covid patients which is reflected with concentrations level of tumor markers and interleukins.**

Material and method: **Case control study include 60 patient, 30 control to evaluate the blood sugar, IL-6, IL-7, CEA, and CA19-9.**

Result: **Statistical significant differences were found in the mean level of sugar, IL-6 and CEA in covid patient group in compare to control group, with, p-value 0.0002, 0.0004 and 0.004.**

Conclusion: **Covid infection will cause an increase in the concentration level of interleukins and tumor markers that related mainly to tissue damage.**

Keywords: Immunity, COVID-19, Tissue damage, Coronavirus

1. Background

In the second half of 2019, develop in Wuhan, Hubei Province, China a sort of sever pneumonia with unknown etiology, The spread of the disease was rapidly in the city that extend to entire country, with no obvious answers for the way of transmission or pathogenesis. The caused pathogen was isolated later on and named 2019 Novel Coronavirus (2019-nCoV) on January 12, 2020 [1].

On February, the International Committee on Taxonomy of Viruses declare the official classification for the virus is "severe acute respiratory syndrome coronavirus 2 "(SARS-CoV-2) [2].

The infection spread in China and causing thousands of deaths, which later on spread to European countries (Italy first followed by the others) and the United States, with increase number of new confirmed cases each day.

The World Health Organization declared the virus infection as a pandemic due to the highly spread infection and high transmission rate. By 28 March 2020, COVID-19 virus has caused death to 26 495 individuals worldwide and infected more than 570 000 [3].

History of coronavirus.

The discovery of coronaviruses to cause human infection has been made recently, however, the viruses were discovered in the 1960s for the first time, with little or no information about the epidemiological, genomic, or pathogenic characteristic of the virus, Its known that the viruses have RNA that surrounded by a membrane composed of 'spike'-shaped proteins [4]. The name of virus family came from the crown-like appearance of 'spike' surface proteins 'corona' meaning crown in latin, The Viruses with its specific shape and structure belonging to "Coronaviridae family" that have 4 genera using

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their phylogeny: "alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV" [5].

As of 2020, the CDC has been recognized 7 strains of coronavirus that can infect humans [6].

2. Epidemiology

The virus is of zoonotic origin but Currently, the main source of COVID-19 is patient, and severely infected individuals are highly contagious source than mild symptomatic. Studies demonstrated that Asymptomatically infected patient or patients in incubation have shedding of virus which made as sources of infection [7].

However, the disease is a self-limiting infectious disease, with recovery in 1−2 weeks in most mildly symptomatic. SARS-CoV-2 infection can cause five different outcomes: asymptomatic infection (form 1.2 %); mild to medium symptom (80.9 %); severe symptom (13.8 %); critical (4.7 %); and death (2.3 %) [8].

3. Clinical features

The most common symptom include fever, cough and myalgia or fatigue while the production of sputum, headache, hemoptysis and diarrhea are less common. The average incubation period of covid infection is about 5.2 [9].

3.1. Pathogenesis and role of interleukins

The transmission by respiratory droplet, contact, and fecal-oral. The upper respiratory tract epithelia is the first replication sit where multiplication occur in lower respiratory tract and GIT [10], Giving rise to a mild viremia. Few patients are remain asymptomatic, while other can show non-respiratory symptoms.

The symptom produced by covid 19 are lower respiratory infection as pneumonia, The pathogenic mechanism to produce pneumonia is complex with many theory to explain many aspects of the clinical presentations of the disease, some of the explanation is the viral infection ability to produce an extensive immune reaction in the host, that called later on by a 'cytokine storm' in which an extensive tissue damage is occur with dysfunctional coagulation.

The term of MicroCLOTS is referred to the lung viral injury that associated with the inflammatory reaction and the microvascularpulmonary thrombosis [11].

Cytokines such as "the tumor necrosis factor α (TNF-α), IL-8, IL-1β, IL-12", macrophage inflammatory protein 1 A (MIP1A), interferon-gamma inducible protein (IP10), and monocyte chemoattractant protein 1 (MCP1) are involved in the sequel of the disease development.

Studies demonstrated that pro-inflammatory cytokines increase production in covid patient's serum a "IL-1β, IL-6, IL-12, IFN-γ, IP-10, and MCP-1" has been linked to disease severity, also MERS-CoV infection increase the concentrations of pro-inflammatory cytokines/chemokines (IFN-γ, TNF-α, IL-6, IL-15, IL-17, IL-1RA, IP-10, and MCP-1) [12].

3.2. IL-6

Is the initiator of the storm that produced by the activated leukocytes involved in inflammatory, immunology, and hematopoiesis. Its has a role in many cell and tissue through its ability of promoting B lymphocytes differentiation as well as induce or inhibit growth of other cells types. The acute-phase proteins that stimulated by the secreted IL-6 travels to the liver which plays a role in body temperature regulation, bone mass maintenance and in the integrity of the central nervous system. However the IL-6 had an anti-inflammatory effects and enhance the pathogenesis of the cytokine release syndrome (CRS) which is an acute inflammatory systemic response in which increase in body temperature and multiple organ dysfunction is observed [13].

