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Effect of Colchicine in Treating Severe COVID-19 Patients on Hospital Discharge: Retrospective Cohort Study

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ABSTRACT
Background: COVID-19 is highly heterogeneous; it ranges from asymptomatic to severe pneumonia that could progress to critical illness with hypoxemic respiratory failure requiring oxygenation, ventilator support or even death. This aim of the present study is to examine the effect of adding colchicine to standard of care in treatment of severely hypoxemic hospitalized COVID-19 patients on patients' 28 days discharge. **Patients and Methods:** This was a retrospective, single-centre cohort study to evaluate the effect of colchicine in the treatment of COVID-19 patients on 28 days discharge and mortality. Out of 201 patients, 153 patients, suspected and confirmed COVID-19, was included from Shebin Elkom Fever Hospital, Monofya Governorate, Egypt, from November 2020, to January 2021. **Results:** Among 201 patients enrolled, 153 (87.5%) patients were included in this study, and divided into two cohorts; 78 patients (51%) in the non-colchicine group and 75 (49%) patients in the colchicine group. Among the 76 patients who were discharged within 28 days, 56 patients (74.67%) were in the colchicine group and 20 patients (25.64%) were in the non-colchicine group. Regarding 28-day mortality was, 77 patients died in the two groups during the 28 days from hospital admission; 19 patients (23.68%) died in the colchicine group and 58 (76.32%) in the non-colchicine group (OR 0.01, 95% CI: 0.001-0.10, p-value 0.000). **Conclusion**: Colchicine exerts an anti-inflammatory effect that has a great impact on decreasing oxygen demand and ICU admission compared to the non-colchicine arm.
Keywords: Colchicine, COVID-19, Pandemic, Hospital discharge rate, ICU, Monofya.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were the cause of a cluster of pneumonia cases in Wuhan, China at the end of 2019; then it had spread to infect millions of people across the world and taken millions of lives resulting in a global pandemic in 2020 [(1)]. More than 83 million cases worldwide had confirmed infections, more than 1.8 million patients died since the beginning of the pandemic to date [(2)].

The clinical presentation of COVID-19 is highly heterogeneous; it ranges from asymptomatic to severe pneumonia that could progress to critical illness with hypoxemic respiratory failure requiring oxygenation, ventilator support or even death [(3,4)]. It is characterized by an initial phase of viral replication followed by a second phase caused by the host inflammatory response that mostly affect the respiratory system, leading to acute lung injury and acute respiratory distress syndrome [(5)]. The pathophysiological features of severe COVID-19 patients are acute pneumonia with extensive opacity, inflammatory infiltrates, and microvascular thrombosis [(6)]. The most critical patients have clinical presentations that resemble cytokine storm, which is characterized by markedly elevated levels of inflammatory markers, including C-reactive protein, D-dimer, ferritin, interleukin-1, and interleukin-6 that can produce long-term lung damage and inflammatory organ injury. So, interrupting the inflammatory pathway has been proposed as the potential therapeutic target for severe COVID-19 cases to prevent disease progression [(6,8)].

The optimal approach to the treatment of COVID-19 is uncertain, current clinical approaches consider the combination of antiviral drugs and immunomodulatory drugs that can interrupt the inflammatory pathway. Approaches that target the virus itself (antivirals, passive immunity) are more likely to work early in the course of infection, while approaches that modulate the immune response work later in the course of the disease [(9)].

Various anti-inflammatory and immunomodulatory drugs evaluated and tested for COVID-19 management, including glucocorticoids, cytokine inflammatory antagonists (such as IL-6 inhibitor, monoclonal antibodies, TNF inhibitors, IL-1 inhibitors, Janus kinase inhibitors). However, safety, contraindication, efficacy, cost, and availability of some of them greatly impact their use to treat severe COVID-19 patients [(9)]. For these reasons, there has been interest in using agents that may slow the progression of the disease and help decreasing cost, especially in limited resources countries.

One of these agents is colchicine, which can exert broad and rapid onset anti-inflammatory and immunomodulatory effects through multiple mechanisms other than that of corticosteroids [(10)]. Colchicine inhibits NOD-like receptor protein 3 (NLRP3) inflammasome that had a major role in the development of lung injury and was activated by viroporin E; a component of SARS-associated coronavirus (SARS-CoV) [(10-13)]. Moreover, it inhibits neutrophil chemotaxis and activity in response to vascular injury, reduces neutrophil-platelet interaction

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and aggregation, suppresses proinflammatory cytokines and chemokines, inhibits tubulin polymerization, and has potential effects on cellular adhesion molecules [17,18].

