Retrospective study of efficiency of Corticosteroids and Anticoagulants in Management of COVID 19 Patients with different comorbidities

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Abstract

Background: Human coronaviruses are one of the principle causes of upper respiratory infections, which were defined for the first time in 1962. A systemic inflammation that includes cytokine storm and thrombosis formation is the underlying cause of severe cases of COVID-19 patients that lead to multi-organ dysfunction**.Aim:** To assess the beneficial effect of corticosteroids and anticoagulants in treatment of COVID-19 in diabetic and hypertensive patients who were associated with other co-morbidities of chronic diseases or not, in addition to determination of the role of the anti-inflammatory markers in the prognosis of the disease and their correlation with CT imaging. **Patients and methods:** The study was conducted in the chest Department, Kobry El Kobba Military Hospital on 110 patients who were diagnosed with moderate and severe COVID-19.
Results: Treatment with corticosteroids and anticoagulants decreased significantly the duration of hospital admission, need for oxygen in the survived treated patients compared to non-survived patients in addition to decline in the inflammatory markers (CRP, IL-6, D-dimer) especially Il6 which was the most prognostic test in all groups regardless the associated morbidity. This was correlated with CT imaging scoring. **Conclusion:** The early administration of corticosteroids and anticoagulants to severe COVID-19 pneumonic cases reduced the negative impacts in all group of patients regardless the associated morbidity or chronic diseases. Mortality was mainly increased in patients with older age, co-morbidity, worse CT findings, a higher oxygen therapy requirement, and a longer duration of hospitalization. IL-6 level after treatment has the best prognostic accuracy, followed by D-dimer level.
Key Words: Corticosteroids, Anticoagulants, COVID 19.

INTRODUCTION

Human coronaviruses are one of the principle causes of upper respiratory infection, which was defined for the first time in 1962. In 2002–2004, outbreaks of coronaviruses were known as severe acute respiratory syndrome (SARS) and in 2013 as middle east respiratory syndrome (MERS) [**1**]. COVID-19 is a novel strain of human coronavirus, known as SARS coronavirus 2 **[2]**, according to the International Committee on Taxonomy of Viruses. WHO announced on March 11, 2020, that COVID-19 is a 'public-health emergency of international concern **[3].**

Systemic inflammation that includes cytokine storms and thrombosis formation is the underlying cause of severe cases of COVID-19 patients that lead to multi-organ dysfunction **[4]**.

Corticosteroids are potent anti-inflammatory agents used in the treatment of patients with COVID-19, which is an inhibitor of cytokine storms that resulted in a decrease in mortality and morbidity of the disease. It is claimed that early administration of glucocorticoids in

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patients could prevent the immune system mechanisms leading to an increase in viral load with more adverse events **[5]**. However, the short-term use of low-dose corticosteroid shows decrease in mortality in cases with Adult Respiratory Distress Syndrome ARDS **[6]**. Prophylactic anticoagulants should be administrated to all patients, especially severe and critical ones, as soon as they are hospitalized, except if contraindicated (active bleeding and platelet counts $<25 \times 10^9$/L) due to the increased risk of thrombosis in patients with COVID-19 [**7**].

Also hospitalized patients with COVID-19 are more prone for thromboembolic events apart from their innate hypercoagulable state as respiratory distress, intubation, general weakness and sedation that led to more complication. Moreover, many infected patients with SARS-CoV-2 have other comorbidities, that are risk factors for thromboembolism as advanced age, cancer, cardiovascular diseases, and obesity. Mortality has also been found to be higher in critically ill patients infected with COVID due to high sepsis-induced coagulopathy (SIC) scores or elevated D-dimers which necessitates thromboprophylaxis [**8**].

OBJECTIVES

This research aimed to assess the beneficial effects of corticosteroids and anticoagulants in COVID-19 in diabetic and hypertensive patients with and without other chronic diseases, in addition to the role of the anti-inflammatory markers in the prognosis of the disease and their correlation with CT imaging.

PATIENTS AND METHODS

This was retrospective cohort research that involved 110 inpatients with COVID infection in the chest department of Kobri El Koba military hospital, diagnosed as moderate and severe patients. The study had an ethical approval number 43 and lasted for 4 months, 1-10-2021 to 31-2-2022. Patients were divided into 6 groups who had diabetes and hypertension with or without associated comorbidities. Cases were categorized into the following 6 groups: Group 1: 26 cases with no comorbid diseases; Group 2: 19 patients with diabetes mellitus (DM) divided into 2 subgroups: those with DM only were 13 patients and those with DM with other chronic diseases were 6 patients. Group 3: 21 patients with hypertension (HTN) divided into 2 subgroups: HTN only: 13 patients and HTN with other chronic diseases: 8 patients; Group 4: 20 patients with DM & HTN only; Group 5: 13 patients with DM & HTN in addition to other chronic diseases; and Group 6: 11 patients with chronic diseases other than HTN & DM.

