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Radiological and inflammatory outcome in severe covid-19 patients received tocilizumab versus high dose of methylprednisolone

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Abstract:

Background: Cytokine storm causes ARDS, multiple organ failure and post covid-19 pulmonary sequale so anti-inflammatory drugs as tocilizumab and methylprednisolone are widely used to treat covid-19 patients. **Methods:** prospective observational study on 60 covid-19 patients >18 years old. Diagnosis of covid-19 infection was based on World Health Organization (WHO) criteria and confirmed by nasal and pharyngeal swab for real time reverse transcriptase polymerase chain reaction analysis. 30 hypoxemic covid-19 who received tocilizumab and 30 hypoxemic covid-19 patients who received high dose of methylprednisolone.then Comparison of both groups regarding duration of admission, length of Oxygen need, resolution of CT findings and inflammatory marker levels. **Results:** There was no significant difference (p-value >0.05) between the two treatment protocols as regards CT findings at time of admission and after a month from discharge. On admission, Higher mean of CRP, D-dimer and a lower mean of procalcitonine were noted among the group treated with Tocilizumab protocol while significantly lower mean of ferritin (p-value <0.05) .After one month follow up there was no difference in CRP level between the two groups. Also there was no statistical significant difference between the two groups regarding hospital stay and length of oxygen therapy between the two groups. **Conclusion:** lower ferritin and higher D-Dimer were noted in tocilizumab treated group while no difference in radiological finding or length of hospital stay between the two groups

Keywords: Covid-19, Tocilizumab CT, Methylprednisolone, hospital stay

1. Introduction:

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the new coronavirus associated with severe acute respiratory syndrome 2 (SARS-CoV-2). Corona-viridian comprises a large family,

of which at least seven members are known to cause respiratory diseases in humans

(1). Various treatments have been used in this phase, although only glucocorticoids have been shown to reduce mean hospital stay, ICU admission, and mortality (2). Observational studies suggest that other drugs such as tocilizumab, a humanized monoclonal antibody directed against the receptor for IL-6, reduces mortality and the need for mechanical ventilation (3). There have been an increasing number of reports of patients who experience persistent symptoms and or organ dysfunction after acute covid-19 .data about the incidence ,natural history and etiology of these symptoms are emerging However, these reports have several limitations For example ,there is currently no agreed-upon case definition for persistent symptoms or organ dysfunction after acute COVID-19 .in addition ,most of these reports only included patients who attended post COVID-19 clinic ,and they often lack comparator group (4).

2. Patients and Methods:

Type of the study

Prospective observational randomized study.

Site of the study:

This study conducted in Beni-Suef university hospital, department of Chest diseases.

Date and Period of the Study :

The study conducted from July 2021 to December 2021.

Inclusion Criteria:

- All patients diagnosed with severe or critical Covid-19 pneumonia
- Patients of both genders were included.
- Patients aged >18 years old.

Exclusion Criteria:

- Patients aged <18 years old
- History of Advanced chest disease
- Renal and hepatic severe impairment or failure

Procedure Technique

The study conducted on patients diagnosed to have Covid-19 infection due to acute respiratory syndrome coronavirus 2 (SARS-CoV-2; proven via COVID-19 polymerase chain reaction (PCR) test and confirmed by CT findings .admitted to the chest department in Beni-Suef university hospital of both sexes.

The study included 60 subjects:

-30 hypoxemic covid-19 with a procalcitonin <0.05 received tocilizumab.

tocilizumab alone

-30 hypoxemic covid-19 patients who received high dose of methylprednisolone (2mg/kg)

Comparison of both groups regarding duration of admission, length of Oxygen need, resolution of CT findings , inflammatory marker levels.

All patients included in the study were subjected to the following:

1. **Clinical assessment.**
   - Risk factors (age , sex , comorbidities)
   - Duration of admission.

- Length of oxygen therapy.