Furthermore, it may exert a direct anti-inflammatory effect by inhibiting the synthesis of tumour necrosis factor-alpha and IL-6, monocyte migration, and the secretion of matrix metalloproteinase. All these mechanisms are potentially beneficial effects that might ameliorate the COVID-19 inflammatory storm associated with severe forms of the disease with an acceptable safety profile [10,14-16]. In this study, we examined the effect of adding colchicine to standard of care in treatment of severely hypoxemic hospitalized COVID-19 patients on patients' 28 days discharge.

PATIENTS AND METHODS

This was a retrospective, single-centre cohort study to evaluate the effect of colchicine in the treatment of COVID-19 patients on 28 days discharge and mortality. Out of 201 patients, 153 patients suspected and confirmed COVID-19, was included from Shebin Elkom Fever Hospital, Menofia Governorate, Egypt.

These patients were admitted to Shebin Elkom Fever Hospital in the period from November 2020, to January 2021. Our data were obtained from patients' files retrospectively. Owing to the retrospective nature of this study, a waiver of consent for use of identifiable data can be granted.

We included all hospitalized adult patients that diagnosed as severe suspected or confirmed COVID-19 infection, diagnosis of COVID-19 patients based on typical CT findings of pneumonia and ground-glass opacity (CO-RADS 4 or 5), oxygen saturation less than 90% on room air and need for supplemental oxygen with or without virus RNA detection using RT-PCR [19,20]. Patients with a history of cirrhosis Child-Pugh C, active hepatitis, inflammatory bowel disease (Crohn's disease or ulcerative colitis), pre-existent progressive neuromuscular disease, pregnant and breast-feeding women as colchicine is harmful for this population and Patients currently taking colchicine for other indications were excluded.

Our population was divided into two groups, one group received colchicine (500 mcg every 12 hours within 48 hours of declined oxygen saturation) in their medication regimen and the other group wasn't. We obtained data from patients' files retrospectively, about colchicine use as exposure and 28 days discharge as the primary outcome and 28 days mortality, ICU admission, length of hospital stay, the clinical improvement according to WHO scale and the need for mechanical ventilation as secondary outcomes. The criteria for discharge were the absence of fever for at least 3 days, and clinical remission of respiratory symptoms [21,22].

Other variables were also collected to be considered as confounders, such as demographics (Age and sex), co-morbidities according to the KDIGO clinical practice guidelines [23]. History of laboratory results (serum lymphocyte counts, liver function tests, serum ferritin, D-dimer, C-reactive protein and blood glucose on admission), oxygen saturation on admission and the least oxygen saturation measured, medications used (ivermectin, remdesivir, dexamethasone, methylprednisolone, hydrocortisone, tocilizumab, a dose of anticoagulants either therapeutic or intermediate or prophylactic dose, antibiotics, vitamin c, zinc, acetylcysteine, aspirin), secondary bacterial infection diagnosed either be microbiological culture or signs and symptoms (remission of fever after the resolution, presence of pus in the urine, change in the colour of sputum) of infection after 48 of hospital admission, ICU admission and development of sepsis or septic shock defined according to 2016 Third International Consensus Definition for Sepsis and Septic Shock were obtained [24].

Clinical improvement was assessed by an ordinal scale recommended by the WHO ((0) non-hospitalized and no clinical or virological evidence of infection; (1) non-hospitalized and no limitation on activities; (2) non-hospitalized, but with limitation on activities; (3) hospitalized, but not requiring supplemental oxygen; (4) hospitalized and on oxygen via mask or nasal prongs; (5) hospitalized, on non-invasive ventilation or high-flow oxygen or pressure support ventilation in weaning mode; (6) hospitalized, intubated and on MV; (7) hospitalized on MV and additional organ support renal replacement therapy, vasoactive drugs or extracorporeal membrane oxygenation), and (8) dead) [25].