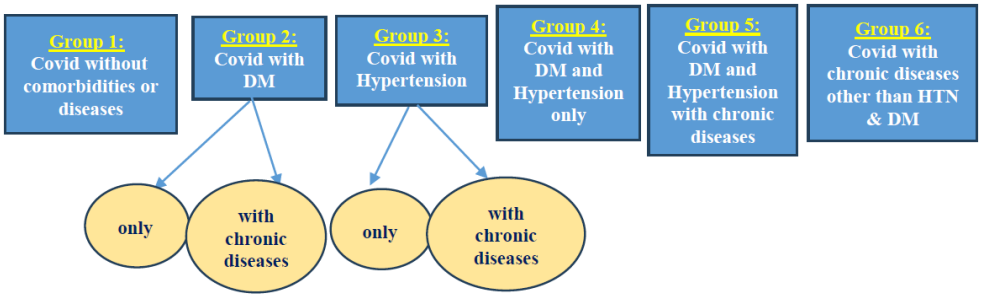

Fig. 1: Classification of patients with covid 19 into different groups

Inclusion criteria: Patient with an age >18 years; gender: male and female; and patient diagnosed with moderate or severe COVID-19.

Exclusion criteria: patients <18 years old, non-compliant patients with the regimen, A pregnant female and a patient diagnosed with mild COVID-19

Methods

Data collection: The patient-informed consent was obtained then clinical data, data regarding pharmacotherapy, examinations, and the clinical progress of cases were gathered using a data collection sheet.

The main data collected were as follows:

- Medical history of the patient, including:
  a) Personal history including demographic characteristics e.g. age and gender.
  b) Present medical history including symptoms of COVID-19.
  c) Past medical history and co- morbidities.
- Clinical examination of patients.
- Laboratory investigation results on admission and follow up laboratory results including:
  a) Complete blood count (on admission and after end of treatment).
  b) Ferritin (on admission)
- Inflammatory markers.
  a) CRP (Normal**:** Less than 0.9 mg/L) (on admission and after end of treatment).
  b) IL-6 (normal range 0–16.4 pg/ml) (on admission and after end of treatment) as indicator for cytokine storm can use as screening and for follow up
  c) D-Dimer (A normal D-dimer range was defined as <500 ng/mL)**)** (on admission and after end of treatment). As screening for clotting formation even DIC or thrombosis
- Radiological investigation: CT- scan (on admission and after end of treatment)

- Full data on the pharmacotherapy during the patient's ICU stay including.
- Drug name (scientific and trade), dose, regimen, route of administration,
- Special precautions during drugs administration, relation to food if present, Date started, date ended and reasons for discontinuation if any.

Drugs administrated:

All patients received

I. Dexamethasone 4 mg intravenous every 12 hours.

II. Enoxaparin sodium (Clexane) 80 mg SC every 24 hours.

III. Antibiotics

a. For inpatients: azithromycin 500 mg oral every 24 hours for 5 days then levofloxacin 750 mg oral every 24 hours for 5 days.

b. For ICU patients: ceftriaxone 1 gram IV every 12 hours for 7 days then levofloxacin 500 mg IV for 5 days.

IV. Paracetamol 500 mg oral for inpatient every 8 hours and 1 gram IV for ICU patients every 8 hours.

However, the duration of therapy was constructed according to the direction of the physician.

Diabetic patients were treated with insulin SC according to sliding scale in addition to receiving to vitamin c and Zinc.

Also, there is no administration for antiviral or hydroxychloroquine for any patients.

Oxygen saturation classification:

The severity of COVID-19 in hospitalized patients infected with COVID-19 had been classified according to the lowest obtained oxygen saturation during hospital course (from time of admission to time of discharge) into:

a) Oxygen saturation >93% don't need oxygen therapy.

b) Oxygen saturation <93% was treated by oxygen without the need for invasive mechanical ventilation.

c) Respiratory failure required invasive mechanical ventilation.

Computerized tomography (CT) assessment:

I. The severity of the disease was assessed using CT as defined in Fleischner Society Glossary of terms for Thoracic Imaging **(9)** as:

a) Predominant pattern of lesions: consolidation, ground-glass opacification (GGO), or mixed consolidation and GGO.

b) Dominant distribution of lesions: central, peripheral, diffuse, or peri- broncho vascular.

c) Shape of the lesions: elongated, round, confluent or wedged.

d) Additional findings: , interlobular septal thickening, crazy paving pattern, reverse-halo sign, air bronchogram sign, linear opacities, tree in bud, lymphadenopathy, pleural effusion, pericardial effusion, adjacent pleural thickening and pulmonary emphysema.

II. Scoring system to detect the extension of lung lesions:

Each of the five lobes of lungs scored visually from 0 to 5 (where 0 = no involvement; 1if < 5% involvement; 2 if 5–25% involvement; 3 if 26–49% involvement; 4 if 50–75% involvement; 5 if > 75% involvement). Then, the total chest CT score was calculated by the sum of each lobe's scores, ranging from 0 to 25 **(10).**

Table (1): The severity of the five lobes is indicated by sum of the individual lobar scores.

Total score	Category of severity
≤ 7	Mild
8-17	Moderate
≥ 18	Severe

Data analysis

- **Data analyses were done according to the following guidelines:**
  - Cardiology patients according to guidelines of European Society of Cardiology (ESC) and American Heart Association (AHA).
  - Chest patients according to American Thoracic Society (ATS).
  - Infections according to Infectious Diseases Society of America (IDSA).
  - GIT patients according to American Gastroenterological Association and American Association for the Study Liver Diseases (AASLD) and European Association for the Study of Liver (ESAL).
  - Neurology patients according to American Neurological Association (ANA).
  - Diabetes and Endocrinology patients according to American Association of Clinical Endocrinologists (AACE) &American Diabetes Association (ADA).
  - Nephrology patients according to Kidney Disease Improving Global Outcome (KDIGO) and American Society of Nephrology.

