Taylor & Francis
Taylor & Francis Group

🔓 OPEN ACCESS ✓ Check for updates

Effect of combined use of ivermectin and colchicine in COVID-19 patients

Rania Gamal El Sayed ⓘ, Amr Fouad Hafez ⓘ, Adham Magdy Ahmed Mohammed Haggag ⓘ and Mohamed A. Alhadidy ⓘ

Anesthesia, ICU, and Pain Management Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT
Background: Despite the great results of the SARS-CoV-2 vaccine, there is an increasing need for effective therapeutics. Increasing viral loads are associated with systemic inflammatory response, more disease progression, and increased mortality, while exaggerated immune responses result in immune overreaction and cytokine storm (CS)-induced acute lung injury. We hypothesize that ivermectin by reducing viral load and colchicine by reducing inflammation when used in combination might improve the outcomes of COVID-19 while offering cheap and safe options.
Methods: A total of 135 COVID-19 patients were divided into three groups, with 45 patients in each group (colchicine/colchicine and ivermectin/neither of them). Group (A): ivermectin + colchicine + standard care, Group (B): colchicine + standard care, and Group (C): (control group) standard care.
Results: We found that colchicine was associated with clinically significant decrease in days of oxygen need, length of ICU stay, less need for mechanical ventilation, and less mortality, while ivermectin failed to add any beneficial effect.
Conclusion: Adding ivermectin to the treatment of moderate cases of COVID-19 is not of clinical value, while we support the use of colchicine in such cases.
Trial registration: The trial was registered in February 2022 in ClinicalTrials.gov (NCT05246072).

1. Background

In December 2021, the total number of confirmed cases of the novel coronavirus disease (COVID-19) worldwide exceeded 474 million [1].

Colchicine is a lipophilic tricyclic alkaloid that has been used as a therapy for gout. It inhibits cellular microtubule assembly and binds to the tubulin to form a tubulin–colchicine complex that interferes with microtubule formation in neutrophils [2].

Recent study suggests that activation of the pyrin domain-containing protein 3 (NLRP3) inflammasome is associated with SARS-CoV-2 infection [3], with subsequent activation of interleukin (IL)-1, responsible for the downstream production of IL-6 [4]. Colchicine is known to block (NLRP3) inflammasome [5]. Studies have shown that patients with gout and familial Mediterranean fever who received colchicine did not suffer from severe respiratory complications [6,7].

Moreover, colchicine has no immune suppressive effect, so it offers a safe anti-inflammatory option without the risk of secondary infection or interference with effective viral clearing [8].

Ivermectin is a broad-spectrum antiparasitic drug with antiviral activities. Some studies have shown that ivermectin can inhibit the replication of SARS-CoV-2 at micromolar concentrations and so can be useful to decrease viral load [9–11]. The Frontline COVID-19 Critical Care Alliance recommends the use of oral ivermectin for both prophylaxis and early treatment of COVID-19 [12]. While the American National Institutes of Health does not recommend for or against ivermectin, instead they allowed its use in the treatment of COVID-19 in the USA [13].

We hypothesize that colchicine and ivermectin when used in combination might improve the outcomes of COVID-19. By decreasing the viral load and diminishing the inflammatory burden, the ivermectin and colchicine combination may be an intervention worthy of being tested, since they have a well-known safety profile, widespread availability, and low cost.

1.1. Trial registration and ethical committee approval

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional research committee, as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This work was approved by the Ethics committee of Ain

---

Shams University Hospital (FMASU R 179/2021) on 30/10/2021. The study was registered with Trial registration and ethical approval: clinical trials (www.clinicaltrials.gov) database ID no (NCT05246072).

2. Methods and measurements

A 3-month prospective randomized controlled clinical trial was conducted at Ain Shams University Isolation Hospitals, from 1 November 2021 to 28 February 2022.