All patients admitted to the hospital in the previously mentioned period was included to avoid selection bias, except patients who were not eligible for the administration of colchicine as it will be harmful for them or who were already on colchicine for treatment of other conditions. Also, our data were from documentation in patients' files to avoid recall bias.

Sample size calculation:

The sample size was calculated based on a propensity score-matched cohort study, in which, patients who were discharged home within 28 days in the colchicine group were 90.9% and in the standard of care group was 66.7%, with 80% power and a two-sided significance level of 0.05. The Sample size, 134 (67 patients in each group) was considered adequate to detect the colchicine effect size [26].

Ethical consent:

An approval of the study was obtained from Shebin Elkom Fever Hospital Academic and Ethical Committee. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were tabulated and analysed using STATA version 16 software. Categorical data were presented as numbers and percentages, while quantitative data were expressed as mean, standard deviation (SD) and median. Chi square (X^2) test, ANOVA, Krauskal Wallis test and. Logistic, linear and Cox regression were used to detect the predictors of 28 days discharge and length of stay and hospital death, respectively. The accepted level of significance was stated at 0.05 (P <0.05 was considered significant).

RESULTS

Among 201 patients enrolled, 153 (87.5%) patients were included in this study divided into two cohorts; 78 patients (51%) in the non-colchicine group and 75 (49%) patients in the colchicine group. Forty-four patients were excluded including 27 patients had oxygen saturation above 90% so they were excluded, 4 patients had severe decompensated liver disease, 13 patients were transferred to another centre (Figure 1).