Statistical analysis design:

Data collected were reviewed and coding of the collected data was done manually. The numerical codes were fed to the computer where statistical analysis was done using the Statistic Package for **Social Science Version 22 (SPSS 22)** for windows.

A) Descriptive statistics:

1- Quantitative data: were presented as mean and standard deviation (mean ± SD)

2- Qualitative data: were expressed as numbers and percentage

B) Analytical statistics:

Comparing groups was done using

1- **Chi square-test (X^2)**: for comparison of qualitative data

2- **Student's " t "- test** for comparison of quantitative data of 2 independent sample with normal distribution and homogeneity of variance

3- **Mann Whitney test** for comparison of quantitative data of 2 independent sample with not normally distributed variable

4- **Pearson correlation** for studying the relationship between variables.
5- **Receiver operating characteristic curves (ROC)** were used to identify sensitivity, specificity and determine optimal cut-off points of inflammatory markers for prediction of outcome. Sensitivity = true positive / (true positive + false negative). Specificity = true negative / (true negative + false positive).
6- **The coefficient interval was set to 95%. The level of significance was calculated according to the following probability (P) values:** P<0.05 was considered statistically significant.

RESULTS

i- Results of the demographic characteristics and clinical state of the patients: (Table 2 & 3).

The current study included 110 patients with COVID infection, 80.9% of them were males; their age ranged between 21-92 years. The most frequent comorbid chronic disease was DM and HTN 48.2% for each. 30.9% of patients need nasal mask, 30% need face mask while 39.1% were on room air. The mean duration of hospital admission was 8.57 ± 3.12 days. Regarding the outcome 60.9% survived and 39.1 did not survive

Table (2): Descriptive data of the demographic characteristics and clinical data of the studied population

Age (years)		No.= 110
	Range	21 - 92
	Mean ± SD	62.14 ± 13.40
Sex	Male	89 (80.9%)
	Female	21 (19.1%)
Chronic disease	No	26 (23.6%)
	Diabetic	53 (48.2%)
	HTN	53 (48.2%)
	Asthmatic	5 (4.5%)
	COPD	3 (2.7%)
	malignancy	1 (0.1%)
	Cardiac	17 (15.4%)
	Hepatic	5 (4.5%)
	Renal impairment	6 (5.4%)
	Neurological	5 (4.5%)
O_2 treatment	Room air	43 (39.1%)
	Face mask	33 (30%)
	Nasal mask	34 (30.9%)
Duration of hospital admission (days)	Range	5-18
	Mean ± SD	8.57 ± 3.12
Outcome	Survived	67 (60.9%)
	Not survived	43 (39.1%)

Table (3): Comparison of the demographic characteristics and clinical data between survived and non-survived patients

		Survived	**Non-survived**	**Chi square test/ Mann Whitney U test**	
		N=67	**N=43**	**t**	**P-value**
Age (years)	Range	21 - 82	25 - 92	-3.391	0.001*****
	Mean ± SD	59.16 ± 12.13	66.79 ± 14.08		
Sex	Male	56 (83.6%)	33 (76.7%)	0.793	0.373
	Female	11 (16.4%)	10 (23.3%)		
Chronic diseases categories	No chronic disease	14 (20.9%)	12 (27.9%)	0.503	0.478
	DM only	8 (11.9%)	5 (11.6%)	0.002	0.96
	HTN only	6 (8.9%)	7 (16.3%)	1.348	0.245
	DM & HTN	13 (19.4%)	7 (16.3%)	0.172	0.678
	Chronic disease with DM & HTN	9 (13.4%)	4 (9.3%)	0.429	0.512
	Chronic disease other than DM & HTN	6 (8.9%)	5 (11.6%)	0.208	0.648
O2 ttt	Room air	22 (32.8%)	21 (48.8%)	7.165	0.028*****
	Face mask	18 (26.9%)	15 (34.9%)		
	Nasal mask	27 (40.3%)	7 (16.3%)		
Duration of hospital admission (days)	Range	5-10	5 -18	-7.713	<0.0001*****
	Mean ± SD	6.69 ± 1.16	11.51 ± 2.95		

***p* <0.05 (level of significance)**

* : There is statistically significant difference for the non-survivors patients in older age, the prolonged duration of hospital admission and the more need for oxygen therapy compared to survived patients

ii-Results of the laboratory investigations: (Table 4 & 5)
The mean HB level, lymphocytes, TLC and ferritin level were recorded.