3. Randomization and patient allocation

Eligibility criteria for this study included the American Society of Anesthesiologists (ASA) physical status II–III, subjects of both sexes, 18–80 years of age, currently hospitalized, and requiring medical care for moderate COVID-19 by the WHO clinical progression scale (score 4–5) [14] (Table 1), with a positive PCR test or positive antibodies. Exclusion criteria included Tocilizumab use, mechanical ventilation or requirement of oxygen supplementation >8 L/min on admission, pregnancy, known hypersensitivity to ivermectin or colchicine, hemodynamic instability, history of liver disease, severe renal disease, Cr.Cl <30 ml/min, colchicine or ivermectin therapy before inclusion, and the patient is on a CYP3A4 inhibitor (e.g., clarithromycin, nelfinavir, ritonavir, saquinavir, telithromycin, atazanavir, diltiazem, verapamil).

4. Sampling method

By using PASS 11 program for sample size calculation, setting confidence level at 90%, margin of error ± 0.15, and after reviewing previous study results, Scarsi et al. [15] showed that adding colchicine to standard of care (SOC) was associated with better survival in patients with COVID-19 pneumonia or acute respiratory distress when compared to (SOC) only (84.4% vs 63.65 respectively); based on that, a sample size of 135 COVID-19 patients (divided into three groups – 45 patients in each group (colchicine/colchicine and ivermectin/neither of them)) will be sufficient to achieve the study objective

Group A: Ivermectin + colchicine + (SOC), Group B: colchicine + (SOC), and Group C (control): (SOC).

4.1. Ethical considerations

Approval of the Ethical Committee of the Faculty of Medicine-Ain Shams University and written informed consent from all participants or their legal guardians will be obtained.

4.2. Patients' interventions and management

Detailed baseline data, including demographics and comorbidities, were recorded.

Patients were allocated to one of the three groups:

Group A: Ivermectin + colchicine + standard of care. In addition to the local (SOC) for COVID-19 patients, the patient received Ivermectin 6 mg (4 tabs daily for 4

Table 1. The WHO clinical progression scale. ECMO = extracorporeal membrane oxygenation. FiO_2 = fraction of inspired oxygen. NIV = non-invasive ventilation. pO_2 = partial pressure of oxygen. SpO_2 = oxygen saturation. *If hospitalized for isolation only, record status as for ambulatory patient [14].

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

successive days on an empty stomach) + Colchicine PO, as such, 0.5 mg TID for 5 days, then 0.5 mg BID for 14 days, or until discharge.

Group B: Colchicine + standard care. In addition to the (SOC) for COVID-19 patients, the patient received Colchicine PO as 0.5 mg TID for 5 days, then 0.5 mg BID for 14 days, or until discharge.

Group C: (control group) standard care [patients received (SOC) according to the established contemporary hospital protocols, which includes Remdesivir 100 mg amp IV (*200 mg on the first day, then 100 mg daily for 5–10 days*), Dexamethasone 6 mg/day for 10 days, Enoxaparin 40 IU SC once daily, Omeprazole 40 mg PO once daily, and Paracetamol 500 g PRN or up to 2 gm/day].

The definition of the requirement of oxygen supply will be a measure of $SatO_2 \leq 92\%$ on room air at rest.

The criteria for discharging patients from the hospital were the absence of dyspnea and $SatO_2 > 92\%$ on room air, both for at least 48 consecutive hours.

5. Main endpoints

Patients were followed up throughout their stay in the hospital until death or discharge

The primary endpoint was:

- 28-day mortality rate.

The secondary endpoints were
- The length of oxygen requirement.
- Clinical deterioration by the WHO clinical progression scale (marked by increase oxygen requirements >8 liters/min to maintain $SPO_2 > 92\%$).
- The need for ICU admission.

- The need for mechanical ventilation.
- The length of stay in ICU.
- Complications observed from study drugs.

5.1. Statistical methods

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY). Numerical data are presented as mean and SD, and intergroup differences are compared using one-way analysis of variance (ANOVA) with application of the Tukey post-hoc test for pairwise comparisons. Categorical data are presented as counts and percentages and differences are compared using the chi-squared test or Fisher's exact test. Time-to-event analysis is done using the Kaplan–Meier method. The log-rank test is used to compare the Kaplan–Meier curves, to adjust for other variables. Cox proportional hazard regression analysis was used for time-to-event analysis. Multivariable binary logistic regression analysis is used to examine the independent effect of ivermectin or colchicine on the occurrence of main outcomes. To examine the independent effect of either intervention on numerical outcomes, multiple regression is used. P-value < 0.05 is considered statistically significant.

