Respiratory Hypersensitivity Concomitant with Covid 19 Infection

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Abstract

Background: The current coronavirus disease 2019 (COVID-19) outbreak is a Worldwide emergency, as its rapid spread and high mortality rate had caused severe disruptions. Patients with COVID-19 can develop pneumonia, severe symptoms of acute respiratory distress and multiple organ failure. Patients with severe diseases showed lymphopenia, particularly the reduction in peripheral blood T cells. Patients with severe diseases were reported to have increased plasma concentrations of pro-inflammatory cytokines. Infections of different types, viral, bacterial and mycotic were accused to induce hypersensitivity reactions in infected patients. Objectives: The study aimed to reveal the relationship between the hypersensitivity factors including serum total IgE , IL5 and eosinophils counts regarding the severity of Covid 19 infection in patients. Patients and Methods: Seventy-Five (75) patients were included in this study proved infected with Covid 19 by PCR and Chest CT scan investigations. They were admitted to AL-Shefaa Hospital, Ramadi city, Anbar Governorate ,Iraq. Blood specimen was taken from each patient, part of the specimen was used soon for CBC to reveal differential leukocyte count while the other part of the blood specimen was employed for serum pooling. Pooled serum was kept frozen to be used for serological investigation for total IgE and IL-5 using ELISA kit for each. Data was analyzed and plotted using SPSS. Results: Males infected with Covid19 were more than females and majority of patients were between 45 and 59 years of age higher mean values for IgE, IL5 and eosinophil count, patients with severe infection had higher values of IL5 and negative correlations between age and IL5 and IgE. Conclusion: In spite of low eosinophil counts were found in the blood of studied patients, high values of IgE and Il-5 were found in sera of Covid 19 patients , this reflects type 2 T helper reaction particularly type 1 hypersensitivity reaction accompanied with Covid 19 viral infections. Males within age group (45 and 59) constituted the majority of patients with severe Covid 19 infection, and low oesinophil counts. In the same time, high serum IgE titers and high serum IL5 values were linked with infection severity.

Keywords: Allergy, IgE, COvid19, Infection and allergy.

1. Introduction

The outbreak of COVID19 is a worldwide emergency, as its rapid spread and high mortality rate has caused severe disruptions. The number of people infected with severe acute respiratory syndrome (COVID-19) is rapidly increased Worldwide.

Patients with COVID-19 can develop pneumonia, severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure 1. Covid19 virus is transmittable between humans and has caused pandemic Worldwide. The number of death tolls continues to rise and a large number of countries have been forced to do social distancing and lockdown. Epidemiological studies showed that elder patients were more susceptible to severe diseases, while children tend to have milder symptoms 2. Regarding the severity of COVID-19, there is a growing interest in the relationship between the severity of disease and gender. Although the Chinese series showed equal number of cases between males and females, the data suggested that men suffered more than women from severe disease and died 3,4,5. Adverse outcomes of COVID-19 were associated with comorbidities, including hypertension, cardiovascular disease, and lung disease6. Patients with severe infection showed lymphopenia, particularly the reduction in peripheral blood T cells and increased plasma concentrations of pro-inflammatory cytokines7,8. One of the most important components of immune hypersensitivity is IgE , which is also involved in allergies, which comprise the hyper-reactivity of the immune system to a variety of factors. People with allergies have immune systems that overreact to seemingly harmless substances in their habitat. IgE activity releases heparin, histamine, and some other mediators. These substances also cause systemic reactions, especially in the respiratory tract, causing bronchoconstriction, which is somewhat similar to the respiratory distress observed in COVID-19 9. Since respiratory viral infections can exacerbate asthma10,11,12.

In particular, it has been reported that blood eosinopenia was observed in more than half of acute COVID-19 patients, both in severe and less severe cases. Normalization of eosinophil counts showed improvement in clinical status in a number of other cases15. During the second and third

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phases of severe COVID-19 infections, eosinophils may participate in a maladaptive immune response and directly contribute to immunopathology in patients . Eosinophils' expansion and activation are stimulated by Type 2 cytokines, especially IL-5. In severe COVID-19 patients, the blockade of eosinophils' activation might contrast harmful immunity16.