Table (4): Descriptive hematological data of the studied population

		No.= 110
HB level gm/dl	Range	7.5 – 16
	Mean ± SD	12.6 ± 1.91
Lymphocytes %	Range	3.4 – 68.25
	Mean ± SD	17.47 ± 12.15
TLC x10^3 cell/mm^3	Range	0.8 - 45
	Mean ± SD	10.38 ± 6.15
Ferritin	Range	34.3 - 2172
	Mean ± SD	464.88 ± 393.11

Table (5): Comparison of the hematological data between survived and non-survived patients

		Survived	Non-survived	Mann Whitney U test	
		N=67	**N=43**	**t**	**P-value**
HB gm/dl	Range	8.9-16.8	8.5 – 18.4	-0.891	0.373
	Mean ± SD	12.79 ± 1.82	12.54 ± 2.13		
Lymphocytes %	Range	3.8 – 52.3	3.4– 68.25	-2.506	0.012*
	Mean ± SD	18.36 ± 10.23	16.08 ± 14.68		
TLC x10^{3}cell/mm^3	Range	2.9 – 17.4	0.8 – 45.1	-2.193	0.028*
	Mean ± SD	9.00 ± 3.75	12.52 ± 8.27		
Ferritin	Range	34.3 – 1274.04	61.63– 2172	-2.077	0.038*
	Mean ± SD	379.44 ± 275.04	598.02 ± 502.39		

***p* <0.05 (level of significance)**

There is statistically significant higher TLC, ferritin but lower lymphocytes in non-survived compared to survived patients in the studied population.

iii- Results of the inflammatory markers: (Table 6 & Figure 2)

Table (6): Comparison of the inflammatory markers before and after treatment in the studied population

		Before ttt	**After ttt**	**Mann Whitney U-test**	
		N=110	**N=110**	**t**	**P-value**
CRP	Range	2.7 – 742	0.3 - 284	5.154	<0.0001*
	Mean ± SD	179.04 ± 151.57	83.44 ± 64.14		
D-dimer	Range	0.05 – 33	0.01 – 5.6	2.492	0.013*
	Mean ± SD	1.76 ± 3.79	0.86 ± 1.15		
IL-6	Range	1.5 – 2147	1.4 - 1386	2.503	0.012*
	Mean ± SD	350.21 ± 433.09	227.90 ± 306.47		

***p* <0.05 (level of significance)**
***** : There is statistically significant decline in the inflammatory markers after treatment compared to before treatment

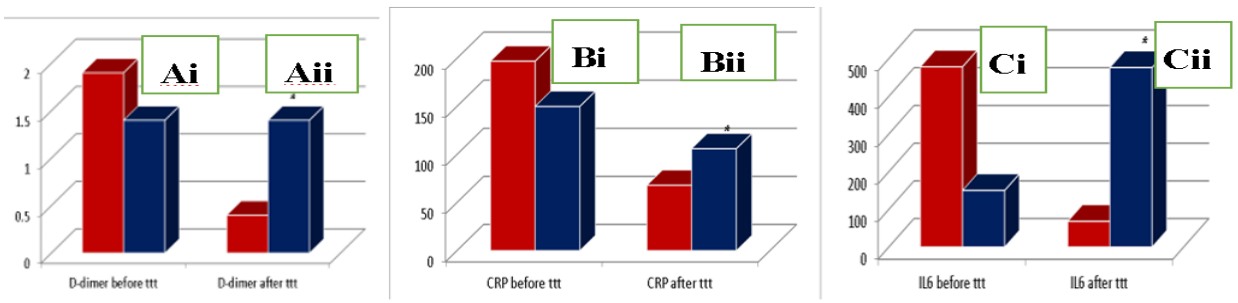

Fig. (2): Comparison of D-dimer (A), CRP (B) and IL 6 (C) before (i) and after (ii) treatment between survived and non-survived

***** : There is statistically significant elevation in the D-dimer , CRP and IL-6 after treatment in non-survived compared to survived patients in the studied population.

iv-Results of the Radiological investigations: (Table 7, Figure 3, & 4)

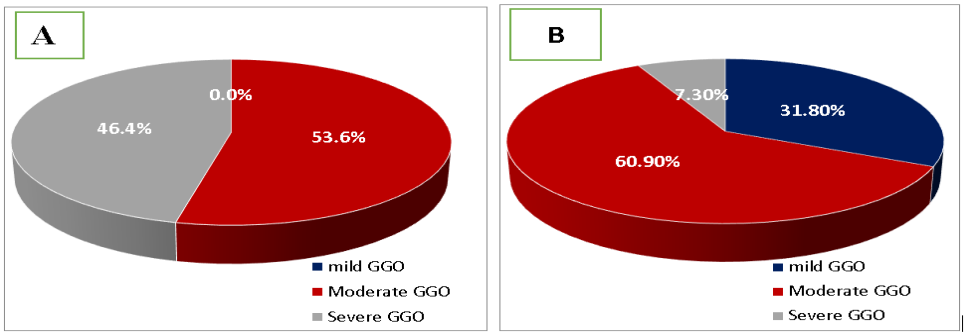

Fig. (3): CT finding on admission (A)and after treatment (B) in the studied population

In CT that was done on admission, 53.6% showed moderate GGO and 46.4% showed severe GGO. On follow up CT: 31.8% showed mild GGO, 60.9% showed moderate GGO and 7.3% showed severe GGO.

Table (7): Comparison of the radiological data between survived and non-survived patients

		Survived	Non-survived	Chi square test	
		N=67	N=43	X2	P-value
CT (1st)	Moderate GGO	43 (64.2%)	16 (37.2%)	7.661	0.006*
	Severe GGO	24 (35.8%)	27 (62.8%)		
CT (2nd)	Mild GGO	18 (26.9%)	17 (39.5%)	4.851	0.088
	Moderate GGO	46 (68.7%)	21 (48.8%)		
	Severe GGO	3 (4.5%)	5 (11.6%)		

***p* <0.05 (level of significance)**

***** : There is statistically significant worse CT findings on admission in non-survived than survived patients in the studied population.

