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Association of COVID-19 severity with interleukin-10 in Babylon Governorate, Iraq

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ABSTRACT

Aim: Cytokines serve as crucial for regulating infection when a virus, such COVID-19, is present. Cytokine genetic polymorphisms can change how the immune system reacts to this infection. Researchers have focused more on the

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FREE CONTENT

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hyper-inflammatory response than the anti-inflammatory compensatory action. This study aim to investigate the relationship between this parameters (Age, gender, blood group, vaccine and geographic distribution) in the two study groups both severe and mild COVID-19 recovered subjects and detection of IL-10 concentration level in severe and non-severe patient with COVID-19.

Methodology and results: The study was performed on the months of November and December 2022, 76 (100%) patients who were treated at the Marjan teaching hospital in the province of Babylon served as the study's subjects. Age, gender, geographic distribution, the ABO system, vaccination, and IL-10 concentration are just a few of the demographic data that were included in the current study. A study found that COVID-19 cases were significantly different between severe and non-severe groups. The prevalence was higher in those aged 18-25 years (31.6%) and 25-40 years (14.4%), and 40-60 years (3.9%). Gender was also a factor, with more male patients reporting a non-severe rate of 31.6% and a severe rate of 33.3%. Geographic location was not significantly related to disease severity, but there was a significant difference in both non-severe and severe effects for rural and urban areas. There was no significant difference between non-severe and severe cases. Blood type O was the most common blood type, with 24.7% of severe cases.

Conclusion, significance and impact of study: Older people are more likely to have severe COVID-19 instances, and rates are higher in males and rural areas. Males are more likely than females to have severe instances, while rural areas are more likely than metropolitan areas to have severe cases. More severe diseases are associated with higher blood group type and IL-10 concentration levels.

Introduction

Humanity hasn't had a pandemic with the infectious disease, morbidity, and death of COVID-19 since the last century. The World Health Organization (WHO) declared a public health emergency and declared the COVID-19 outbreak in Wuhan to be an international concern

JOMBC Journal of Medical Pest Control
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FREE CONTENT

in late January 2020. The virus then spread to other nations, and in March 2020, a worldwide pandemic was declared. (Cucinotta and Vanelli, 2020).

Due to the presence of many proinflammatory mediators, people with COVID-19 are more likely to die from severe pneumonia and damage to key organs. Clinical studies have not yet demonstrated that blocking GM-CSF, IL-1, or IL-6 significantly lowers mortality in COVID-19 patients. IL-10 is one possible way to reduce COVID-19 mortality. Serum cytokine concentrations, including IL-10, are significantly higher and correlate with the severity of the disease in critically ill COVID-19 patients, as was previously mentioned. Accordingly, new research indicates that COVID-19 patients also experience inflammation and immunological activation (Lu, *et al.*, 2020). It supports the hypothesis that via stimulating inflammation and the immune system, IL-10 may have a role in the pathophysiology of COVID-19.

First, in critically ill COVID-19 patients, peripheral blood levels of the inflammatory and immune-stimulating cytokines (IL-2R, IL-4, IL-7, IL-18, IFN-, GM-CSF, TNF-, and chemokines IP-10 and CXCL9) discussed previously in the previous text are high (Zhao, *et al.*, 2020). Second, even if the number of severe or critically ill COVID-19 patients has completely decreased, there are still growing cytotoxic CD8+ T cells in the bloodstream and hyperactive peripheral CD8+ T-cell numbers. Furthermore, the proportion of peripheral blood CD4+ and CD8+ T lymphocytes that produce interferon may rise in COVID-19. Individuals with high serum IL-10 levels who are critically unwell or experiencing severe illness (Wang, *et al.*, 2020). Third, people's peripheral blood levels of fatigued PD-1+ TIM3+ CD8+ T cells have been found to increase as COVID-19 disease worsens. These results are consistent with the blood IL-10 concentrations of the patients, indicating that IL-10 contributes to T cell weariness, most likely due to over-activation and proliferation (Diao, *et al.*, 2020).

The immunological characteristics of COVID-19 patients with severe or critical illness and their elevated systemic IL-10 suggest that IL-10 may be harmful in the course of the disease. This notion has to be tested more thoroughly, though. How, if at all, might more IL-10 affect COVID-19 mortality in this case? The immunopathological cascade that resulted in patient death following SARSCoV-2 infection is composed of three stages: start, amplification, and completion (Lu, *et al.*, 2020). A negative feedback mechanism that helps reduce other

proinflammatory mediators that cause inflammation may be the early rise of IL-10 after SARS-CoV-2 infection during the lung's start phase. On the other hand, we hypothesise that endogenous IL-10 might act as an immune-stimulating and pro-inflammatory agent, causing the production of additional cytokine storm mediators when it rises. According to this study, IL-10 could have an immune-stimulating and pro-inflammatory effect, leading to an increase in the synthesis of cytokine storm mediators.