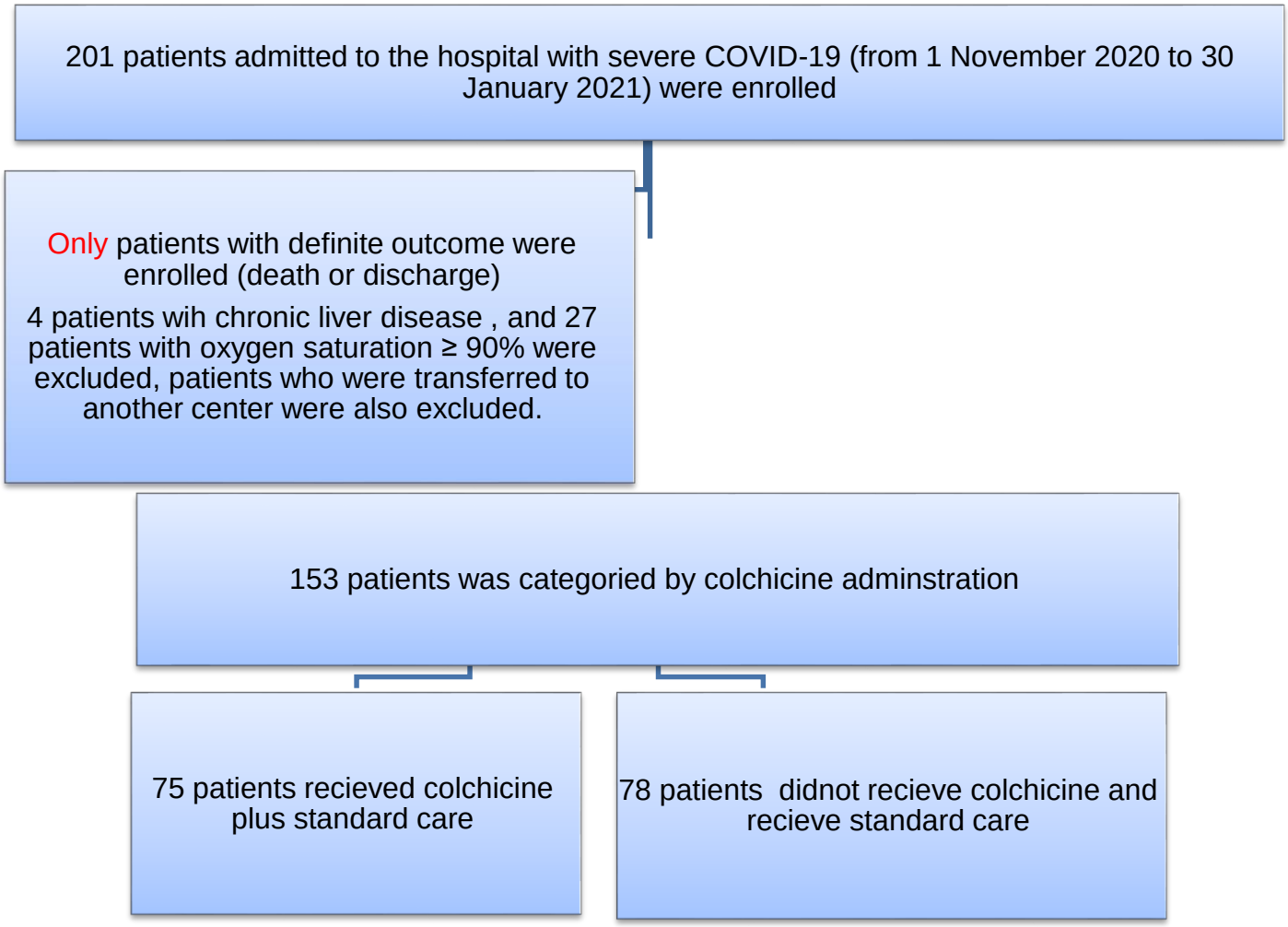

Figure (1): Colchicine for COVID-19 Study Flowchart.

The characteristics of colchicine-treated and non-colchicine-treated patients are shown in **Table 1**. We found that there was non-significant difference between the two groups in all basic characteristics shown in table I except lymphopenia, corticosteroid use and its duration and the use of prophylactic dose of anticoagulants.

Table (1): Comparison between colchicine and non-colchicine groups regarding patients' basic characteristics, demographics and medications.

Basic Characteristics	Non-Colchicine treated group (78)	Colchicine treated group (75)	P-value
Age Mean	64.18 ±13.33	62.65 ±11.14	0.44
Sex (male)	38 (48.72%)	38 (50.67%)	0.81
(Female)	40 (51.28%)	37 (49.33%)	0.81
Ischemic heart disease	24 (30.77%)	21 (28%)	0.71
Congestive heart failure	3 (3.85%)	1 (1.33%)	0.33
Hypertensive	52 (66.67%)	51 (68%)	0.86
Diabetes	45 (57.69%)	42 (56%)	0.83
CKD	8 (10.26%)	3 (4%)	0.13
Lymphopenia	25 (32.05%)	12 (16%)	0.02
Elevated liver enzymes	22 (28.21%)	17 (22.67%)	0.43
Ferritin level	745.1 ± 177.65	761 ±188.31	0.8046
D-dimer level	0.7 ± 0.11	0.635 ± 0.11	0.76
CRP	48 ± 10.1	96 ± 18.4	0.318
Blood glucose on admission	200 ± 39.8	192.5 ± 37.5	0.95
Oxygen saturation on admission	88 (81-92)	87 (80-90)	0.298
Least oxygen saturation median	70 (62-82)	72 (66-79)	0.93
Secondary bacterial infection	59 (75.64%)	65 (86.67%)	0.08
Medications			
Dexamethasone	58 (74.36%)	43 (57.33%)	0.026
Methylprednisolone	55 (70.51%)	71 (94.67%)	0.00
Duration of solumedrol	4 (0-8)	8 (5-15)	0.0001
Therapeutic anticoagulant	52 (66.67%)	60 (80%)	0.063
Prophylactic anticoagulant	26 (33.33%)	14 (18.67%)	0.039
Remdesivir	19 (24.36%)	18 (24%)	0.959
Ivermectin	27 (34.62%)	31(41.33%)	0.392
Vitamin c	49 (62.82%)	44 (58.67%)	0.599
Lactoferrin	41 (52.56%)	41 (54.67%)	0.794
Zinc sulfate	52 (66.67%)	45 (60%)	0.392
Acetyl cysteine	45 (57.69%)	51 (68.92%)	0.152
Tocilizumab	9 (11.54%)	11 (14.67%)	0.566
Outcome			
Primary outcome			
28-days Discharge	20 (25.64%)	56 (74.67%)	0.000
Secondary outcomes			
28-days Mortality	58 (74.36%)	19 (25.33%)	0.000
ICU admission	33 (42.31%)	20 (26.67%)	0.061
Intubation and mechanical Ventilator	19 (24.36%)	5 (6.67%)	0.003
Shock	23 (29.49%)	8 (10.67%)	0.004
Length of hospital stay	10 (6-13)	15 (10-20)	0.0001
Clinical improvement (who ordinal scale)			
4 (hospitalized and on oxygen via mask)	4 (66.67%)	2 (33.33%)	0.000
5 (hospitalized on high-flow oxygen or NIM))	16 (22.86%)	54 (77.14%)	0.000
8 (dead)	58 (74.36%)	19 (25.33%)	0.000