6. Results

A total of 135 patients with COVID-19 were enrolled in our study, and there was no statistically significant difference between both groups in terms of demographic data and baseline characteristics at inclusion (Table 2).

Table 2. Baseline characteristics and comorbidities of the three study groups.

Variable	Ivermectin–Colchicine (N = 45)	Colchicine (N = 45)	Control (N = 45)	P-value
Age (years), mean ± SD	57.1 ± 6.6	57.0 ± 7.3	57.6 ± 5.9	0.901a
Male Sex, n (%)	23 (51.1%)	24 (54.5%)	23 (51.1%)	0.933b
Smoker, n (%)	11 (24.4%)	5 (11.1%)	14 (31.1%)	0.067b
Ex-smoker, n (%)	0 (0.0%)	0 (0.0%)	2 (4.4%)	0.328c
Alcohol consumption, n (%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	>0.999c
DM, n (%)	14 (31.1%)	9 (20.0%)	12 (26.7%)	0.481b
HTN, n (%)	15 (33.3%)	14 (31.1%)	10 (22.2%)	0.469b
IHD, n (%)	3 (6.7%)	1 (2.2%)	2 (4.4%)	0.871c
CHF, n (%)	1 (2.2%)	2 (4.4%)	0 (0.0%)	0.773c
AF, n (%)	3 (6.7%)	0 (0.0%)	1 (2.2%)	0.323c
MVR, n (%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	>0.999c
BA, n (%)	3 (6.7%)	1 (2.2%)	3 (6.7%)	0.699c
COPD, n (%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	>0.999c
CVS, n (%)	1 (2.2%)	0 (0.0%)	2 (4.4%)	0.773c
HCV, n (%)	0 (0.0%)	2 (4.4%)	2 (4.4%)	0.546c
CKD, n (%)	1 (2.2%)	1 (2.2%)	3 (6.7%)	0.618c
Hypothyroidism, n (%)	1 (2.2%)	1 (2.2%)	2 (4.4%)	>0.999c
SLE, n (%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	>0.999c
WHO-CPS 5, n (%)	43 (95.6%)	42 (93.3%)	43 (95.6%)	>0.999c

a. One-way analysis of variance
b. Pearson chi-squared test
c. Fisher's exact test

Incidence of death was 17.8% in group A (colchicine- ivermectin combination),13.5% in group B (colchicine group) and 35.6% in group C (control group) differences between groups using Pearson chi-squared test were statistically significant (P = 0.027). In terms of secondary outcomes, there was a statistically significant reduction in length of oxygen need in group A (colchicine–ivermectin combination) compared to the control group (p = 0.001) all three groups were comparable regarding need for ICU admission and rate of deterioration by the WHO clinical progression scale marked by increase oxygen requirement >8 liters/min to maintain SPO2 > 92% (p = 0.183). There was a statistically significant less length of stay in ICU and hospital in group A compared to the control group, also differences between groups in terms of need for invasive mechanical ventilation were significant (p = 0.042) (Table 3 and Figure 1).

To assess each independent variable and its impact on each outcome, we used multivariable binary logistic regression and the results were as follows:

(1) Use of colchicine was associated with a statistically significant reduction in mortality (adjusted odds ratio = 0.199, 95% CI = 0.059 to 0.663, P = 0.009), while increased age was associated with a statistically significant increase in mortality (adjusted odds ratio = 1.202, 95% CI = 1.102 to 1.312, P < 0.0001).

(2) Use of ivermectin was not associated with a statistically significant effect on mortality (adjusted odds ratio = 1.596, 95% CI = 0.450 to 5.658, P = 0.469) (Supplementary table 1).

(3) Use of colchicine was associated with a statistically significant reduction in days of oxygen need (B = −3.387, SE = 1.618, P = 0.038), while increased age was associated with a statistically significant increase in days of oxygen need (B = 0.392, SE = 0.101, P = 0.0002).

(4) Use of ivermectin was not associated with a statistically significant effect on the length of oxygen need (B = −2.777, SE = 1.617, P = 0.088) (Supplementary table 2).