2. Investigations:

a. Laboratory:

- CBC,
- CRP, Ferritine, D-dimer (on admission and one month follow-up)
- ALT & AST, urea , creat and procalcitonin

b. Radiological:

High resolution CT chest at admission and one month after discharge (complete resolution , GGO/consolidation or fibrosis)

Data analysis and statistics:

The collected data will be coded-and transferred to the statistical package of social science software program, version 25 (SPSS) to be statistically analysed as follow :

- Description of qualitative variables by frequency and percentage.
- Description of quantitative variables in the form of means and standard deviation (mean ± SD).
- Chi-square (X^2) test was used for comparison for qualitative variables with each other.
- Comparison between quantitative variable was carried by using:
  - Student t test of two independent sample
  - One way ANOVA test (analysis of variance)

*significance level (P) was expressed as following:

-P value <0.001 is highly significant

-P value <0.05 is significant

3. Results:

Table (1): Comparisons of demographic characters in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
Age (years)						
Mean /SD	60.3	10.6	59.7	10.9	0.7	NS
Sex						
Male	16	53.3%	18	60%	0.8	NS
Female	14	46.7%	12	40%		
Smoking						
No	22	73.3%	24	80%	0.7	NS
Yes	8	26.7%	6	20%		
Medical history (Co-morbidities)						
DM	12	40%	18	60%	0.2	NS
HTN	13	43.3%	16	53.3%	0.6	NS
Other*	2	6.6%	0	0%	0.3	NS

*other (stroke, and COPD)

There was no statistical significant difference between treatment protocols as regards age, sex, smoking and co-morbidities. That indicated matching between both groups in these variables.

Table (2): Comparisons of routine labs on admission in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
	Mean	**SD**	**Mean**	**SD**		
Complete blood count						
HB	10.7	1.8	10.8	1.6	0.6	NS
PLT	261.8	96.6	239.3	91.2	0.4	NS
TLC	6.7	2.2	7.4	3.5	0.3	NS
Neutrophil %	77.03	12.8	79.4	11.5	0.4	NS
Neutrophil count	8.7	7.6	12.3	14.4	0.2	NS
Segmented	74.3	12.5	76.7	11.4	0.5	NS
Band	2.7	1.6	2.8	1.2	0.9	NS
Lymphocytes %	14.7	11.8	13.2	9.1	0.6	NS
Lymphocytes count	1.6	2.3	0.96	0.43	0.1	NS
N/L ratio	9.1	6.7	10.6	9.04	0.5	NS
Other investigations						
Procalcitonin	0.84	4.3	0.03	0.03	**<0.001**	**HS**
Creatinine	1.6	1.3	1.1	0.38	**0.04**	**S**
Urea	58.3	40.1	67	30.8	0.4	NS
AST	36.6	17.04	45.4	29.9	0.2	NS
ALT	37.1	18.9	50.1	27.01	0.09	NS

There was a statistical significant a lower mean of procalcitonine and creatinine among group treated with Tocilizumab protocol with p-value <0.05. On the other hand, there was no statistical significant difference with p-value >0.05 as regards other investigations between two protocols.

Table (3): Comparisons of routine investigations on admission in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
	Mean	**SD**	**Mean**	**SD**		
CRP	74.4	47.1	117.8	63.3	**0.004**	**HS**
Ferritin	517.01	353.5	360.5	294.8	0.2	NS
D-dimer	0.84	0.32	2.2	1.02	**<0.001**	**HS**

There was a statistical significant higher mean of CRP, D-dimer among group treated with Tocilizumab protocol with p-value <0.05.

Table (4): Comparisons of routine investigations after one month in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
	Mean	**SD**	**Mean**	**SD**		
CRP	49.5	34.3	37.3	24.6	0.8	NS
Ferritin	327.3	190.9	247.6	98.05	**0.04**	**S**
D-dimer	0.49	0.21	0.79	0.43	**0.001**	**HS**

There was a statistical significant lower mean of ferritin and a higher mean of D-dimer with p-value <0.05 among group treated with a Tocillizumab after one month follow up with no difference in CRP level between two groups

Table (5): Comparisons of routine investigations after one month from discharge in different treatment protocols.