Among the 126 patients who were on methylprednisolone, 69/76 (90.8%) patient were discharged and 57/77 (74.03%) patient died with significant difference (P-value 0.007). Regarding the 37 patients who received remdesivir, 11/76 (14.5%) patients were discharged and 26/77 (33.77%) patients died with significant difference (P-value 0.005). The use of zinc and vitamin c was associated with higher death rate with significant difference. ICU admission and mechanical ventilation was also associated with higher death rate as shown in (Table 2).

Table (2): Comparison between discharged and died COVID-19 patients.

Characteristics	Discharged (76)	Died (77)	P-value
Age	61.47 ±11.33	65.36 ±12.96	0.05
Sex (male)	32(42.11%)	44 (57.14%)	0.063
Female	44 (57.89 %)	33 (42.86%)	0.063
Lymphopenia	11(14.47%)	26 (33.77%)	0.005
Diabetes	44 (57.89%)	43 (55.84%)	0.798
Hypertensive	49 (64.47%)	54 (70.13%)	0.456
CKD	5 (6.58%)	6 (7.79%)	0.771
Ischemic heart disease	20 (26.32%)	25 (32.47%)	0.404
Ferritin level	673.3 ± 118.2	943.35 ± 207.3	0.0724
D-dimer level	0.62 ±0.11	0.9 ± 1.6	0.26
Elevated liver enzymes	16 (21.05 %)	23 (29.87%)	0.211
Secondary bacterial infection	60 (78.95%)	64 (83.12%)	0.511
Oxygen saturation on admission	88 (81.5-92)	86 (79-91)	0.324
Least oxygen saturation	76.5 (70.5-82)	68 (58- 72)	0.0001
CRP	96 ± 21.1	96 ± 23.2	0.9518
Medications			
Colchicine	56 (73.68%)	19 (24.68%)	0.000
Dexamethasone	46 (60.53%)	55 (71.43%)	0.155
Methylprednisolone	69 (90.79%)	57 (74.03%)	0.007
Therapeutic anticoagulant	53 (69.74%)	59 (76.62%)	0.336
Prophylactic anticoagulant	19 (25%)	21 (27.27%)	0.358
Remdesivir	11 (14.47%)	26 (33.77%)	0.005
Ivermectin	25 (32.89%)	33 (42.86%)	0.204
Vitamin c	36 (47.37%)	57 (74.03%)	0.001
Lactoferrin	38 (50%)	44 (57.14%)	0.376
Zinc	38 (50%)	59 (76.62%)	0.001
Acetyl cysteine	51 (68%)	45 (58.44%)	0.222
Actemra	6 (7.89%)	14 (18.18%)	0.059
Outcome			
ICU admission	5 (6.58%)	48 (62.34%)	0.000
Ventilator	0 (0%)	24 (31.17)	0.000
Shock	0 (0%)	31 (40.26%)	0.000
Length of hospital stay	14 (9-19)	11 (7-15)	0.0055

Primary analysis

Among the 76 patients who were discharged within 28 days, 56 patients (74.67%) in the colchicine group and 20 patients (25.64%) in the non-colchicine group. The adjusted odds ratio (OR) for discharge was 85.89 (95% CI: 10.17-725.58, P-value 0.000).

Regarding 28-day mortality, 77 patients were died in the two groups during the 28 days from hospital admission, 19 patients (23.68%) died in the colchicine group and 58 (76.32%) in the non-colchicine group (OR 0.01, 95% CI: 0.001-0.10, P-value 0.000). Among the 53 patients who were admitted to the ICU, 20 (37.74%) patients were from the colchicine group and 33 (62.26%) from the non-colchicine group, (OR 0.25, 95% CI: 0.1-0.64, P-value 0.004).