Material And Method

From September to February 2023, clinical samples from 76 COVID-19 patients were collected at the Marjan Teaching Hospitals in Babylon, Iraq. The patients are between the ages of 18 and 90.Five millilitres of venous blood were extracted from each patient. To identify the blood type, a sample of the blood roughly two millilitres in volume was drawn and placed in tubes with EDTA. The second part of blood was separated by centrifugation at 3000 rpm for 15 minutes. Until the immunological parameters are assessed, the remaining serum samples are stored in a refrigerator at -20°C.

Principle of estimation of ABO blood group system, agglutination response is the starting point of the Rh and ABO blood grouping systems. Visible agglutination, or clumping, results from the interaction between red blood cells containing one or both antigens and the associated antibodies. The terminal sugar residues that are visible on the surface of red blood cells indicate which of the two ABO blood group antigens A or B are present in these O-linked glycoproteins. RBCs from blood group A persons have A antigens, while their serum contains anti-B antibodies. Similarly, serum anti-A antibodies and B antigens on RBCs are present in blood group B persons. RBCs from blood group AB persons have both A and B antigens, however their serum does not contain any anti-A or anti-B antibodies. On the other hand, people Anti-A and anti-B antibodies can be found in the serum of individuals with blood group O, but neither A nor B antigens are. Red blood cells' exposed loops interact with antibodies that are specific to them to form the Rh antigens, which are transmembrane proteins (Mujahid and Dickert, 2015).

Estimation of IL-10, This ELISA kit runs on the sandwich-ELISA concept. The micro-ELISA plate supplied with this kit has been pre-coated with an antibody that is specific to human IL-10.

JOMBC Journal of Medical Pest Control
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FREE CONTENT

The proper antibody and samples (or standards) are put in to the micro-ELISA plate wells. Subsequently, each microplate well is filled with a biotinylated detection antibody specific for human IL-10 and the Avidin-Horseradish Peroxidase (HRP) conjugate, it is subsequently raised in an incubator. Free parts are removed by washing. In each well, the substrate solution is added. The only wells that will show blue are those that contain the biotinylated detection antibody, human IL-10, and the Avidin-HRP conjugate. When stop solution is added, the enzyme-substrate reaction is stopped, and the color changes to yellow (Stearns, *et al.*, 1995). Standard curve for standard IL-10, different concentrations of IL-10 were prepared and measured spectrophotometrically. Using spectrophotometry, the optical density (OD) is measured at 450 nm ± 2 nm wavelength. There is a clear link between human IL-10 concentrations with the OD value. By comparing the optical density (OD) of the samples to the standard curve, and can establish the amount of human IL-10 present in the samples.

Statistical Analysis: The research data was reviewed by using mean ±standard deviation in XLXs program from office, 2016. The significance tested at probability less than 0.05 by using online tool: https://www.medcalc.org/calc/comparison_of_means.php

Discussion

a. Distribution of age in COVID-19 case for both severe and non-severe

This study included 76 (100%) patients, were attended for Marjan teaching hospital in Babylon province. There were 38 (50%) severe cases and 38 (50%) non severe case, the age of most severe cases were over forty years while most non severe cases were under thirty years. According to Age, there are four categories include (18-25, 25-40, 40-60 and 60-96), The incidence of COVID-19 was highest in people aged 18-25 years (31.6%) for non-sever group and (17.1%) for sever group, and in 25-40 years (14.4%) for non-sever group and (10.6%) for sever group, (3.9%) for non-sever and (10.6%) in age 40-60 years, whereas it was (0%) for non-sever group and (11.9%) for sever in age over than 60, No significant difference was observed between sever and non-sever group according to age ($p > 0.05$), as shown in table (1).

This study revealed that, when compared to younger groups or older groups, the age group (18 to 25 years) was the one most affected by the corona virus. Despite the fact that research has shown

JOMBC Journal of Medical Pest Control
Immunology and Microbiology
ISSN : 10036245
FREE CONTENT

that older people are more likely than younger people to be-come infected with COVID-19 (Lu, *et al*., 2020). Additionally, because they are exposed to respiratory illnesses more frequently than older people, children's bodies have built immunity that may help them fight infection better, and a rigorous immunization schedule. The respiratory system's inherent pathophysiological changes as well as the increased prevalence of persistent comorbidities with age may influence the worst effects of aging (Libertini, *et al*., 2019).