Variables	Before		After		P-value	Sig.
	Mean	SD	Mean	SD		
Methyl-presdnisolone						
CRP	74.4	47.1	49.5	34.3	**<0.001**	**HS**
Ferritin	517.01	353.5	327.3	190.9	**<0.001**	**HS**
D-dimer	0.84	0.32	0.49	0.21	**<0.001**	**HS**
Tocillizumab						
CRP	117.9	63.3	37.3	24.6	**<0.001**	**HS**
Ferritin	630.5	294.8	247.6	98.05	**<0.001**	**HS**
D-dimer	2.2	1	0.79	0.43	**<0.001**	**HS**

There was a statistical significant decrease with p-value >0.001 as regards CRP, ferritin and D-dimer level after a month follow up in each protocols of treatment illustrated by Figures (1:3).

Figure (1)

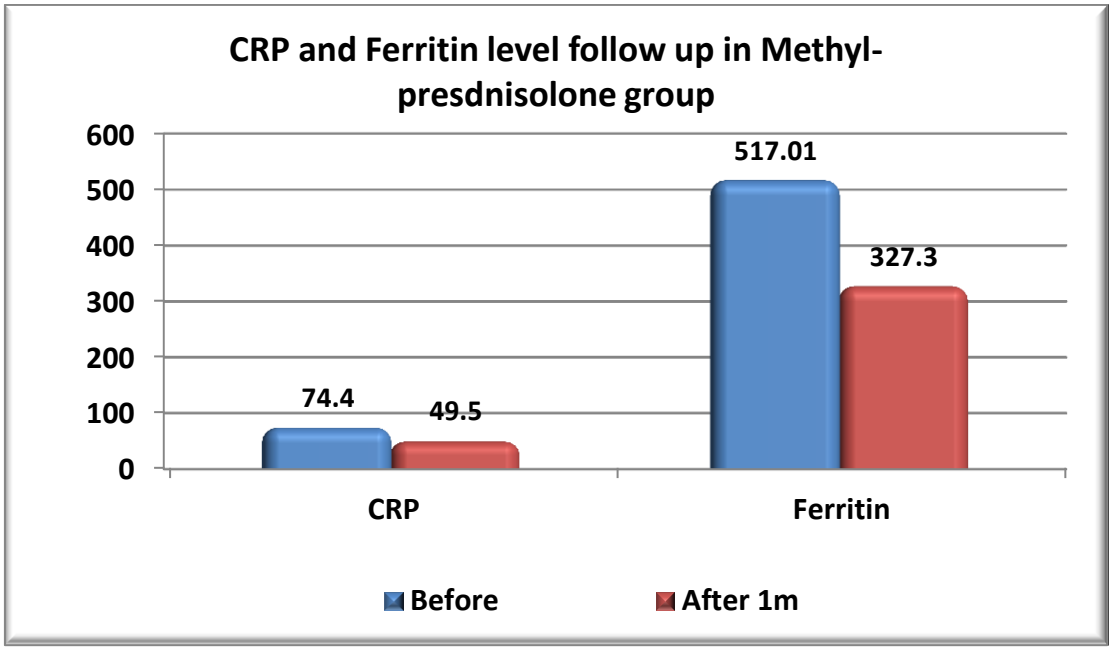

Figure (2)