After admission to the ICU, 24 patients need intubation and mechanical ventilation, 5/75 (6.76%) patients who needed intubations were from the colchicine treated group and 19/78 (24.36%) patients were from the non-colchicine group (OR 0.08, 95% CI: 0.01-0.55, P-value 0.01). There were 8/75 (10.67%) patients from the colchicine group and 23/78 (29.49%) patients from the non-colchicine group was diagnosed with ICU shock (OR 0.21, 95% CI: 0.05-0.81, P-value 0.024).

Using linear regression model, the incidence rate for the length of hospital stay in the colchicine group was 1.31 (95% CI: 1.14-1.51, P-value 0.000) The OR for clinical improvement (using the ordinal scale for clinical improvement recommended by the WHO) in the colchicine group was 0.07 (95% CI: 0.02-0.27, P-value 0.000) compared to the non-colchicine group. As regards colchicine and tocilizumab use and antiviral use on 28-days discharge, no interaction found between colchicine and tocilizumab use, methylprednisolone and remdesivir use (P values 0.991, 0.45, and 0.45, respectively) (**Table 3**).

Table (3): Univariate analysis of predictors of primary and secondary outcomes regarding the studied groups.

Outcome	Non-Colchicine treated Group (78)	Colchicine treated Group (75)	Adjusted Odds ratio	P value
Primary outcomes				
28-days Discharge	20 (25.64%)	56 (74.67%)	85.9 (10.2-725.6)	0.00
Secondary outcomes				
28-days Mortality	58 (74.36%)	19 (25.33%)	0.01 (0.001-0.10)	0.00
ICU admission	33 (42.31%)	20 (26.67%)	0.25 (0.1-0.64)	0.004
Intubation and mechanical Ventilator	19 (24.36%)	5 (6.67%)	0.08 (0.01-0.55)	0.01
Shock	23 (29.49%)	8 (10.67%)	0.21 (0.05-0.81)	0.024
Clinical improvement (who ordinal scale) 4 (hospitalized and on oxygen via mask) 5 (hospitalized on high-flow oxygen or NIM) 8 (dead)	 4 (66.67%) 16 (22.86%) 58 (74.36%)	 2 (33.33%) 54 (77.14%) 19 (25.33%)	 0.07 (0.02-0.27)	 0.000
Length of hospital stay	10 (6-13)	15 (10-20)	1.31 (1.14-1.51)	
Hospital death	58 (74.36%)	19 (25.33%)	0.35 (0.19 -0.63)	

Multiple Cox regression model:

From the 77 patients who died, 19 patients (23.68%) died in the colchicine group and 58 (76.32%) died in the non-colchicine group. The adjusted hazard ratio for hospital death in the colchicine treated group is 0.35 (95% CI: 0.19-0.63, P-value 0.000) (**Figure 2**).