(5) Use of neither ivermectin (adjusted odds ratio = 1.292, 95% CI = 0.494 to 3.375, P = 0.601) nor colchicine (adjusted odds ratio = 0.427, 95% CI = 0.167 to 1.090, P = 0.075) was a determinant for clinical deterioration by the WHO clinical progression scale marked by increase oxygen requirements >8

Table 3. Main outcome measurements in the three study groups.

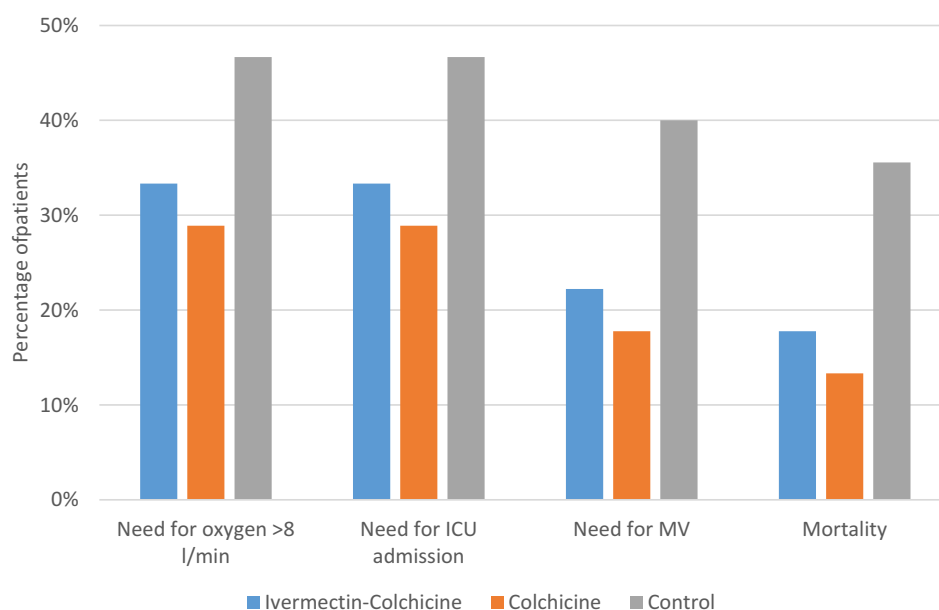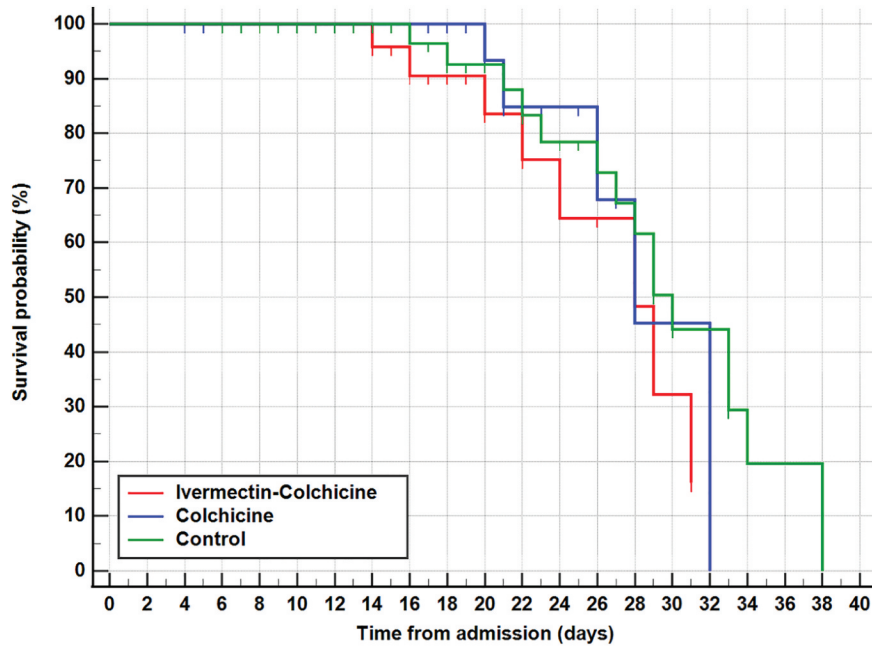| Variable	Ivermectin–Colchicine (N = 45)	Colchicine (N = 45)	Control (N = 45)	P-value
Days on oxygen, mean ± SD	12.9 ± 8.1c	15.6 ± 7.0	19.3 ± 9.0	**0.001**a
Need for oxygen >8 l/min, n (%)	15 (33.3%)	13 (28.9%)	21 (46.7%)	0.189b
Need for ICU admission, n (%)	15 (33.3%)	13 (28.9%)	21 (46.7%)	0.189b
Days in ICU	11.9 ± 3.9d	12.8 ± 5.8	17.1 ± 6.0	**0.005**a
Need for MV, n (%)	10 (22.2%)	8 (17.8%)	18 (40.0%)	**0.042**b
Mortality, n (%)	8 (17.8%)	6 (13.5%)	16 (35.6%)	**0.027**b
Hospital LOS (days), mean ± SD	15.5 ± 7.0e	16.2 ± 6.9	20.0 ± 9.0	**0.009**a