Barek *et al*., (2020) evaluated the effect of age on the severity of COVID-19 in a meta-analysis study in order to diagnose and evaluate the current outbreak in clinical decision-making. The study indicated that individuals who are 50 years of age or older and elderly are more susceptible to obtaining severe cases of COVID-19. Additionally, the prognosis and severity of the virus can be strongly affected by comorbidities and clinical symptoms. Over 3.54 million cases of SARS-CoV-2 infection have been reported in children and adolescents, not just in elderly people. Although Serious SARS-CoV-2 infections are less frequent. In children and adolescents than in adults, hospitalization, intensive care admission, and even death have been reported in children and adolescents (Guzman, et al., 2022).

Table 1. Distribution of patients according to age.

Age (year)	Non sever (%)	Sever(%)
18-25	24(31.6%)	13(17.1%)
25-40	11 (14.4%)	8 (10.6%)
40-60	3 (3.9%)	8 (10.6%)
60-96	0 (0%)	9 (11.9%)

P-value > 0.05

b. Distribution of gender in COVID-19 case for both severe and non-severe

The number of male patients (37) was higher than the number of female (29). According to gender Table 2, the results showed non-significant differences (p>0.05), in male was (31.6%) for

JOMBC Journal of Medical Pest Control
Immunology and Microbiology
ISSN : 10036245
FREE CONTENT

non-sever and (30.3%) for sever. While in female group was (18.4%) for non-sever and (19.8%) for sever.

Testing across age groups may have an impact on the age range of confirmed cases and positive results for SARS-CoV-2 testing. This is the first study to look at the connection between age group and the severity of COVID-19 disease. The foundation of case and laboratory surveillance is the regular accessibility of diagnostic testing to all demo-graphic segments. Though testing availability has varied by location, time, and test provider, it is doubtful that this was the only cause of the observed age change. Although it is unclear if these represent real differences in men and women's risks of contracting COVID-19 or just changes in who is seeking or receiving testing, our data imply that gender disparity may contribute to epidemiologic variations by sex.

Due to this review, men are more exposed to the coronavirus than women. The result was supported by research conducted in 2015 by Langer and colleagues, who also discovered that woman are less likely than men to get the disease. Males will generally have worse clinical results and are more likely to die with COVID-19 than females. Social factors that influence the gender gap include differences in the likelihood that individuals will focus on work-related interactions that are crucial for the spread of infectious illnesses spread through close contact or respiratory routes. For instance, COVID-19 was found to be a lifestyle virus, with 95.4% of male patients and only 89.3% of female

patients not participating in any form of physical activity. It is evident from the ongoing pandemic that sex and things related to sex have a significant impact. Notable variations in risk throughout the sexes, with males experiencing higher risks than women (Caramelo, *et al*., 2020). It could have something to do with the presence of other risk factors, such as diabetes, high blood pressure, and heart disease, which affect men more than women, and sex hormones like estrogen and testosterone, which appear to be crucial in shaping the body's immunological response.

Table 2. Gender distribution in severity of COVID-19 cases

Gender	Non sever (%)	Sever (%)

JOMBC Journal of Medical Pest Control
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FREE CONTENT

Male	24 (31.6%)	23 (30.3%)
Female	14 (18.4%)	15 (19.8%)

P-value > 0.05

c. Geographic distribution and Severity

The relationship between severity of disease and geographic, there is non-significant difference (p>0.05) between rural and urban settings for every patient. While, it showed significant difference (p<0.05) in both non-sever and sever for ruler areas and urban area, as illustrated in Table (3).

The findings indicated that living in a rural area lowers the risk of contracting an infection because peasants' lifestyles differ greatly between urban and rural areas, according to a study that examined people's way of life. Compared to people who live in cities or urban areas, villagers are actually more active. 18% of the villagers are actually active, compared to 10% and 7% of the population in the cities and towns, respectively. These studies verified that the patient's occupation and COVID-19 infection exposure are related. Consequently, it has been thought that work is a key factor in determining the risk of infection (Marinaccio, *et al*., 2020).