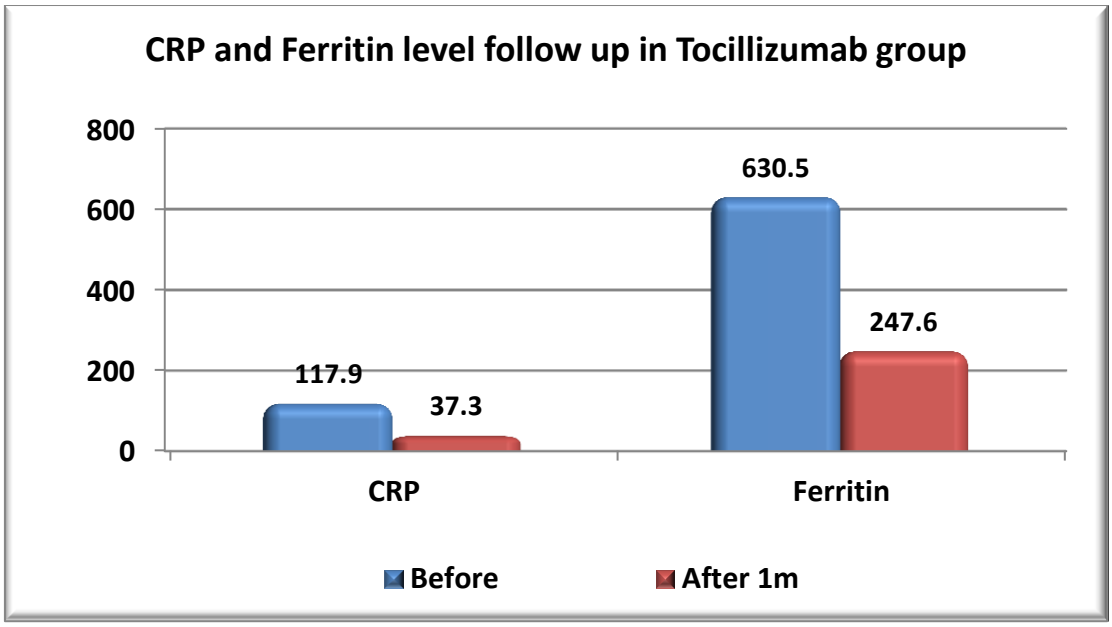

Figure (3)