High IL-6 in covid patient is linked to bad prognosis [14]. In Qin et al., 2020 study, 452 patients who are infected with covid 19 reported elevation in IL-6, the marked elevation was more prominent in severely Symptomatic patient. Its has been demonstrated that the capacity of the azithromycin effectivity in reduction of nasopharyngeal levels of SARS-CoV-2 is linked to blocking of IL-6 and TNF-α [15].

3.3. IL-7

The IL-7 pleiotropic cytokine that has an important role in lymphocyte differentiation, development of T cells and peripheral homeostasis. IL-7 is the activator of T cells, increases the production of pro-inflammatory cytokines beside regulation growth factor beta (TGF-β) trans formation [16]. Studies showed that administration of IL-7 cause increases circulating and tissue lymphocytes that is safe to patients. IL-7 showed a great efficacy as an antiviral agent [17]. Using IL-7 in covid showed lymphocyte regaining function and counts, caused a reduction in viral load as well as clinical improvement in several life-threating viral infections [18].

However, sever infected covid patients, show a higher level of IL-7 on their serum released from the damaged lung tissue and are early immune drivers

of the immune response in COVID-19 that observed mainly in ICU patients [19].

Carcinoembryonic antigen (CEA) is a glycoprotein found in colonic epithelium in embryonic life, its used as a tumor marker for tumor progression monitoring as well as its relation to infectious disease, recent studies found an elevation in CEA level in some COVID-19 pneumonia patient show elevation in serum of CEA. Also, its cell adhesion molecule that connect the pathogens or stromal cells to other members of epithelial triggers, its act as mediator that communicate and activate integrin signaling pathways in human endothelial cells. Abnormal epithelial proliferation can cause elevation in CEA, in covid-19 the hyperplasia of type II alveolar epithelial cells and the interstitial fibrosis was found in autopsy of covid patients [19].

This raise can be explained by the acute phase protein increment with its association of inflammation that induced by viral infection as well as the gastrointestinal damage caused by viral infection [20].

CA 19-9 is a carbohydrate antigen, using as a screening marker for pancreatic cancer in asymptomatic individuals or patients with suspected to have pancreatic cancer [21]. Its formed by the pancreatic cell, biliary ductal cells, gastric cells, colonic, endometrial and salivary epithelia cells, its can be found in small amounts in serum, over expression is seen in benign gastrointestinal disorders. Covid-19 viruses has the ability to cause a multiple organ damage, that cause elevation in many tumor marker.

Diabetic patients are more likely to have a poor prognosis in coronavirus infections. In retrospective study the hyperglycemia is considered ad an independent predictors factor for death and morbidity in SARS patients [22]. In covid-19 pandemic, Recent clinical studies declared that DM is a major comorbidity of COVID-19 [23]. and carful glycemic control will carry a more improvement in clinical outcomes in COVID-19 patients, poor glycemic control regarded a poor covid 19 prognosis.

4. Material and method

The study is case−control study enrolled 60 patient of covid-19 (positive PCR, CT scan), and 40 healthy control, samples were collected through the duration of ( ) to ( ), from ( ).

5 ml of venous blood was collected from each participant to evaluate blood sugar, IL-6, IL-7, CEA, and CA19-9 in their blood.

The normal reference value for blood sugar was 70−110 mg/dl, 22 pg/ml, 0−2.5 ng/ml in non-smoker and CA19-9 is 37 U/mL. The spss 25 has been used to detect the effect of difference factors in study parameters. The difference between means was tested using T-test. correlation coefficient ® was calculated to test the correlation between variables in this study.

5. Result

The current study included 90 participant divided into two groups, 60 participant as a patient group and 30 participant as a control group.

Each participant has been tested for blood sugar, IL-6, IL-7, CEA, and CA19-9.

In Table 1, independent t-test is used to measure the difference in the mean level of blood sugar between patients (183.11 ± 11.43) and control as mean was (117.17 ± 8.06), that is statistically ($p = 0.0002$) higher in patients than control.

The mean serum level ±SE of IL-6 and IL-7 in patients and control is presented in Table 2, the mean level of IL-6 in patients was 99.18 ± 8.00, while the mean level of CEA in patients was 5.823 ± 0.72 and in control was 2.31 ± 0.22, result show that there is a statistical significant differences in mean

Table 1. Comparison of blood sugar between patients and control groups.

Group	No	Mean ± SE of Sugar ( )
Patients	60	183.11 ± 11.43
Control	30	117.17 ± 8.06
T-test	–	33.48 **
P-value	–	0.0002

** ($P \leq 0.01$).

Table 2. Comparison between patients and control groups in IL-16 and IL-17.

Group	Mean ± SE	
	IL-6 ( )	IL-17 ( )
Patients	99.18 ± 8.00	67.76 ± 6.65
Control	91.16 ± 7.12	73.45 ± 10.79
T-test	24.26 **	23.96 **
P-value	0.0005	0.638

** ($P \leq 0.01$).

Table 3. Comparison between patients and control groups in mean serum level of CA19-9 and CEA.