Patients and Methods: Seventy Five (75) adult patients from both genders were included in this study who were admitted to Al-Shefaa Hospital , Ramadi City, Anbar Governorate ,Iraq. These patients were examined by senior physicians and their infection with Covid19 was proved and documented with PCR, Chest CT scan and full history information taken from patients or their relatives regarding complaining symptoms and its duration and then fully examined in respiratory Wards and all vital parameters listed in receiving and follow up charts. Exclusion criteria, patients with a history of bronchial asthma and allergy were excluded from this study. A written Consent was taken from patients or their attendants following Ethical approval for research. Infected Patients were classified according to classification guidelines into moderate, severe and life-threatening infections .Truly , mild cases were not included in this study because this group of patients refusing admission to hospital because of mild symptoms and normal oxygen saturation .

Two blood specimens were taken from each patient, part of the specimen was transferred in citrated tube for CBC to reveal leukocyte differential count using Kimmato X 5 Differential System (Germany). The other part of the blood specimen was transferred in plan tube (without anticoagulant) and employed for serum pooling. Pooled serum was kept frozen at (-20 C) to be used for serological investigation for total IgE using IgE Kit (Demeditec / Germany) and IL-5 using ELISA kit manufactured by Shangha Yehua China. The Elisa reader used in this study was (BioTek, USA). Data were analyzed using SPSS.

2. Results

1-Gender and Age of patients:

Male patients were more than females in this study's results for the gender distribution 49 (65.3%) & 26 (34.7%) for each, respectively (Table 1). The age distribution of the studied participants revealed that patients under 44 years old were 25 (33.3%), those between 45 and 59 were greater than other age groups at 32 (42.7%), and those beyond 60 years old were 18 (24%) (Table 2, Fig-1).

Table-1: Distribution of Patients according to the Gender

Gender	Frequency	%
F	26	33.3
M	49	65.3
Total	75	100

2: Distribution of patients according to their Age

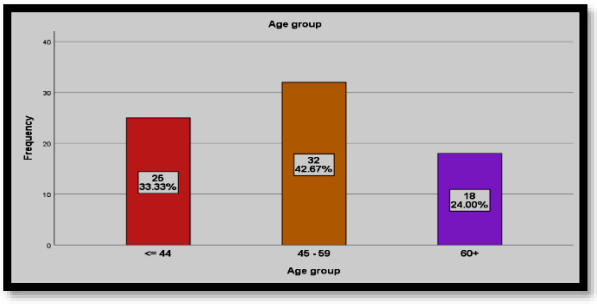

Figure 1: Age distribution of Covid19 patients

2-Severity of COVID19 infection in patients:

In this study, there were thirty-eight patients (38) who had severe covid 19 infection at Respiratory Care Unit, while 21 (28%) had mild infections. The remaining 16 (21.33%) were identified as having a life-threatening ill (Fig-2A).

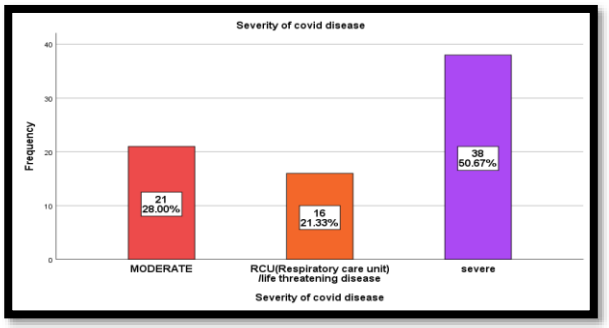

Figure 2-A: Severity of Covid19 infection

Males scored higher than females on all of the mentioned severity scales. The overall percentage of male patients with severe illness was 22 (29.3%), whereas the percentage of female patients with severe illness was 16 (21%) and the percentage of patients with life-threatening illness was 3 (4%). Male patients 13 (17.3%) resembled the majority of patients admitted to the RCU with life-threatening infections, and female patients ratio 14(18.7%) constitued the majority of patients with mild infections Fig-2-B.