a.One-way analysis of variance
b.Pearson chi-squared test
c.P = 0.001 vs Control (Tukey test)
d.P = 0.015 vs Control (Tukey test)
e.P = 0.016 vs Control (Tukey test)

Figure 1. Main outcome measurements in the three study groups.

Figure 2. Kaplan–Meier survival curves in the three studied groups. Median survival (95% CI) = 28 (22, 31) days, 28 (26, 32) days, or 30 (26, 34) days in the Ivermectin–Colchicine Group, Colchicine Group, or Control Group, respectively. Differences among the three groups are not statistically significant (log-rank chi-squared = 2.210, df = 2, P = 0.331) .

liters/min to maintain SPO^2 > 92%. However, age was an independent predictor for oxygen need for >8 days (adjusted odds ratio = 1.136, 95% CI = 1.063 to 1.214, P = 0.0002) (Supplementary table 3).

(6) Use of neither ivermectin (adjusted odds ratio = 1.292, 95% CI = 0.494 to 3.375, P = 0.601) nor colchicine (adjusted odds ratio = 0.427, 95% CI = 0.167 to 1.090, P = 0.075) was a determinant for ICU admission. However, age was an independent predictor for admission to the ICU (adjusted odds ratio = 1.136, 95% CI = 1.063 to 1.214, P = 0.0002) (Supplementary table 4).

(7) Use of colchicine was associated with a statistically significant reduction in the need for mechanical ventilation (adjusted odds ratio = 0.297, 95% CI = 0.107 to 0.824, P = 0.020), while increased age was associated with a statistically significant increase in the need for mechanical ventilation (adjusted odds ratio = 1.113, 95% CI = 1.039 to 1.193, P = 0.002).

(8) Use of ivermectin was not associated with a statistically significant effect on the need for mechanical ventilation (adjusted odds ratio = 1.376, 95% CI = 0.466 to 4.059, P = 0.563) (Supplementary table 5).

Median survival (95% CI) = 28 (22, 31) days, 28 (26, 32) days, or 30 (26, 34) days in the Ivermectin-Colchicine Group, Colchicine Group, or Control Group,

respectively, as shown in the Kaplan–Meier survival curves. Differences among the three groups are not statistically significant (log-rank chi-squared = 2.210, df = 2, P = 0.331) (Figure 2).

(9) There was no statistically significant difference between groups regarding complications of study drugs (Supplementary table 6).

(10) Colchicine–ivermectin combination was associated with significant shorter length of hospital stay when compared to control (P = 0.009) and significant less length of ICU stay when compared to control (P = 0.005). However, further analysis using Cox proportional hazard regression analysis for time to event analysis showed that

i. Increased age was the only determinant of survival to hospital discharge (Cox proportional hazard = 1.111, 95% CI = 1.040 to 1.188, P-value = 0.002). Neither ivermectin (Cox proportional hazard = 1.788, 95% CI = 0.603 to 5.302, P-value 0.295) nor colchicine (Cox proportional hazard = 1.633, 95% CI = 0.581 to 4.594, P-value 0.353) was a predictor of survival to hospital discharge (supplementary table 7).

ii. Increased age was the only determinant of survival to ICU discharge (Cox proportional hazard = 1.097, 95% CI = 1.030 to 1.168, P-value = 0.004). Neither ivermectin (Cox proportional hazard = 1.983, 95% CI = 0.671 to

5.862, P-value 0.216) nor colchicine (Cox proportional hazard = 1.830, 95% CI = 0.661 to 5.066, P-value 0.245) was a predictor of survival to ICU discharge (supplementary table 8).