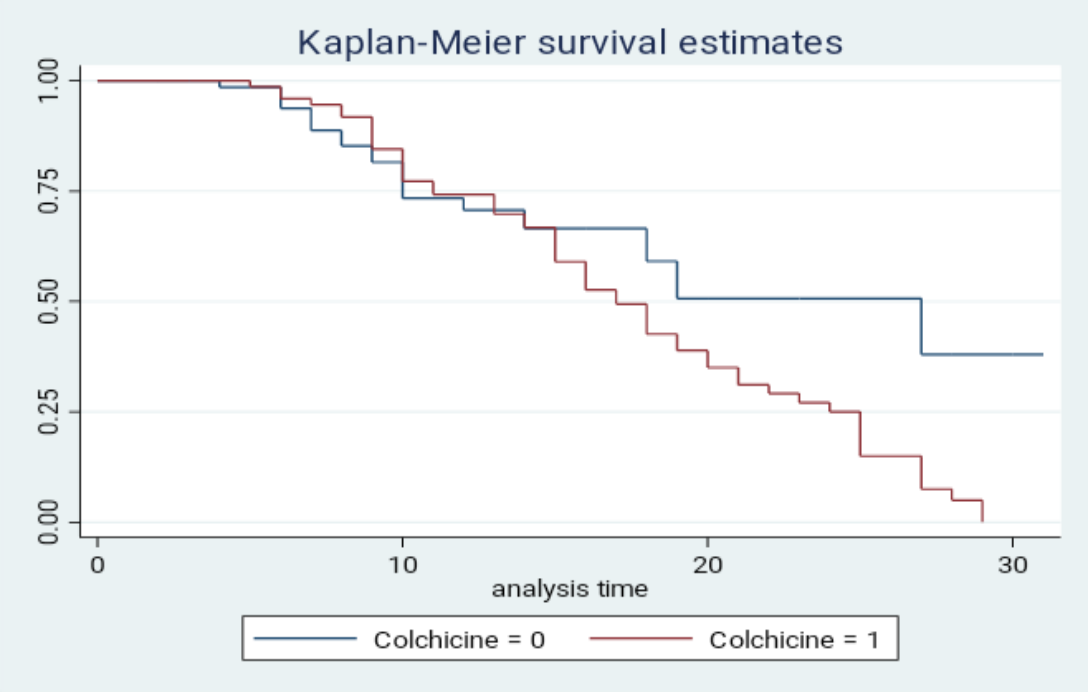

Figure (2): Kaplan Meier survival by discharge

Subgroup analysis

The association between Colchicine treatment and hospital discharge was lower in the younger age groups (OR 21031.6 for <65 years, and 47.65 for ≥65 years) [P value 0.65 for the interaction]. Treatment with colchicine and discharge was higher among female patients but with non-significant result for interaction; OR was 187.94 for males and 3764.31 for female (P-value 0.89). However treatment with colchicine and hospital discharge was significantly different among patients admitted to the ICU compared to patients not admitted to the ICU.

Table (4): Comparisons between colchicine and non-colchicine treated groups.

Subgroup analysis	Non-Colchicine treated group (N 78)	Colchicine treated group (N 75)	Adjusted Odds ratio for hospital discharge	P-value*
Age				
Hospital discharge <65 years	13 (38.24%)	30 (78.95%)	21031.6 (0.80-5.47e)	0.65
Hospital discharge ≥65 years	7 (16.28%)	26 (70.27%)	47.65 (4.83-467.79)	
Sex				
Hospital discharge in male	7 (18.42%)	25 (65.79%)	62.04 (5.62-684.50)	0.89
Hospital discharge in female	13 (32.50%)	31 (83.78%)	3764.3 (10.16-1394805)	
ICU admission				
Discharge among patients Admitted to ICU	0 (0%)	5 (25%)	1	0.001
Discharge among patients Not admitted to ICU	20 (44.44%)	51 (92.73%)	156.89 (3.52-6996.55)	

* P-value for interaction

Sensitivity analysis:

Using IPW regression adjustment, the average treatment effect can be observed if the entire population was treated is 0.34 (95% CI: 0.32-0.59, P-value 0.000), meaning that colchicine treated patients have 35 more times to be discharged in the entire population.

DISCUSSION

This study set out with the aim of assessing the importance of colchicine use in hospitalized severe COVID-19 patients. The most important clinically relevant findings in this study were that colchicine significantly increased 28-day discharge, decreased 28-day mortality and decreased ICU admission.

As mentioned earlier, the use of colchicine is associated with various anti-inflammatory mechanisms, inexpensive, available worldwide and has a good safety profile; this makes colchicine an attractive agent for decreasing the harmful consequences of cytokine storm associated with COVID-19, which will result in reducing lung injury, decreasing oxygen demand and improving patients survival.

Of the discharged patients about 74.7% from the colchicine arm (56 patients), and about 25.6% from the non-colchicine arm (20 patients) were discharged, although both arms were similar in most demographic and clinical characteristics as showed before in table 1, this may be due to the anti-inflammatory effect of colchicine, that decreases oxygen demand and consequently ICU admission.

The percentage of discharge was higher in females 57.9% (44 patients), this higher rate of discharge among females may be due to females' better immunity system with lower severity of viral infection than males; perhaps this is due to the effect of sex hormone on the inflammatory cascade in addition to the high risk of thromboembolic events in males compared to females, as mentioned in many previous studies. Annalisa **Capuano *et al.*** [27] found that the sex hormone difference, the high tendency of males to cardiovascular diseases, also coagulation pattern has been demonstrated as important factors that affect the sex immune response to COVID-19 infection.