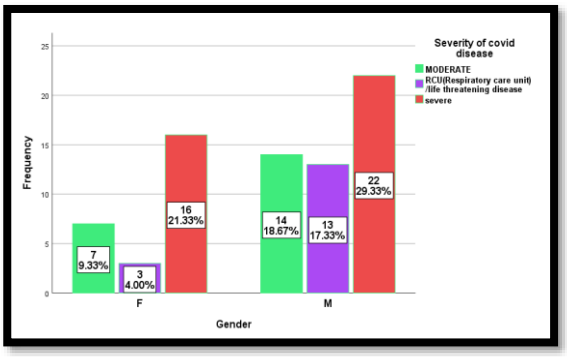

Figure 2-B: Severity of Covid19 disease and gender

2-A: Severity of Covid19 infection and Age of patients:

Patients between the ages of 45 and 59 represent the higher number of cases who were admitted to the RCU with severe infections (17.7%) and 7 (9.3%) life-threatening illnesses, while those

below the ages of 44 and above 60 represented the smaller number of cases, 5 (6.7%) and 4 (5.3%) correspondingly. There were 21 individuals (28.3%) with moderately severe infections, including 8 cases of people below 44 years old were (10.7%), 8 cases of people between 45 and 59 (10.7%), and only 5 patients beyond 60 (6.7%). In contrast, patients displayed greater mean values of IL-5, IgE, and eosinophils, with respective values of 47.41 STD 87.386, 120.96 STD 179.534, and 9.86%. Fig.-3.

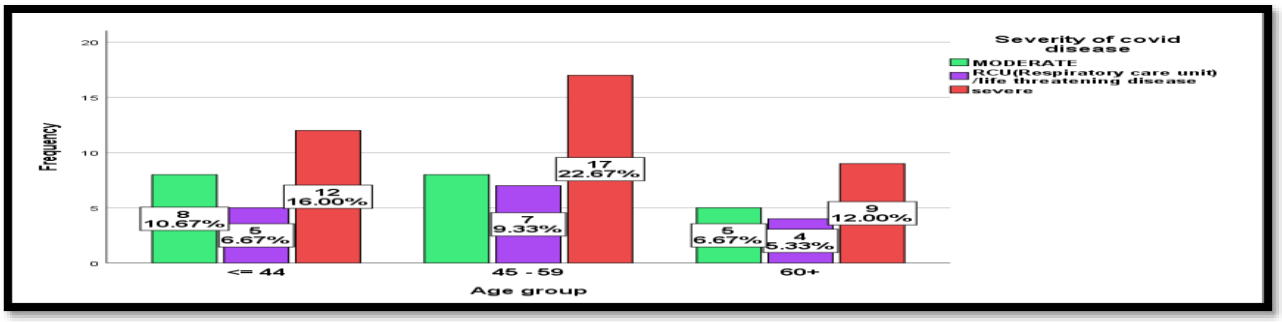

Figure 3: Severity of Covid 19 in patients according to the age

3-Parameters in patients with Covid 19 infections regarding severity

Patients with moderate COVID 19 diseases had mean IgE, IL-5, and oesinophil percentage values higher than those of other patients (308.95 STD ±256.869, 180 STD ±33.662, and 9.86 ±STD ±2.546, respectively). IL-5 mean values were higher in patients with severe Covid infection (19, 59.45 STD ±119.386)(Table-5).

Table 5: Parameters in patients regarding severity and age.

Severity of COVID-19 disease		N	Min.	Maxi.	Mean	Std.±
Moderate	Age	21	33	72	48.67	10.956
	IL5	21	20	180	37.43	33.662
	IgE	21	90	980	308.95	256.869
	Esinophil /L	21	.030	.940	.20405	.253632
	Esinophils %	21	.52	9.86	1.9300	2.54620
	Valid N (listwise)	21				
RCU	Age	16	31	73	50.12	11.442
	IL5	16	15	80	31.94	15.563
	IgE	16	10	60	26.88	15.279
	Esinophil /L	16	.000	.020	.00938	.006801
	Esinophils %	16	.01	.42	.1056	.12868
	Valid N (listwise)	16				
severe	Age	38	33	68	50.63	9.477
	IL5	38	20	750	59.45	119.386
	IgE	38	10	98	56.68	23.980
	Esinophil /L	38	.000	.120	.01789	.019053
	Esinophils %	38	.00	.41	.1800	.14298
	Valid N (listwise)	38				

E-Correlation between IgE, IL-5 and age of patients.