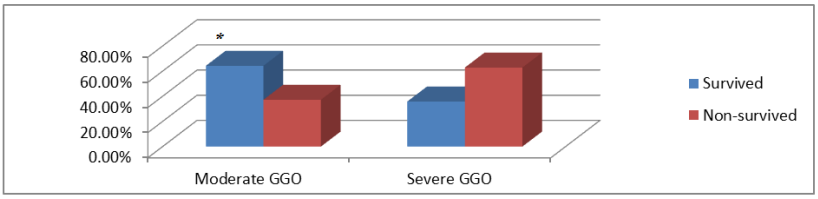

Fig. (4): Comparison of the radiological data between survived and non-survived patients

***** :There is statistically significant worse CT findings on admission in non-survived than survived patients in the studied population.

v- Results of comparative prognostic factors in patients with different comorbidities:

a) Radiological comparative results in patients with different comorbidities: (Figure 5)

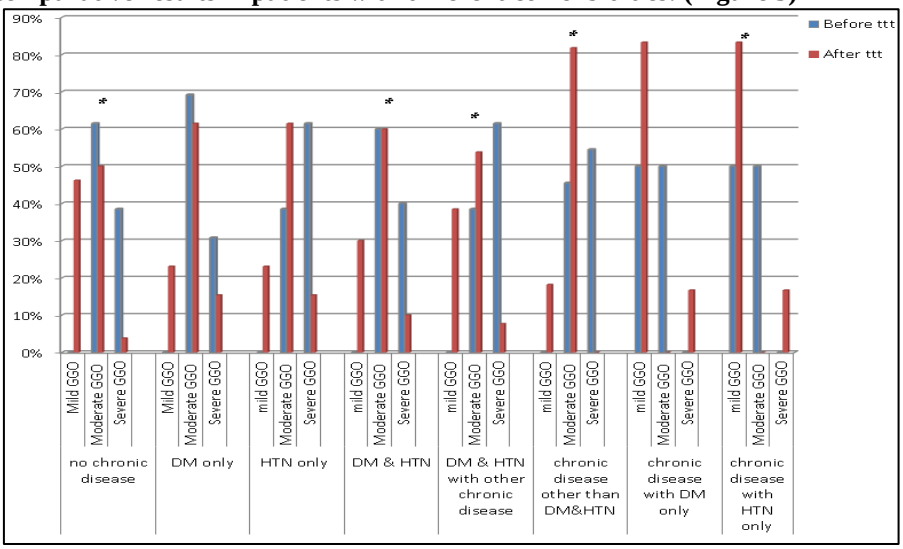

Fig. (5): CT findings before and after treatment in all groups of patients

*** :**There is statistically significant less severe GGO in CT after treatment than before in all group of patients except patient with DM only, HTN only & chronic disease with DM only.

b) Inflammatory comparative results in patients with different comorbidities: (Figure 6,7 &8)

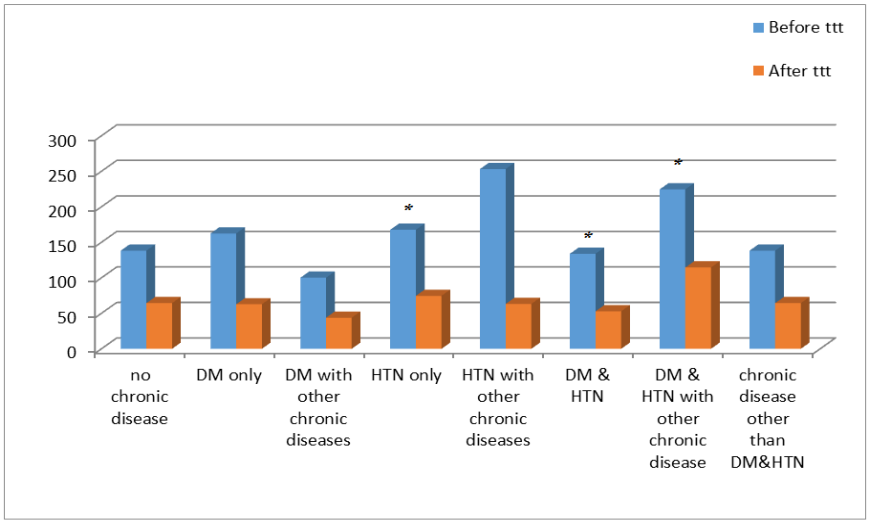

Fig. (6): CRP level before and after treatment in all groups

***** : There is statistically significant lower in CRP after treatment than before in patients with HTN only, DM & HTN and in patient with DM, HTN and other chronic disease.