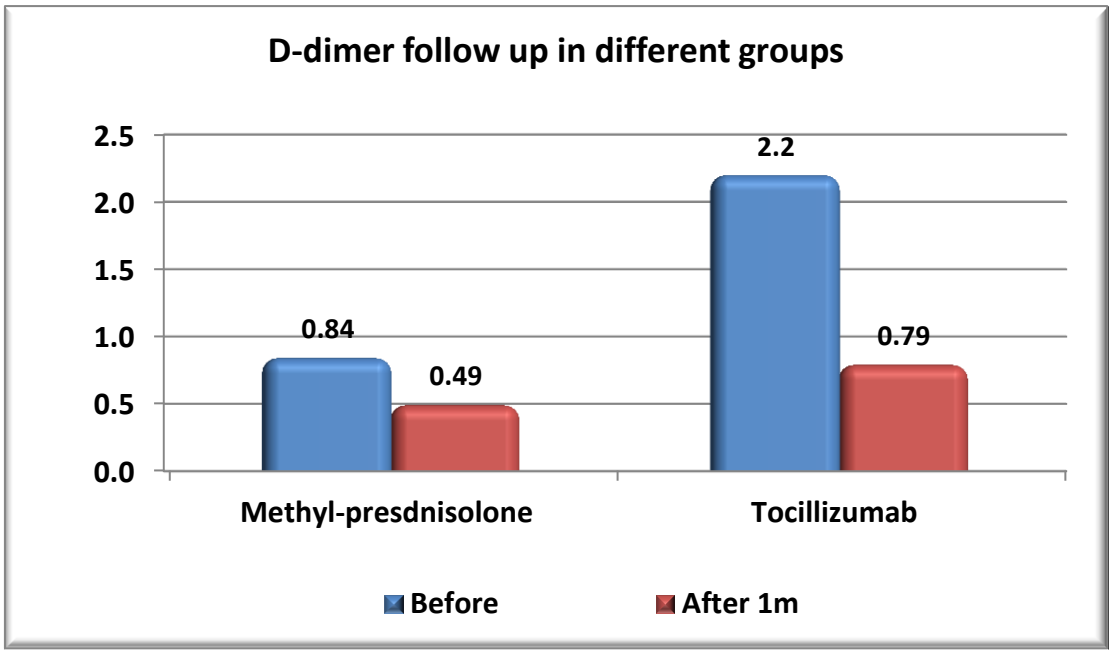

Table (6): Comparisons of patients CT findings in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
	No.	**%**	**No.**	**%**		
CT chest on admission						
Corad 3	4	13.3%	1	3.4%	0.07	NS
Corad 4	18	60%	13	43.3%		
Corad 5	8	26.7%	16	53.3%		
CT chest 1 month from discharge						
Complete resolution	8	26.7%	13	43.3%	0.4	NS
GGO-reticulation	13	43.3%	11	36.7%		
Fibrosis	9	30%	6	20%		

The Table (6) and Figure (4) illustrated that there was no statistical significant difference with p-value >0.05 between two treatment protocols as regards CT findings at time of admission and after a month from discharge

Figure (4)

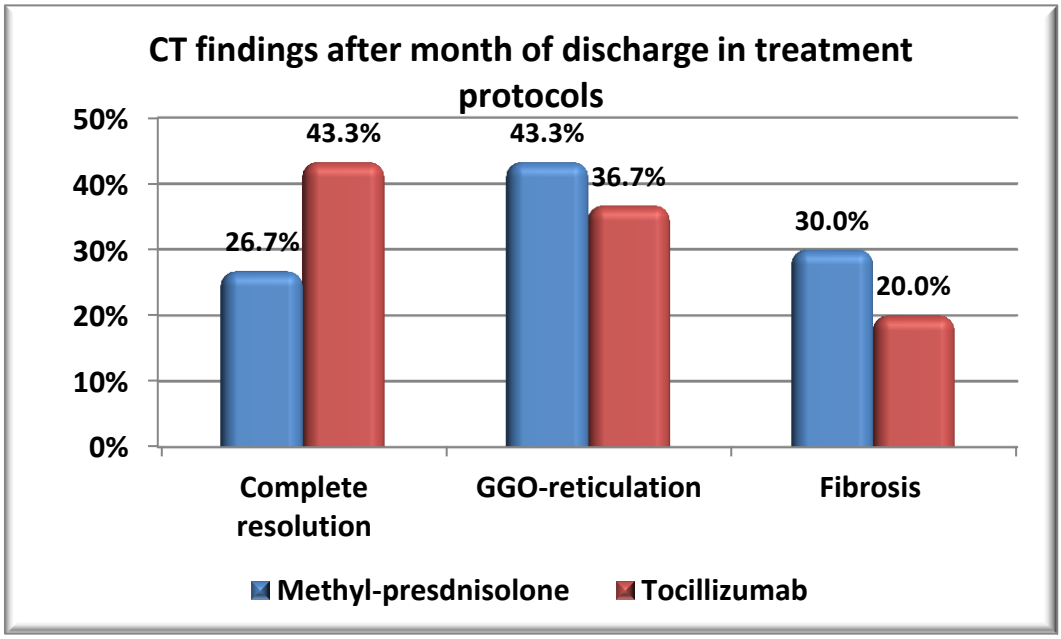

Table (7): Comparisons of Duration of admission and Length of oxygen therapy in different treatment protocols.

Variables	**Methyl-presdnisolone** (N=30)		**Tocillizumab** (N=30)		**P-value**	**Sig.**
	Mean	**SD**	**Mean**	**SD**		
Duration of admission (days)	13.6	6.5	16.1	6.4	0.1	NS
Length of oxygen therapy (days)	22.07	13.3	17.9	7.2	0.1	NS

There was no statistical significant difference in duration of admission and length of oxygen therapy between cases treated wit.