Negative correlation was found between age of patients and IL-5 and IgE (r=-032) (r=-050) for each respectively (Table-6A &B).

Table 6-A: Correlation between age and IL5 in covid19 patients.

Correlations			
		Age	**IL5**
Age	Pearson Correlation	1	-.032
	Sig. (2-tailed)		.785
	N	75	75
IL5	Pearson Correlation	-.032	1
	Sig. (2-tailed)	.785	
	N	75	75

Table 6-B: Correlations between age of patients and IgE

Correlations		IgE	Age
IgE	Pearson Correlation	1	-.050
	Sig. (2-tailed)		.669
	N	75	75
Age	Pearson Correlation	-.050	1
	Sig. (2-tailed)	.669	
	N	75	75

F-Mean values of Il-5 and Age of patients

Regarding the age of patients, patients were showing high mean value of Il-5 in those below 44 years of age 58.64(SD 144.315) and the lowest mean value of IL-5 was in patients above 60 years old 49.83(SD 47.390) . While the mean value of IL-5 in patients between 45-59 years was 37.28(SD 25.728),(Table-7).

Table 7: IL-5 mean values versus age of Covid19 patients.

Age group		N	Minimum	Maximum	Mean	Std. Deviation
<= 44	IL5	25	15	750	58.64	144.315
	Valid N (listwise)	25				
45 - 59	IL5	32	20	170	37.28	25.728
	Valid N (listwise)	32				
60+	IL5	18	20	180	49.83	47.390
	Valid N (listwise)	18				

G- IL-5 mean values versus age of Covid19 patients.

Higher mean value of IgE was found in patients within age group (45-59) years, 142.44(SD ±231.107) while the mean value of IgE in patients below 44 years was118.12(SD ±154.880) and the lowest mean value of IgE was found in patients above 60 years of age 86.72 (SD± 83.207) (Table-8).

Table 8: IgE versus age of Covid 19 patients.

Age group		N	Minimum	Maximum	Mean	Std. Deviation
<= 44	IgE	25	10	660	118.12	154.880
	Valid N (listwise)	25				
45 - 59	IgE	32	10	980	142.44	231.107
	Valid N (listwise)	32				
60+	IgE	18	20	258	86.72	83.207
	Valid N (listwise)	18				

H-Eosinophil Mean counts regarding age of patients:

The eosinophil mean counts were high in those below 44 years of age , 0.10380 (SD ±0.190839) followed by the mean value of eosinophil counts were 0.07500(SD ±0.216964) in patients above 60 years old. The lowest mean value of Eosinophil count was in age group (45-59) years old patients 0.03656 (SD ±0.057057),(Table-9)

Table 9: Eosinophil mean count relation with Covid 19 patient's age

Age group		N	Minimum	Maximum	Mean	Std. Deviation
<= 44	Esinophil /L	25	.000	.610	.10380	.190839
	Valid N (listwise)	25				
45 - 59	Esinophil /L	32	.000	.310	.03656	.057057
	Valid N (listwise)	32				
60+	Esinophil /L	18	.000	.940	.07500	.216964
	Valid N (listwise)	18				

3. Discussion

In this study, males were infected with COVID19 more than females and majority of patients were between 45 and 59 years of age. This was in agreement with a study that revealed that the mean age of the patients was 47 years and the majority of patients were females 18. In another study, the gender-related incidence has been 50/50 in countries Italy, Scotland, Switzerland, Sweden and Belgium 19. In the same time, the finding of this study revealed that males were infected more than females in Iran, Costa Rica, Thailand, Greece, Pakistan and Mexico 20. This study revealed that the majority of patients with COVID 19 had severe infections, then moderate severity and remaining were identified as having a life-threatening ilness. Patients within the age group (45-59) years resembled the majority of infected patients admitted to the RCU with severe infections.