7. Discussion

Most of the published data report the superiority of colchicine in COVID-19 patients, some of which evaluated its use in prehospitalization settings like the ColCORONA trial [16] and others during hospitalization [17,18].

In our study, we thought about evaluating the efficacy of combining colchicine with ivermectin vs colchicine vs neither of them in the management of non-severe cases of COVID-19 admitted in the hospital.

Our study initially revealed that combining colchicine and ivermectin was superior in terms of mortality, and only after adjustment, colchicine was shown to be the key for lower mortality, while ivermectin was not. Also neither colchicine nor ivermectin was a predictor of length of hospital or ICU stay among survivors, and after adjustment, we were also able to show that colchicine was the key for early weaning from oxygen and less need for mechanical ventilation, while ivermectin was not .

Regarding days of oxygen need, our results agree with the results of Lopes and his colleagues [19], who found that colchicine reduced the length of supplemental oxygen therapy as half of the patients receiving colchicine in their study were weaned off oxygen on day 4 (median 4.0; IQR 2.0–6.0 days) of intervention, while it took 7 days for patients receiving placebo (median 6.5; IQR 4.0–9.0 days; p < 0.001).

Also, agreeing with our results, a cohort study done by Brunette et al. [18] showed that the receipt of colchicine was associated with the WHO ordinal scale for clinical improvement (OSCI) score <4 by day 28 (indicating weaning of oxygen requirements) (78.8%) vs (54.5%) in non-colchicine group OR 3.10 (p = 0.040).

While those who received ivermectin–colchicine combination showed significant fewer days of oxygen need, multivariable binary logistic regression showed that ivermectin was not the key for success of that group and it offered no additive benefits to colchicine in terms of weaning from oxygen requirements; this goes with findings by López-Medina and colleague [20] who found no difference between ivermectin vs placebo as regard the time of symptoms resolution (median, 10 days vs 12 days; difference, −2 days, IQR, −4 to 2; hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = 0.53).

Neither colchicine nor ivermectin was a determinant factor in the prevention of clinical deterioration by the WHO clinical progression scale (indicated by increasing oxygen requirements >8 liters/min to maintain SPO_2 > 92%). Regarding colchicine, Pascual-Figal [21] and his colleagues mentioned that in the adjusted analysis of their results; colchicine administration to hospitalized patients with non-severe COVID-19 seemed to protect against 1-point deterioration on WHO scale (OR 0.11, 95% CI 0.01, 0.68, P = 0.03).

When it comes to ivermectin, our results agree with the conclusion by Lim et al. [22] who found that ivermectin given to hospitalized patients with mild-to-moderate COVID-19 disease did not prevent progression to severe disease.

Our results showed that neither colchicine nor ivermectin was a determinant factor in the rate of ICU admission. In line with our study, Karakaş Ö and his colleagues [23] failed to show a significant difference in the rate of ICU admission between colchicine-recipient and non-colchicine groups. However, they observed reduced rates of ICU admission in patients who received colchicine with a dose of 1 mg/day when compared to patients who received 0.5 mg/day (p = 0.011) which pointed to the beneficial effect of higher colchicine dosages.

Regarding ivermectin, a meta-analysis by Karale and his colleagues [24] included a total of 38 studies found that there were no significant benefits for ivermectin in decreasing the need for admission to ICU (OR 0.48, 95% CI 0.17–1.37; I2 = 59%) and mechanical ventilation (OR 0.64, 95% CI 0.40–1.04; I2 = 17%).

Colchicine was associated with a statistically significant reduction in the need for mechanical ventilation, in line with our study Diaz [25] and his colleagues showed a modest benefit from colchicine in some patients through a lower rate of new intubation or respiratory failure deaths (p = 0.04). Also in a retrospective study by Sandhu et al. [26] Patients who received colchicine showed lower rates of intubation when compared to the control group (7.1% vs 87.2%, P < 0.0001).