4. Discussion:

SARS-CoV-2 replicates in pulmonary alveolar epithelial cells. Once the virions are released, they will either infect neighbouring cells or be captured and destroyed by macrophages, dendritic cells and neutrophils (5). During this time, damaged epithelial cells produce alarmins, which will lead to the release of pro-inflammatory cytokines, increased permeability of the alveolar vessels and cell recruitment to the site of infection. This will cause the pathological activation of IL-6, IL-1, TNF and other pro-inflammatory cytokines (6) data collected from the COVID Symptom Study suggest that although most people recover from COVID-19 within 2 weeks, approximately 10% of patients might still have symptoms after 3 weeks and some for months. Post-COVID-19 sequelae have been reported to include pulmonary fibrosis; pulmonary and systemic vascular disease; chronic fatigue; and mental disorders, including posttraumatic stress disorder, depression, and anxiety (7)

Several studies have shown a strong correlation between serum IL-6 levels and future respiratory failure (8). Even moderately elevated IL-6 levels above 80 pg/mL have been shown to be sufficient to identify patients infected with COVID-19 at high risk for respiratory failure (9).

Since IL-6 overexpression appears to be associated with severe COVID-19 findings, anti-IL-6 receptor antibodies targeting the host's exacerbated inflammatory immune response may provide a vital approach in preventing cytokine release syndrome (6).

In patients with severe SARS CoV-2 pneumonia and moderate inflammation, immunosuppressive therapies are used due to the pathogenic role of proinflammatory cytokines. Glucocorticoids have been shown to reduce mortality and admission to the ICU (2) & (10). Tocilizumab has been widely used based on observational studies that suggest a reduction in the risk of intubation and/or death (3) and (11) although clinical trials have not showed a lower mortality at 28 days given the discrepancies in the scientific evidence, we decided to analyze in our cohort of patients the clinical evaluation at 30 days according to the immunosuppressive treatment received (12). Glucocorticoids and tocilizumab have been among therapies that have proven a survival benefit in large randomized clinical trials (RCTs) (13). So we compare in this work which of them is more effectiveheir effect seems to be synergic as the benefit for patients treated with tocilizumab was evident only in the glucocorticoids-treated group in the RECOVERY trial (14).

Our prospective observational study conducted on patients diagnosed to have Covid-19 infection due to acute respiratory syndrome coronavirus 2 (SARS-CoV-2); proven via COVID-19 polymerase chain reaction (PCR) test and confirmed by CT findings, admitted to chest department in Beni-Suef university hospital of both sex .The study was conducted on 60 patients, out of which 30 patients were offered Tocilizumab besides the routine treatment and 30 patients were offered high dose (2mg/kg)of methylprednisolone besides the routine treatment for comparing the efficacy of both modalities of treatment regarding hospital stay , Oxygen need , resolution of CT findings and inflammatory marker levels. COVID-19 can occur in any age group (15). Our data showed that the average age of (60,3±10.6) years old in methylprednisolone group and the average age of (59,7,3±10.9) years old in tocilizumab group , however this difference was statistically non-significant (p=0.05). The most commonly reported age group for COVID-19 is 45–60 years (16). A meta-analysis conducted by Yang et al., (17) suggest that age and comorbidities are highly related in

COVID-19 patients. Severe disease is associated with advanced age, male sex, residence in a nursing home, underlying comorbidities (e.g., cardiovascular disease, diabetes, chronic lung disease, hypertension etc.) and higher computed tomography (CT) severity scores (18) and (19).

In the current study, the routine laboratory findings provide important insights on the strong association between the elevated level of CRP, D-dimer, Ferritin with the severity of COVID-19.we found that there was a statistical significant higher mean of CRP, D-dimer and a lower mean of procalcitonine and creatinine at admission among group treated with Tocilizumab protocol (30 hypoxemic covid-19 with a procalcitonin <0.05 received tocilizumabalone)besides the routine treatment with p-value <0.05. On the other hand, there was no statistical significant difference with p-value >0.05 as regards other investigations between two protocols Tocilizumab protocol and methylprednisolone protocol (30 hypoxemic covid-19 patients who received high dose (2mg/kg)of methylprednisolone) besides the routine treatment.