d. Distribution of patients according to vaccine for both severe and non-severe

The relationship between severity of disease and vaccine, there is non-significant difference (p>0.05) between non-sever and sever. While sever group between vaccinated and none vaccinated, showed significant difference also in non-sever group vaccinated and non-vaccinated (p<0.05), as illustrated in Table (4). To absolutely comprehend the advantages of COVID-19 vaccination, disease attenuation must be taken into account. This is done by examining whether COVID-19 cases that occur despite vaccination are less severe than those that do not receive the vaccine. Building public trust and lowering vaccine hesitancy require communicating such re-search on the effectiveness of vaccines (Veger and Dube, 2020). The most accurate measure of US uptake of the COVID-19 vaccine was perceived vaccine efficacy (Kreps, *et al*., 2020). The

Table 3. Geographic distribution of COVID-19 cases

COVID-19 cases	**Rural areas**	**Urban areas**	**P value**
Total n=76 (100%)	35 (46%)	41 (54%)	> 0.05
Sever n=38(100%)	26 (68.4%)	12 (31.6%)	< 0.05
Non sever n=38(100%)	9 (23.7%)	29 (76.3%)	< 0.05

efficiency of immunizations in preventing disease is a particularly important argument, according to research by Sherman, *et al*., (2021) on people's willingness to receive the COVID-19 vaccine and their attitudes toward vaccines. It's critical to emphasize what we are not attempting to accomplish with this dataset.

Table 4. Relationship between vaccination and severity of COVID-19 cases

COVID-19 cases	Vaccinated	Non vaccinated	Chi square	P value
Total cases n=76 (100%)	35 (46%)	41 (54%)	0.477	> 0.05
Sever n=38 (100%)	9 (23.6%)	29 (76.4%)	8.082	< 0.05
Non sever n=38 (100%)	26 (68.4%)	12 (31.6%)	4.412	< 0.05

e. ABO and Severity

Figure (1) showed relationship between severity of disease and ABO. There is non-significant difference ($p>0.05$) for all categories. Blood group O were 34 (44.8%), and 18 (23.7%) were severe cases. The non-severe cases were 16 (21.1%), the blood group A was 19 (25%), the severe cases were 10 (13.2%), the non-severe cases were 9 (11.8%), and the blood group B was 16 (21%). Severe cases 6 (7.9%), non-severe cases 10 (13.1%), AB blood group 7 (9.3%), severe cases 4 (5.3%), and non-severe cases 3 (4%).

Blood group O may possess a shielding impact, those have blood type A may evolve more likely to contract COVID-19 and die at a greater rate than those with non-A blood groups (Zhao, *et al*., 2020). One plausible cause for inconsistency is the variation in blood types across individuals of different ethnicities and geographical locations. Individuals with O blood type were found to have a lower hazard of getting COVID-19 infection (Zietz, *et al*., 2020). After further stratification by Rh, it was also suggested that there was only a significant association between blood types A+ and O+. Since there weren't as many Rh blood types found in our specimens, we didn't do any more studies; therefore, more research `and debate on this subject are required.

JOMBC Journal of Medical Pest Control
Immunology and Microbiology
ISSN : 10036245
FREE CONTENT

Research shows blood group O reduces severe COVID-19 risk, but not protection due to small sample size, a blood group increases infection incidence (Zeng, *et al*., 2020).

Research suggests ABO blood type plays a role in COVID-19 infection, with alveolar epithelial cells, airway epithelial cells, and bodily fluids displaying specific blood group antigens. Initially, we postulated that blood group glycoproteins' hereditary susceptibility could serve a purpose by binding receptor-mediated affinity, specifically as an invasion mechanism. Furthermore, Cooling's work has demonstrated that blood group antigens can identify certain germs that cause infections. Anti-A antibodies may particularly prevent SARS-COV S protein-expressing cells from adhering, based on our understanding of the SARS virus (Stowell and Stowell, 2019). Furthermore, the receptor combination and nucleic acid sequence of SARS-COV and SARS-COV-2 are comparable to those of ACE2 (Li, *et al*., 2017).

