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The occurrence of cytokine storm syndrome among ICU patients with covid-19 in Basrah city, southern of Iraq: Does Tocilizumab affect the outcome?

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Abstract

Cytokine release syndrome or cytokine storm is a potentially life-threatening condition that results from the pathologic over-activation of T cells, leading to hypersecretion of cytokines. COVID-19 patients showed increased serum levels of proinflammatory cytokines such as IL-6 and the evidence shows that cytokine storm is directly related to the severity of the disease process. Interleukin-6 receptor antagonist which is known as Tocilizumab was issued by the FDA for emergency treatment of COVID-19 with cytokine storm. A cross sectional observational study hold in Basrah governorate aims to assess the prevalence and the characteristics of cytokine storm syndrome among patients with COVID-19 at intensive care unit in addition to the evaluation of the role of tocilizumab in the management of this syndrome. The research includes 206 hospitalized ICU patients with clinical, radiological and laboratory diagnosis of COVID 19. The results of this study show that (78%) of ICU admissions have developed cytokine storm and noticed that the recovery was higher among those with no cytokine storm and the duration of hospitalization became longer and exceed ten days in patient with cytokine storm. The more sever desaturation and the higher degree of lung involvement associated with increased incidence of cytokine storm. In addition, the results showed higher percentage of storm among those with chronic medical illnesses and comorbidities, but there was no significant difference between male and female ,however in regard to the age, the younger age group appear to be more vulnerable for the development of cytokine storm. This study also highlights on the use of tocilizumab which significantly increase the recovery and reduce the death.

Introduction

Cytokine release syndrome or cytokine storm is a potentially life-threatening condition that results from the pathologic over-activation of T cells, leading to hypersecretion of cytokines by T cells and other immune cell types (Iyer RK et al. 2018). This syndrome is usually seen in the context of rheumatological diseases; however, it can be seen in patients with severe infection. It results from an excess of proinflammatory and inadequate anti-inflammatory stimuli. Some of the proinflammatory stimuli include foreign antigens, cytokines such as interleukin (IL)-1 β , IL-2, IL-6, IL-7, IL-12, IL-18, tumour necrosis factor (TNF)- α , interferon

(IFN) γ , and granulocyte colony-stimulating factor (GCSF) (Canna SW et al. 2012). Cytokine release syndrome is characterized by unremitting fever and multiorgan involvement, including acute respiratory distress syndrome (ARDS) and acute cardiac and renal injury. Laboratory abnormalities include cytopenia, increased ferritin, D-dimer, and increased serum levels of proinflammatory cytokines (Iyer RK et al. 2018).

At the end of 2019, a novel coronavirus started as an emerging pathogen for humans and resulted in a pandemic. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the virus causing coronavirus disease 2019 (COVID-19) (Zhu N et al. 2019). Evidence gathered to date shows that cytokine storm is directly related to the severity of the disease process and the laboratory analysis of confirmed COVID-19 patients showed leukopenia and increased serum levels of proinflammatory cytokines such as IL-2, IL-6, IL-7, TNF α , IFN γ , and GCSF, suggesting a possible mechanism for tissue injury (Mehta P et al. 2020) A retrospective multicentre study from Wuhan, China of COVID-19 patients showed statistically significant increased mortality in patients with elevated ferritin (>1200 ng/mL) and elevated IL-6 levels (Ruan Q et al. 2020).

IL-6 is a pleiotropic proinflammatory cytokine produced by various cell types, including lymphocytes, monocytes, and fibroblasts. SARS-CoV-2 infection induces a dose-dependent production of IL-6 from bronchial epithelial cells (Rizk JG et al. 2020). Tocilizumab is an interleukin-6 receptor antagonist; was issued an emergency use authorization and approved by the FDA (food and drug administration) on June 24, 2021 for hospitalized adults and paediatric patients (aged 2 years and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation and the Infectious Disease Society of America guidelines recommend tocilizumab for hospitalized adults with COVID-19 who have elevated markers of systemic inflammation. (Bhimraj A et al. 2021). Furthermore, the National institute of health (NIH) guidelines recommend use of tocilizumab (single IV dose of 8 mg/kg, up to 800 mg) in combination with dexamethasone in recently hospitalized patients who are exhibiting rapid respiratory decompensation caused by COVID-19. (NIH guidelines 2021).