More unfavorable , after using Tocilizumab, the first change in laboratory tests was seen in % lymphocytes, which increased during the first day. CRP dropped sharply one day after Tocilizumab. Two days after Tocilizumab, IL-6 strongly decreased, but ferritin and d-dimer decreased slightly (20). In our study There was no statistical significant difference with p-value >0.05 between two treatment protocols as regards CT findings at time of admission with results CORAD3 (tocilizumab 3.4% vs methylprednisolone 13.3%) , CORAD4 (tocilizumab 43.3% vs methylprednisolone 60%) , CORAD5 (tocilizumab 53.3% vs methylprednisolone 26.7%) .At one month after discharge there was a slight decrease in GGO and fibrosis in the tocillizumab group and a higher number of complete resolution but these values were not statistically significant . GGO (tocilizumab 36.7% vs methylprednisolone 43.3%) , fibrosis (tocilizumab 20% vs methylprednisolone 30%) and complete radiological resolution (tocilizumab 43.3% vs methylprednisolone 26.7%) .

Studies from other viral infections with pulmonary involvement suggest that functional and radiologic impairments persist beyond hospital discharge. In the original SARS-CoV outbreak in 2003, which had 8,000 confirmed cases and a 9% mortality rate (21), reticular

abnormalities were first noticed at 2 weeks when CT abnormalities were most severe (22).While the GGOs and consolidations slowly improved, fibrosis was seen in 50 to 60% of patients on follow-up scans after discharge. Fibrosis was more common in the elderly, those with a longer length of stay, those with a higher lactate dehydrogenase (LDH) in the acute phase (23). A recent meta-analysis in preprint of 60 studies looking at follow-up imaging after inpatient admissions for SARS-CoV, SARS-CoV-2, MERS or influenza pneumonia found inflammatory changes (ground glass opacity or consolidation) in 56% of scans and "fibrosis" (reticulation, lung architectural distortion, interlobular septal thickening, traction bronchiectasis, or honeycombing) in 40% (24).

Our prospective observational study show that there was a statistical significant decrease with p-value less than 0.001 as regards CRP, ferritin and D-dimer level after a month follow up in each protocols of treatment. A retrospective observational cohort study involving 142 patients with severe COVID-19 pneumonia and moderate inflammation divided into three treatment groups (pulses of methylprednisolone alone [group I], tocilizumab alone [group II] and methylprednisolone plus tocilizumab [group III]). The aim was to assess intergroup differences in the clinical course with a 60-day follow-up and related analytical factors, the study show that Tocilizumab seems to be not associated with better clinical outcomes and should be reserved for clinical trial scenario, since its widespread use may result in higher rate of ICU admission and longer mean hospital stay without differences in mortality rate and potentially adverse events (25).

While a cohort study including 35 propensity score-matched couples of patients with and without corticosteroids (methylprednisolone, 40–50 mg/day) found no significant differences in outcomes (10) and (26). It should be noted that corticosteroids in our study were used at higher doses in most patients, and were started only once the patients had developed a hyperinflammatory state based on clinical and laboratory data.

The efficacy of MPP and dexamethasone was compared in patients with severe COVID-19. Pinzon (27) examined the inflammatory biomarkers and clinical outcomes of 105 patients who received MPP (250 to 500 mg daily for three days followed by prednisolone 50 mg daily for 14 days) versus 111 patients who were treated by dexamethasone (6 mg daily for 7 to 10 days). At the end of

study, serum levels of inflammatory biomarkers, requirement for ICU admission and recovery time were significantly reduced following treatment with MPP compared with dexamethasone.

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