Group	Mean ± SE	
	CA19-9 ( )	CEA ( )
Patients	24.22 ± 3.15	5.823 ± 0.72
Control	11.08 ± 1.53	2.31 ± 0.22
T-test	8.93 **	2.027 **
P-value	0.0044	0.0009

** ($P \leq 0.01$).

Table 4. Estimation of correlation coefficient between parameters study in patients.

Parameters	Correlation coefficient-r	P-value
Sugar & IL-16	−0.20 *	0.049
Sugar & IL-17	−0.17 NS	0.092
Sugar & CA19-9	0.11 NS	0.316
Sugar & CEA	0.16 NS	0.118
IL-16 & IL-17	0.61 **	0.0001
IL-16 & CA19-9	−0.06 NS	0.561
IL-16 & CEA	0.07 NS	0.472
IL-17 & CA19-9	−0.07 NS	0.475
IL-17 & CEA	0.04 NS	0.703
CA19-9 & CEA	0.30 **	0.0046

* ($P \leq 0.05$), ** ($P \leq 0.01$), NS: Non-Significant.

level of CEA that is higher in patient than control (see Table 3).

But the mean level of IL-7 in both group patients and control show non statistical significant differences between the groups as p-value o.63, the mean in patients group was 67.76 ± 6.65 and in control group 73.45 ± 10.79.

Regarding CA19-9 and CEA markers, both show statistical significant differences in mean level of CA19-9 and CEA in patients group 24.22 ± 3.15, 5.823 ± 0.72 that is statistically higher than control group as mean level in control were 11.08 ± 1.53, 2.32 ± 0.22, p-value 0.0044, 0.0009.

To test the correlation between studied markers is presented the Spearman correlation coefficient was calculated as presented in Table 4.

The result showed that there an inverse statistical significant weak correlation between sugar and IL-6 in participants, r was −0.2, p-value 0.04. A positive moderate significant correlation between IL-6 & IL-7 in participant as r was 0.61 and p-value 0.0001. Another significant correlation was found in the study between CA19-9 and CEA, the correlation was weak positive significant correlation as r was 0.3 and p-value 0.004.

However, no statistical significant correlation was found between Sugar & IL-17, Sugar & CA19-9, Sugar & CEA, IL-16 & CA19-9, IL-16 & CEA, IL-17 & CA19-9 and IL-17 & CEA.

6. Discussion

The pandemic of covid-19 change the world, the disease show an extensive damage to lung tissue in patient sever clinical symptom, that end mostly with death.

The tissue damage, inflammatory response by host cells as well as the cytokines storm, can be detect biochemically which show high level of IL-6, C-reactive protein, procalcitonin, fibrinogen, total bilirubin, aspartate aminotransferase, alanine aminotransferase, ferritin, fibrinogen, D-dimer and others.

In the current study the RBS of covid patient control was measured, that showed that covid patient has statistically higher RBS in compare to non covid patient.

In Kapoor et al. which is retrospective study included 93 non covid patient and 469 covid patient to evaluate the blood sugar in patient, amount of consumed insulin and the effect of blood sugar on patient prognosis, result showed that covid patient have significantly higher RBS in compare to non covid patient with higher insulin consumption that support current study result which can be explained by there is suggestion that covid 19 will contribute to the hyperglycemia as SARS-CoV cause destruction to the pancreatic endocrine parts which suggesting that SARS-CoV may cause acute DM that is insulin dependent [21,24].

IL-7 and it role in WBC activation is measured in current study. Result show a statistical higher level of IL-6 in patient in compare to control, with non statistical significant difference in IL-7 level between the two groups [25].

In Kathim et al. study to detect interleukin 6 and 10 gamma interferon in 40 covid patient and compare them to 40 healthy control that demonstrate patients have higher significant mean of IL-6 in compare to control that support current study result [23]. In Gorham et al. study that evaluate IL-6 in survival and non-survival patient, and it was higher in non-survival which support current study result in increase IL-6 level in covid patient. The interleukins molecules especially IL-6 and its essential role in cytokines storm as well as the inflammatory response of the host cell that explain the raise in IL-6 level [26].

No study was found that measure the IL-7 in covid patient and control, all the studies evaluate the efficiency of IL-7 to sever ill covid patient as in Laterre et al. study [27].

The result show high CEA level in compare to control patient, Yang et al. saw that is retrospective study include 171 patient report a significant higher level of CEA from the upper normal limit in covid patient, and it was much higher in non-survival patient in compare to survival patient [28,29].

The mean level CA19-9 tumor marker in current study dhow no statistical significant differences between the two group. In Purut et al., study that evaluate the effect of covid 19 infection on the tumor markers, result of study show covid 19 has on effect on the studies tumor markers (CA125, CA19-9, CA15-3, AFP, and CEA) that inconstant with current study result in CEA section. [30], that may be relate to the small sample size as well as time of taking sample, in which early period of infection and mild

symptomatic patient has no or slight elevation of markers [31].

Regarding the correlation between studied markers, its found that there is an inverse statistical significant weak correlation between sugar and IL-6, A positive moderate significant correlation betweenIL-6&IL-7 and weak positive significant correlation between CEA and CA 19-9, however no study was found that evaluate the correlation between the studied marker in the current study.

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