Objectives

This study aims to assess the prevalence and the characteristics of cytokine storm syndrome among patients with COVID-19 at intensive care unit in addition to the evaluation of the role of tocilizumab in the management of this syndrome.

Methods

A cross sectional observational study hold in Basrah governorate at the south of Iraq, Basra teaching hospital which is a specialized center for dealing with COVID 19 patients, and the data collected from 1st of July 2020 to 1st of January 2021. the study includes 206 hospitalized ICU patients with clinical, radiological and laboratory diagnosis of COVID 19. The data were collected from the medical records in intensive care units. The variables used in the study includes: The age of patients which further categorized into 3 groups (less than 35 years , from 35 to 65 years , more than 65 years). The Sex (male and female). The comorbidities (diabetes mellitus, hypertension, cerebrovascular disease, ischemic heart diseases, heart failure, atrial fibrillation, chronic kidney disease, bronchial asthma, or COPD, hemoglobinopathies, malignancy, and immunocompromised patients) and plotted as absent if the patient has no

comorbidities or present if the patient has any. The degree of lung involvement from the chest CT (below 50% and higher than 50%). The oxygen saturation which categorized into (below 70% , from 70%-90%). The presence cytokine storm or release syndrome which plotted as present or absent (through clinical and biochemical assessment which includes elevated interleukin-6 levels and serum ferritin). The outcome of the patient was assessed in this study and categorized as (Died) due to respiratory failure or other COVID-19 related complication, or (Recovered) and this was assessed clinically through the improvement of the O2 saturation and biochemically through the decline of inflammatory markers and hospital discharge). The duration of hospitalization which was either short (less than 10 days) or long hospital staying (more than 10 days) and finally the use of tocilizumab(Actemera) during the treatment course which was either used or not.

All patients involved in this study have received the COVID-19 protocol which includes the steroids, the antiviral drug, remdesivir and antibiotics in certain situation with supplemental oxygen in addition to other supportive therapy. The statistical analysis was done by using SPSS (Statistical package for the social sciences) version 20, the categorized variables were expressed by count and percentage, the results was expressed in form of tables, the association between the variables was assessed by using Qi square test and the significant threshold was set at a P value less than 0.05.

Results

The total number of patients involved in this study is **(206)**, their characteristics in relation to age, sex, comorbidities, degree of lung involvement and oxygen saturation are summarized in the table (1) below.

Table (1): The characteristics of patients

The Age		The sex		Comorbidities		Lung involvement		O2 saturation	
Mean	SD	Male	Female	Present	Absent	< 50 %	> 50 %	< 70 %	70 % -90 %
58.63	13.16	108	98	188	18	106	100	94	112

From the total number of patients, **(162) (78.6%)** developed cytokine storm, the table (2) below shows the relationship between the outcome of patients (Recovery and discharge home Vs. Death) and the development of cytokine storm, during the course of illness.

Table (2): The association between the outcome and the storm

Storm Vs. outcome		Out come		Total
		Recovery	Death	
Cytokine storm	Yes	118 (72.9 %)	44 (27.1 %)	162
	No	34 (77.2 %)	10 (22.7 %)	44
Total		152	54	206
Statistical numbers		P value : 0.553		

The Table (3) below shoes the duration of hospitalization in relation to the development of cytokine storm.