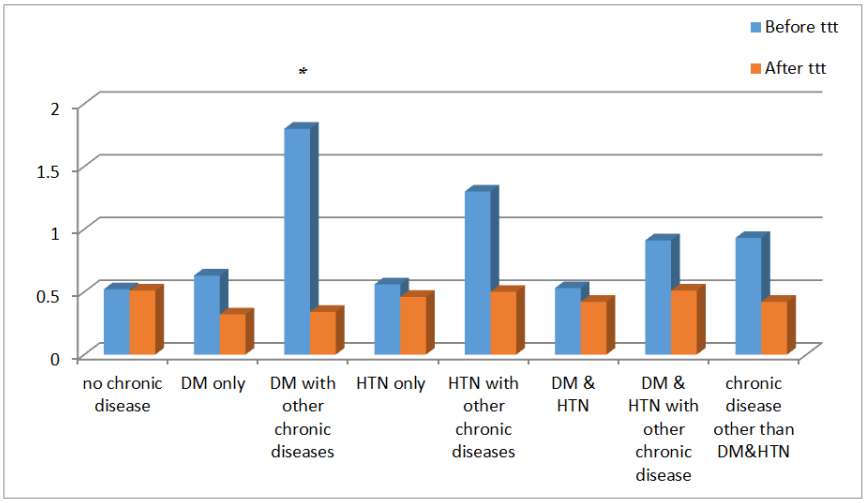

Fig. (7): D-dimer level before and after treatment in all groups

*** *:*** There is statistically significant lower in D-dimer after treatment than before in patients with chronic disease with DM only.

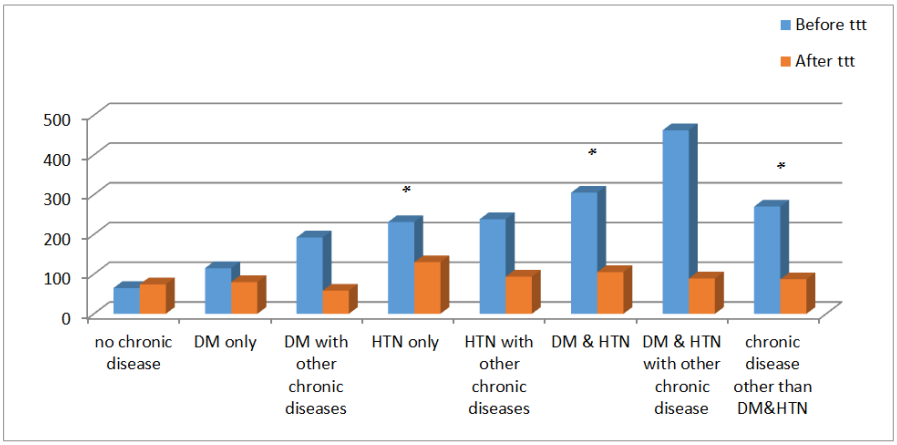

Figure (8): IL-6 level before and after treatment in all groups

*** *:*** There is statistically significant lower in IL-6 after treatment than before treatment in patients with HTN only and in patients with DM,HTN and other chronic diseases.

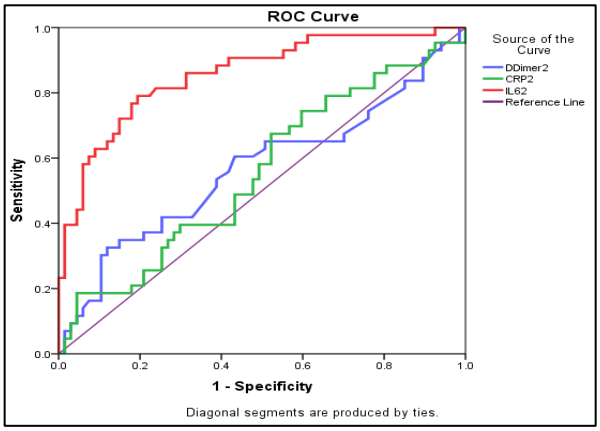

Fig. (9): ROC curve Sensitivity, Specificity and cutoff value of inflammatory markers level that predict poor outcome

At cutoff value ≥0.45, post treatment D-Dimer level has 69.8% sensitivity, and 62.7% specificity and post treatment CRP has 62.8% sensitivity and 47.8% specificity at cutoff point ≥59.6 while post treatment IL-6 level has 86% sensitivity and 79.1% specificity to predict poor outcome at cutoff value ≥81.9%

DISCUSSION

The etiological agent of COVID-19 mortality is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It caused the death of more than two million individuals globally in March of 2021 [World Health Organization (WHO), 2020]. Complications of severe COVID-19 affected mainly the lungs **[11]**, kidney [**12]**, and heart [**13]**, occurring more frequently in the elderly patients with certain comorbidities, like hypertension and he art disease which were usually correlated with intensive care unit (ICU) admission, mechanical ventilation requirement, and finally death [**14]**. The increased numbers of diseased patients due to COVID-19 made it a healthcare emergency and demonstrated the insistence of establishing effective drug therapy for management of such pandemics.

COVID-19 patients pass in an inflammatory phase, with a cytokine storm, that has a prothrombotic effect [**15]**. In fact, as enhanced by Qin et al. [**16**] stated that such hyperinflammation was mediated by IL-1, tumor necrosis factor-alpha (TNF-α) and IL-6 l associated with an increase of plasma concentrations of fibrinogen, plasminogen activator inhibitor-1 (PAI-1), lactate dehydrogenase (LDH) and neutrophil to lymphocytes ratio (NLR), due to T CD4+ lymphocytes reduction mainly. This happened mainly due to a close molecular interaction between coagulation and inflammatory cytokines. IL-6, TNF-α and IL-8 contribute to a pro-coagulant state through the activation of platelets, endothelial cells and the expression of tissue factor [**17**]. Furthermore, there is a decrease in natural anticoagulants production during inflammation such as antithrombin III, Protein C and tissue factor inhibitor, favoring a prothrombotic state [**18**]. The severity of clotting processes and inflammatory responses determines the prognosis of COVID-19 patients, so investigating the efficiency of anticoagulant drugs and anti-inflammatory might be crucial in decreasing morbidity and mortality caused by the COVID-19 pandemics.