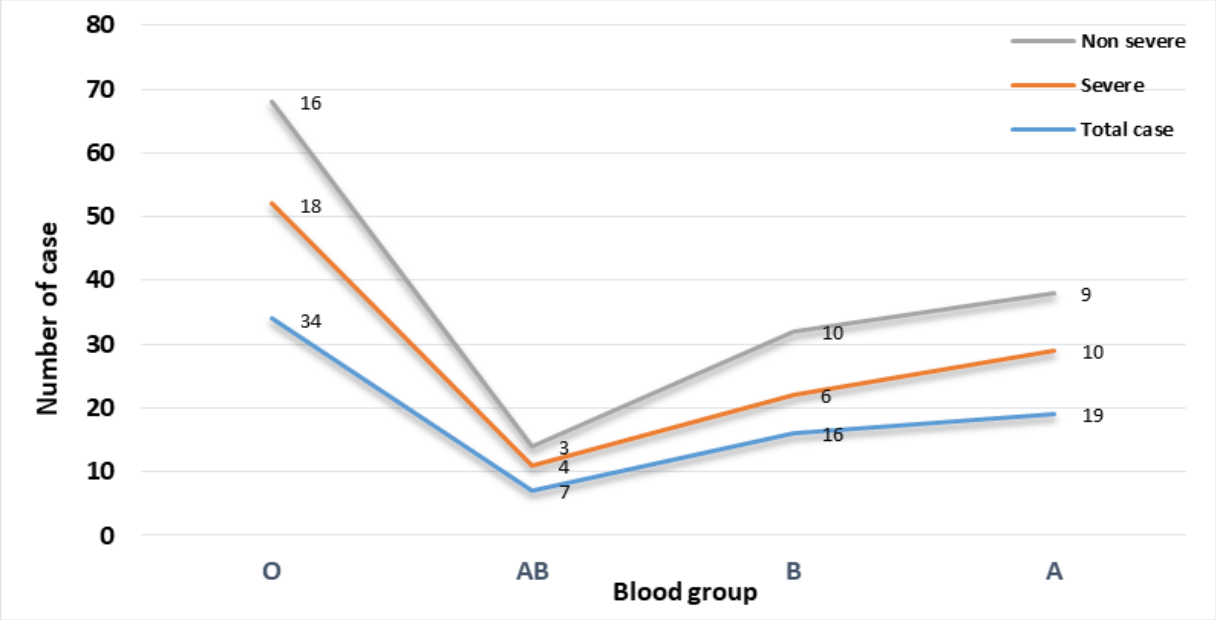

Figure 1. Distribution of blood group and severity of COVID-19 cases

f. Detection IL-10 in patients who are both severe and not with COVID-19

JOMBC Journal of Medical Pest Control
Immunology and Microbiology
ISSN : 10036245
FREE CONTENT

Out of 76 cases of COVID-19 of both severe and non-severe subjected to detection IL-10 parameters, the results revealed non significant differences between male and female in non-sever and sever cases. In sever cases the concentration of IL-10 were 9.74 and 15.06 for male and female, while in non-sever cases the concentration of IL-10 were 5.78 and 6.96 for male and female, as shown in table 5.

Li et al. found that in sepsis patients admitted to the critical care center, the IL-10/Lymphocyte Count Proportion was related to the degree and prognosis of infection. The primary source of the elevated IL-10 levels in COVID-19 seems to be the inflammatory response that is dysregulated overall. However, this immunological dysregulation most likely limits the usefulness of directly connecting Cytokines that promote or inhibit inflammation (Lauder, *et al*., 2013). The elevated levels of CRP, IL-6, IL-10, and neutrophilia show that innate cells might potentially important in the etiology of severe illness. IL-6 has garnered a great deal of interest as a severity indicator and as a possible target for therapy with anti-IL-6 or anti-IL-6 receptor monoclonal anti-bodies (Lauder, *et al.*, 2013).

Table 5. IL-10 concentration for COVID-19 severity cases

Covid-19 Cases Sever	Male IL-10 concentration SD Mean± N=22	Female IL-10 concentration Mean± SD N=16	P- value	Total IL-10 concentration Mean± SD N=38
IL-10 Conc.	9.7469± 11.66	15.068± 19.979	P > 0.05	11.774± 15.3579
Covid-19 Cases Non-Sever	Male IL-10 concentration SD Mean± N=23	Female IL-10 concentration Mean± SD N=15	P- value	Total IL-10 concentration Mean± SD N=38
IL-10 Conc.	5.7845± 1.6068	6.9649 ± 2.0317	P > 0.05	6.4672± 1.838

Conclusion

The age of most severe cases were over forty years while most non severe cases were under thirty years. Increasing in severe cases of male compared to female and in severe cases of rural areas compared to urban areas. Elevated levels of IL-10 concentration and blood group type are linked to more severe conditions. IL-10 parameters showed significant differences in severe cases, but not between male and female. The study found that severe COVID-19 cases are more prevalent in older individuals, with males and rural areas experiencing higher rates. No-vaccinated patients also face higher severity. High blood group type and IL-10 concentration levels are associated with increased severity. Increasing in severe cases of Non vaccinated patients. While there is a decreasing in the severe cases of the vaccinated patients. High severe cases in (O and A) blood group type can be associated with increasing severity of COVID-19 and high serum level of IL-10 concentration can be associated with increasing severity of COVID-19.

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