Table (3): The association between hospitalization days and storm

Storm Vs. hospitalization		Hospitalization		Total
		Short (< 10)	Long (> 10)	
Cytokine storm	Yes	72 (44.4 %)	90 (55.6 %)	162
	No	30 (68.2 %)	14 (31.8 %)	44
Total		102	104	206
Statistical numbers		P value : 0.005		

The relation between the development of cytokine storm and the severity of respiratory disease through the lung involvement and the degree of desaturation as well as with Age, sex, and comorbidities of the patients. The table (4) below show these associations.

Table (4): The association between the development of storm with the severity and patients' characteristics

the severity and patients' characteristics Vs. outcome		Storm		Total
		Not developed	developed	
Saturation	< 70 %	16 (17 %)	78 (83 %)	94
	70 - 90 %	28 (25 %)	85 (75 %)	112
Total		44	162	206
Statistical numbers		P value : 0.164		
Lung involvement	< 50 %	24 (22.6 %)	82 (77.4 %)	106
	> or = 50 %	20 (20 %)	80 (80 %)	100
Total		44	162	206
Statistical numbers		P value : 0.644		
Co-morbidities	Present	37 (19.7 %)	151 (80.3 %)	188
	Absent	7 (38.9 %)	11 (61.1 %)	18
Total		44	162	
Statistical numbers		P value : 0.057		
Sex	Male	24 (22.2 %)	84 (77.8 %)	108
	Female	20 (20.4 %)	78 (79.6 %)	98
Total		44	162	
Statistical numbers		P value : 0.751		
Age / years	< 35	Zero	8 (100 %)	8
	35 – 65	22 (20.4)	86 (79.6 %)	108
	> 65	22 (24.4)	68 (75.6)	90
Total		44	162	206
Statistical numbers		P value : 0.253		

From the total number of patients who developed cytokine storm (162) , one hundred thirty-four patients received (tocilizumab “Actemra”) while twenty-eight patients did not receive it during the course of illness, the table (5) below shows the relationship between the outcome of patients (Recovery and discharge home Vs. Death and the usage of (Tocilizumab).

Table (5): The association between the outcome and the use of Tocilizumab

Tocilizumab Vs. outcome		Out come		Total
		Recovery	Death	
Tocilizumab	Not Used	11 (39.3 %)	17 (60.7 %)	28
	Used	107 (79.9 %)	27 (20.1 %)	134
Total		118	44	162
Statistical numbers		P value : 0.001		

Finally, the association between the outcome and the severity of cytokine storm through the levels of inflammatory markers (Interleukin 6 and serum ferritin) was assess the results are shown in table (6) below .

Table (6) : The Cross tab between the outcome and the severity of the storm

The severity of the storm		Out come		Total
		Death	Recovery	
Interleukin level	Less than 100	3 (4.9 %)	58 (95.1 %)	61
	100 – 1000	22 (32.8 %)	45 (67.2 %)	67
	1000 – 2000	4 (40 %)	6 (60 %)	10
	Higher than 2000	15 (62.5 %)	9 (37.5 %)	24
Total		44	118	162
Statistical numbers		P value : 0.001		
Ferritin level	Less than 1000	13 (15.2 %)	73 (84.8 %)	86
	1000 or higher	31 (40.8 %)	45 (59.2 %)	76
Total		44	118	162
Statistical numbers		P value : 0.001		

Discussion

The study involves (206) hospitalized ICU patients with clinical, radiological and laboratory diagnosis of COVID-19. All patients involved in this study have received the COVID-19 protocol which includes the steroids, the antiviral drug, remdesivir and antibiotics in certain situation with supplemental oxygen in addition to other supportive therapy. The mean age of the patients was 58.63 years (SD=13.16) and (52.42%) of them were males and (47.58%) were females. About (90%) of study population already had pre-existing medical illnesses and comorbidities. As well as approximately half of patients presented with lung involvement above 50% in chest CT. Moreover, in regard to oxygen saturation, (45.63%) of patients their oxygen saturation was below 70% and (54.36%) of them with oxygen saturation from 70% to 90%.