This observational retrospective cohort study was conducted on 110 inpatients diagnosed as moderate or severe COVID-19.

The main results of this study were **as follows:** The current study included 110 patients with COVID infection whose mean value of age was 62.14 ± 13.40 years, and most patients were males. The most frequent comorbid chronic disease was DM and HTN 48.2% for each. 32.7% of them have single chronic disease. 30.9% of patients needed nasal mask, 30% needed face mask while 39.1% were on room air. The mean duration of hospital admission was 8.57 ± 3.12 days. Regarding the outcome, 60.9% survived and 39.1% did not survive.

In agreement with this study, **Hassan et al [19]** reported that patients with COVID-19 were mainly males (73%) whose mean age was 50.62 ± 16.4; metabolic syndrome was the most prevalent comorbidity in the studied patients and were presented as (30%) hypertension; (27.6%) diabetes mellitus (DM); (22%) dyslipidemia; and obesity whose (mean BMI was 28.29 ± 4.8). As well, **Ghalilah et al** [**20]** reported that most patients were males with percentage of (87.3 %). 58.7 % of them had comorbidity, where the percentage of diabetic patients was 38.1%. Also, more than half of the patients (50.8 %) were on low flow oxygen therapy, 4-9L oxygen, while (49.2 %) patients were on low flow oxygen therapy 10L oxygen or more.

The current study showed that on admission CT results revealed that 53.6% showed moderate GGO and 46.4% showed severe GGO while after treatment and follow up there were improvement represented as 31.8% showed mild GGO, 60.9% showed moderate GGO and 7.3% showed severe GGO. This was also in line with the study by **Zhang, et al** [**21**] which reported that 99.3% of the patients had abnormal Chest CT images, 89.6% with Bilateral lung, 3.7% Single lung-left and 5.9% Single lung-right.

The first assessment on COVID-19 patients was performed by measuring HB level, TLC, lymphocytic count and the ferritin level in addition to the inflammatory markers (D-dimer, CRP, IL-6) and CT imaging before and after treatment.

Zhang et al., [22] reported that the mean hemoglobin 12.3 (11.2-13.5) g/dl, which was in accordance with our study but Controversy, to the level of WBC and lymphocytes were 6.1 (4.6-7.9) × 10^9/L and 1.2 (0.8-1.6) × 10^9/L

In the present study, comparison of the inflammatory markers before and after treatment in the studied population, showed that there is statistically significant decline in inflammatory markers (D-dimer, CRP and IL-6) after treatment than before treatment.

In case of a severe COVID-19 case, the initial immune response has not terminated the infection of the pulmonary system. The potential benefit of prescribing

corticosteroids is thought to be the downregulation of lung injury mediated by the immune response [**23**]. Corticosteroids decrease inflammation and cytokine storm associated with a dysregulated immune response, so reducing mortality especially if given early in the severe stage of the illness [**24**] preventing the progression to acute respiratory distress syndrome (ARDS), respiratory failure, or death. Indeed, it has been suggested that SARS-CoV-2 elevates inflammatory cytokines as IL-6, leading to a cytokine storm, an important contributor to mortality and poor prognosis [**23]** which was in accordance with this study.

In addition, **Yamashita et al., [25]** found that low molecular-weight heparin (LMWH) exerts an anti-inflammatory response through IL-6 reduction and lymphocyte% elevation as well as improving the coagulation dysfunction. Furthermore, **Braz-de-Melo et al., [26]** concluded that the use of corticosteroid mainly dexamethasone and anticoagulant mainly heparin are the prominent treatments for COVID-19 which resulted in significant decline in inflammatory markers (IL-6 and IL-8)

In the current study, comparison of the clinical data between survived and non-survived patients showed that there is statistically significantly higher age in non-survived than survived patients which was supported by the Systematic Review and Meta-Analysis by **Dessie & Zewotir, [27]** which enlisted 42 studies with a total of 423,117 patients reported that older age has shown increased risk of mortality due to coronavirus.

Comparison of the radiological data between survived and non-survived patients showed that there were statistically significant better CT findings in survived than non-survived patients. This was supported by **Raoufi et al., [28]** who revealed that there was a significant correlation between characteristics of chest CT scan and mortality of COVID-19 cases. Patients with lower CT scan Severity Score, round shape opacity and lower pulmonary artery CT diameter, had lower mortality. Also, the study by **Kazemi et al., [29]** concluded that total chest CT-score and chest CT features can be used as prognostic factors in COVID-19 patients. There was a correlation between total CT-score and chest CT features with mortality.

Comparison of the hematological data between survived and non-survived patients showed that there was statistically significant lower TLC and ferritin and higher lymphocytes in survived than non-survived patients. These results were supported by **Anastasio et al., [30]** who reported that Ferritin and Neutrophils/leucocytes ratio were significant predictors of mortality in cases with COVID-19.