Although females have a lower burden of mortality 42.86% (33 patients), but from the 22 female patient who were admitted to the ICU, 19 (86.36%) female patients died. So it was concluded once the case become severe and require ICU admission, the risk became the same among both sex groups. This was similar to what was observed by **Raimondi *et al.*** [28]**,** the females have less 28-day mortality, but once admitted to ICU with higher oxygen demand, no differences in mortality was observed between males and females.

Oxygen demand was lower in the colchicine arm leading to lower ICU admission, but it did not prevent ICU admission completely, 26.67% (20 from 75 in the colchicine group), while 42.31% (33 from 78 patients) in the non-colchicine group was admitted to ICU. One of the most interesting findings was that among patient who was admitted to ICU only 6.67% (5 patients) need intubation in colchicine group compared to 24.36% (19 patients) in the control group, with a note that steroids use was similar in both groups, this is consistent with the results of **Lopes *et al.*** [29]**,** a small randomized control double-blind trial that supports the evidence of decreasing oxygen demand and systemic inflammation when colchicine was used in moderate to severe cases compared with the non-colchicine group.

The 28-day mortality was lower in the colchicine arm compared to the non-colchicine; 19 patients died in the colchicine arm 15 patients were severe cases needed ICU admission while 4 only died in the medical ward. On the other hand, 58 patients died in the non-colchicine group 33 were in the ICU, while 25 in the medical ward. Mortality was almost 5 folds in the medical ward, and 2 folds in ICU among the non-colchicine group compared to the colchicine group.

About 86.7% (65 patients) had a secondary bacterial infection in the colchicine arm while 75.6% (59 patients) had a secondary bacterial infection in the

control arm. In both arms, 21.6% (33 patients) developed septic shock mainly and needed ICU admission, divided as 10.7% (8 patients) in the colchicine arm and 29.5% (23 patients) in the non-colchicine arm. Unfortunately, no one was survived from those who have been shocked; this highlights the high risk of mortality due to septic shock in addition to the respiratory failure due to COVID-19 disease. Such findings were reported before in many studies which linked between causes of death and septic shock in COVID-19 patients.

Sefer Elezkurtaj *et al.* [30] identified septic shock or multi-organ dysfunction as the first cause of immediate death by 30.8% in patient with COVID-19 infection while **Beltrán-García *et al.* [31]** show that patients with COVID-19 have the criteria of severe sepsis or septic shock, the coagulopathy and hyperinflammation associated with COVID-19 cause multi-organ failure that consistent with severe sepsis, sepsis in about 80% of patients were due to viral infection, leading to 8-38% mortality in ICU, which differs from one country to another.

Although our results show that the mortality percentage was lower in the colchicine arm, but we still uncertain if this result can be attributed totally to the colchicine, this is due to the fact that most of the patients died after ICU admission and there are many risk factors as multidrug resistant nosocomial infection, high APACHE II score and mechanical ventilation, these risk factors may be responsible for the high mortality rate in the ICU [32], many of the patients included in the trial have more than one of these risk factors.

Different doses strategies had been used in several studies to examine the effect of colchicine in hospitalized patients. In this study, the colchicine dose that was used with all patients included was 0.5 mg/12 hr started 48 hours from oxygen saturation decline till discharge without recording any significant adverse effect. Where GRECCO-19 study used a loading dose of 1.5 mg followed by 0.5 mg after 1 hour then a maintenance dose of 0.5mg/12hr for 21 days as a maximum duration, on the other hand, **Lopes *et al.* [29]** go further by using a higher dose of 0.5 mg/8 hrs for the first 5 days then 0.5mg/12hr for the next 5 days.

LIMITATION

This study has some limitations including that most of the study participants' ages were around sixty, which didn't give a true result about the effect of colchicine on younger or older ages. Also most of the patients were admitted to hospital late due to unavailability of hospital beds due to the pandemic and one of the most serious limitations which affects mortality results were the fact that 124 patients from 153 had a secondary bacterial infection, that affects mortality percentage especially those who developed septic shock. Although of all these serious limitations, colchicine showed statistically and clinically significant results.

CONCLUSION

This study shows that colchicine exerts an anti-inflammatory effect that has a great impact on decreasing oxygen demand and ICU admission compared to the non-colchicine arm. However, its effect on mortality is still unclear. Further randomized controlled clinical trials may be needed regarding this point.

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