Based on clinical criteria of increasing tachypnea and decreasing oxygen saturation in addition to biochemical tests of elevated level of inflammatory markers for instances serum ferritin and proinflammatory markers as interleukin 6, the occurrence of cytokine storm is recorded in (78%) of patients. According to Bengül G. et al. 2021, they found in a retrospective cohort study of patients admitted to a single institution with COVID-19 pneumonia includes 150 confirmed COVID-19 patients with severe pneumonia and after they become complicated with severe respiratory distress shows hyperferritinemia (72.5%), they were considered to develop cytokine storm or release syndrome.

Many causes of death are associated with covid-19 infection, one of these causes is the cytokine storm syndrome (Yujun Tang et al. 2020). The results of this study showed that the recovery is higher among those with no cytokine storm although this did not significant statically, but what important to highlight is the association between the level of inflammatory marker and the death and the results showed the higher level of interleukin-6 and serum ferritin was associated with higher incidence of death. Many studies showed that severely ill patients tended to have a higher concentration of pro-inflammatory cytokines, especially interleukin (IL) 6, than moderately ill patients in COVID-19 and the high level of cytokines also indicates a poor prognosis in COVID-19. (Chen G. et al. 2020) (Chen L. et al. 2020) (Qin C. et al. 2020) (Tan M. et al. 2020) (Huang C. et al. 2020). Moreover, the duration of hospitalization became longer

and exceeded ten days in patient with cytokine storm and as current evidence, approximately 55% of patient with storm admitted in ICU for more than 10 days in compare with 30% of patient with no storm in whom they hospitalized for longer than 10 days and this difference was statistically significant.

The more sever desaturation and the higher degree of lung involvement associated with increased incidence of cytokine storm although cytokine storm could develop in patients with moderate lung involvement particularly when other risk factors are present for example diabetes mellitus and obesity . In addition, the results showed higher percentage of storm among those with chronic medical illnesses and comorbidities. This result was consistent with a results of meta-analysis and systematic review for cytokine storm and covid-19 which argued that, the inflammatory cytokines, especially circulating interleukins 6, 8, 10, and TNF-alpha levels were significantly elevated among severe and critical cases, as compared to the mild or moderate patients (Rubina M. et al. 2020) Furthermore, there was no significant difference between male and female ,however in regard to the age, the younger age group appear to be more vulnerable for the development of cytokine storm.

This study also highlights on the use of tocilizumab which significantly increase the recovery and reduce the death and as was seen in the results above, the mortality rate in those who used tocilizumab was only 20% in compare with 60% among those who kept on no tocilizumab. These results were similar to The EMPACTA trial that found nonventilated hospitalized patients who received tocilizumab in the first 2 days of ICU admission had a lower risk of progression to mechanical ventilation or death by day 28 compared with those not treated with tocilizumab (Gordon AC. et al. 2021). In addition to their similarity with The RECOVERY trial that assessed 4,116 hospitalized adults with COVID-19 infection who received either tocilizumab (n = 2,022) compared with standard of care (n = 2,094) in the United Kingdom from April 23, 2020, to January 24, 2021, and most patients (82% in both treatment groups) were receiving systemic corticosteroids at randomization. Tocilizumab mortality benefits were clearly seen among those who also received systemic corticosteroids (the recovery trial group 2021). Probably this explained by the dual anti cytokine effect and in the current study, the enrolled patients, all were kept on steroids.

Finally, it is worthy to suggest the early use of remdesivir (moderate COVID-19 and early desaturation) for decreasing the occurrence of storm and this evidence was taken from a study performed in the same centre which declares the positive outcome in regard to the hospital stay and mortality (Ali et al. 2021)

Conclusions and Recommendations

The study revealed that disease severity is linked with cytokine storm that follows the extreme immune response due to the COVID-19 infection. Besides the cytokine storm in the progress of the disease is one of the causes of death.

In patients that show increasing tachypnoea with elevated level of inflammatory markers in particular for those with co-morbidities could be a predictor to admission to ICU and a directive way to start an anti-cytokine treatment (tocilizumab).

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