This study showed that there was statistically significant lower D-dimer after treatment in survived than non-survived patients. This demonstrated that post treatment D-dimer was significantly improved in survivors and remains unchanged in non-survivors. The study by **Yao et al., [31]** reported that D-dimer levels correlate with disease severity and are a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19. Also, these results were supported by **Anastasio et al., [30]** who reported that D-dimer was a significant predictor of mortality in cases with COVID-19. As well, **Soni et al., [32]** reported that during hospital stay D-dimer had the highest C-index patients especially if its value ≥ 2.01 μg/mL and could predict in-hospital mortality in COVID-19.

This study showed statistically significant lower CRP after treatment in survived than non-survived patients. demonstrating that post treatment CRP was significantly improved in survivors and non-significantly improved in non-survivors. These results were supported by **Hassan et al., [19]** who revealed that increased C reactive protein was a significant predictor of cases with COVID-19 treated with Steroid and Anticoagulant. Also, **Ho et al., [33]** reported that Patients with CRP ≥150mg/ on admission had lower mortality associated with corticosteroid treatment.

In the current study, there was statistically significantly higher IL-6 after treatment in non-survived than survived patients. This was supported by **Mammen et al., [34]** who reported that on admission IL-6 levels were significantly ($p<0.001$) higher (76.00, 18.27–171.77) in non-survivors than in survivors (18.51, 4.26–56.86). By day 3, IL-6 levels dropped to 11.6 (2.64–45.84) in survivors while it nearly doubled in non-survivors (140.35, 21.56–427.36). Also, **Ho et al., [33]** reported that Patients with IL-6 ≥20pg/mL on admission had lower mortality associated with corticosteroid treatment.

To test the prognostic accuracy of different inflammatory markers, ROC curve analysis was performed It showed that at cutoff value ≥0.45, post treatment D-Dimer level has 69.8% sensitivity, and 62.7% specificity and post treatment CRP has 62.8% sensitivity and 47.8% specificity at cutoff point ≥59.6. While post treatment IL-6 level has 86% sensitivity and 79.1% specificity to predict poor outcome at cutoff value ≥81.9%.

This study demonstrated that post treatment IL-6 level has the best prognostic accuracy followed by post treatment D-Dimer level. This was in line with the study by **Milenkovic et al., [35]** which revealed that the cutoff value of IL-6 was 74.98 pg/mL (Sn 69.7%, Sp 62.7%) for in-hospital death prediction; cutoff value of CRP was 81 mg/L (Sn 60.7%, Sp 60%); while cutoff value of D dimer was 760 ng/mL FEU (Sn 63.4%, Sp 57.1%).

The present study showed that there was statistically significant lower in CRP after treatment than before in patients with HTN only, DM & HTN and in patients with DM, HTN and other chronic disease. Also, there is statistically significant lower in D-dimer after treatment than before in patients with chronic disease with DM only. Furthermore, there is a statistically significant lower in IL-6 after treatment than before treatment in patients with HTN only and in patients with DM, HTN and other chronic diseases. As well there is statistically significant less severe GGO in CT after treatment than before in all group of patients except patient with DM only, HTN only & chronic disease with DM only.

This study demonstrated the correlation between the type of chronic disease and the response to treatment of COVID-19.In agreement with this study **Carbone et al., [36]** concluded that hypertension in metabolic syndrome was independently associated with baseline low CRP levels, which might suggest a critical role for inflammation in sustaining high blood pressure levels. As well, **Ebrahimi et al., [37]** revealed that CRP was independently increased with fasting blood sugar. Also, **Pullamsetti et al., [38]** stated that there is emerging evidence for a role of inflammatory mediators, primarily IL-6, in the pathogenesis of hypertension. However, the mechanisms by which IL-6 potentially affects hypertension are unknown.

Furthermore, **Akbari et al., [39]** showed that dysregulation of IL-6 release is associated with the pathogenesis of T2D. However, the effects of IL-6 on glucose metabolism and insulin sensitivity are markedly divergent in different tissues.as well **Mammen et al., [34]** reported also that there is statistically non-significant relation between mortality and presence of either comorbid diabetes or hypertension. Furthermore, **Martins-Filho et al., [40]** reported that both comorbid diabetes and hypertension were non-significantly correlated with mortality.

Also **Torregroza *et al.*, [41]** interestingly, noted that there was no significant difference between the control group and the dexamethasone group regarding the adverse effects, as hyperglycaemia which occurred in 70% of the control group and 76% in the dexamethasone group, with both groups being in ICU. also **Mansourabadi *et al.*, [42]** demonstrated that all the patients showed hyperglycemia following corticosteroids administration, and this was corrected with insulin.

CONCLUSION

The early administration of corticosteroids in conjunction with anticoagulants to severe COVID-19 pneumonic cases has the potential to reduce negative impacts and enhance the general outcome in all group of patients regardless the associated morbidity or chronic diseases. Mortality in cases with COVID-19 was related to older age, co-morbidity, worse CT findings, a higher oxygen therapy requirement, and a longer duration of hospitalization. The post-treatment IL-6 level has the best prognostic accuracy, followed by the post-treatment D-dimer level. To verify such findings and determine risk factors for negative outcomes, additional research is required with a larger sample size and a longer follow-up.

Declarations:

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