Other studies revealed that the highest rate of infection was among patients within age group 30-39 years 21 . while the study was done in UK revealed the highest rate of infection was among individuals aged below 80 years particularly individuals aged <30 years 22. In This study, male patients were more infected with severe and life threatening COVID19 infections, this result was disagreed with the findings of the other study done by (Sobotka ,et al 2020)23 who found significant higher infections in females than in males . In the same time ,the finding of this study agreed with another study found that the proportion of severe and critical cases were significantly lower among females than males24. This can be explained by the fact that female immune status is better than the males due to female hormones like estrogen and progesterone.

The female-to-male differences were age dependent, , in which females have higher susceptibility but lower severity and fatality.25

The patients displayed higher mean values for IgE, IL5 and eosinophils count ,patients with moderate

severity of infection had high mean values of IL5 and IgE while those with severe infection had high level of IL5. Negative correlation was found between the age of patients and IL5 . COVID-19 patients with eosinopenia may progress to critical disease and have a significantly higher chance of mortality this can be explained by oesinopenia correlates with biomarkers of coagulation disorder and those of tissue damage in kidney, liver, and other tissues.26

In another study, eosinophil counts significantly undergo change in the early stages of the COVID-19 and were more sensitive than lymphocytes in terms of disease diagnosis and cured patients underwent a dynamic recovery process of eosinophils, while peripheral blood eosinophils were dramatically reduced in diseased patients27. Patients with low eosinophil counts at admission were more likely to have fever, fatigue, and shortness of breath, with more lesions in chest CT and radiographic aggravation, and longer length of hospital stay and course of disease than those with normal eosinophil counts. Thus Peripheral blood eosinophil counts may be an effective and efficient indicator in diagnosis, Evaluation, and prognosis monitoring of COVID-19 patients 28.

Absolute eosinophil count on admission is a valid predictive marker for ICU transfer among elderly COVID-19 patients from general isolation wards and, therefore, can help case triage and optimize ICU utilization, especially for health care facilities with limited ICU capacity[29].The Eosinophil percent in patients with COVID-19 who required hospitalization had an independent prognostic value for all-cause mortality and a milder course[30]. The severity of Covid disease in this study consisted with low eosinophils count , high IL5 and low IgE levels. Eosinopenia was not found in mild disease, but was present in 52.8%, 70% and 44.4% of patients with moderate, severe and critical illness respectively in those older than 40 years of age[31]. There was a significantly higher ICU transfer rate in the eosinopenia group in those higher than 65 years of age than in the non-eosinopenia group [29]. The percentage and absolute number of eosinophils are decreased. In one study conducted , eosinopenia was found more often in patients with severe COVID-19 when compared with the influenza patients in those over 50 years of age [32]. Eosinopenia on admission conferred a higher risk of severe disease (requiring ICU/RICU care), but was not associated with increased mortality [33]. The maximal concentrations of IL-5 and other cytokines were significantly higher among the diseased patients but did not significantly differ between those with mild/moderate and severe symptoms[34]. The levels of serum SP-IgE (protein-specific IgE) and NP-IgE (nucleocapsid protein-specific IgE) were significantly higher in severe cases, and were correlated with the total lung severity scores (TLSS) and the PaO_2/FiO_2 ratio[35]. So we can justify severity of COVID-19 in some patients due to production of elevated levels of cytokines during the clinical course of the disease. In the same time ,these patients showed a pattern of Th1 activation, also they showed a Type 2 immune response which characterized by an increase of IL-5, IL-13, eotaxin-2, immunoglobulin E (IgE), and eosinophils. Type 2 biomarkers remain elevated in patients with severe COVID-19 and correlate with the worst course of the disease [17,33,34,35].

4. Conclusion

In spite of low eosinophil counts were found in the blood of studied patients , high values of IgE and Il-5 were found in sera of Covid 19 patients , this reflects type 2 Thelper reaction particularly type1hypersensitivity reaction accompanied with Covid 19 viral infections.

Males within age group (45 and 59) constituted the majority of patients with severe Covid 19 infection, and low oesinophil counts . In the same time , high serum IgE titers and high serum IL5 values were linked with infection severity , patients who were admitted with low eosinophil counts at the time of infection had more severe symptoms, radiological insult, and they were transferred to an Intensive Care Unit.

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