Agreeing with many other clinical trials [22,24,27], ivermectin did not reduce the need for mechanical ventilation.

Data about the effectiveness of colchicine on long-term outcomes of mortality rates are conflicting. In a meta-analysis by Chiu et al. [28], evaluating eight studies on 16,248 patients showed that when colchicine is administered in hospitalized patients and excluding the Recovery trial [29], it was associated with a lower risk of mortality Hazard ratio of 0.25 (95% CI: 0.09, 0.66) and odds ratio of 0.22 (95% CI: 0.09, 0.57), while the Recovery trial that included 11,340 patients reported no difference in mortality odds ratio of 1.02 (95% CI: 0.94, 1.11), our study showed less mortality with colchicine usage (adjusted odds ratio = 0.199, 95% CI = 0.059 to 0.663, P = 0.009), it should be taken in consideration that colchicine therapy in the RECOVERY trial was of smaller dose and for a shorter duration than ours.

First look at our results regarding the length of ICU stay and the length of hospital stay suggests a significant earlier discharge when combining colchicine and ivermectin in the therapy protocol (p = 0.005 and p = 0.009, respectively). However, when Cox proportional hazard regression analysis for time to event was used to calculate length of stay among survivors only (excluding early deaths as a cause of less length of stay), patients' age was shown to be the only predictor for length of stay in ICU and hospital and neither colchicine nor ivermectin had an impact, this agrees with the recovery trial [29] which found that colchicine was not associated with earlier discharge from hospital (p = 0.44), on the other hand, Abd-Elsalam and his colleagues [30] found nonsignificant reduction in length of hospital stay when ivermectin was added to standard of care (p = 0.085).

It was noticeable that the older age was an independent predictor for admission to ICU, and was associated with a significant increase in the rate of need for invasive mechanical ventilation, length of hospital stay, and length of ICU stay.

While we failed to show any beneficial effect of ivermectin, we think this might owe to the elapsed time till ivermectin was provided to the selected patients in our study since drugs with the antiviral property are less effective when started in the late course of the disease. Also, it suggested that ivermectin like other TMPRSS2 inhibitors might be less effective in the omicron variant which shows TMPRSS2-independent fusion [31].

Drugs in our study have a well-known safety profile, widespread availability, the majority of events that occurred during therapy were mild and could be attributed to viral infection itself or its subsequent complications and not necessitating drug withdrawal.

8. Limitation

(1) Sample size.
(2) We started ivermectin in hospitalized patients (moderate disease) taking into consideration that ivermectin may work better in the earlier course of the disease; better results might have evolved if ivermectin was started in ambulatory patients (mild disease).
(3) Lack of data on inflammatory markers.
(4) We cannot generalize our findings since our study population age group was older. However, younger, and healthier age groups are less likely to develop severe disease.

9. Conclusion

Our data suggest that adding ivermectin to for hospitalized patients with moderate COVID-19 WHO clinical progression scale (score 4–5) is not of clinical value, while we support the use of colchicine since it is associated with reduced mortality and accelerated recovery.

ORCID

Rania Gamal El Sayed http://orcid.org/0000-0001-6922-6137
Amr Fouad Hafez http://orcid.org/0000-0002-3198-8491
Adham Magdy Ahmed Mohammed Haggag http://orcid.org/0000-0002-7069-6707
Mohamed A. Alhadidy http://orcid.org/0000-0002-6430-4332

References

[1] University JH. Coronavirus resource center. 2022. Published 2020 [cited 2022 March 23]. Available from: https://coronavirus.jhu.edu/.
[2] Leung YY, Yao Hui LL, Kraus VB. Colchicine–Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015 Dec;45(3):341–350.
[3] Pan P, Shen M, Yu Z, et al. SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. Nat Commun. 2021 Aug 2; 12 (1):4664.
[4] Bonaventura A, Vecchié A, Dagna L, et al. Colchicine for COVID-19: targeting NLRP3 inflammasome to blunt hyperinflammation. Inflamm Res. 2022Mar;71 (3):293–307. Epub 2022 Feb 3. PMID: 35113170; PMCID: PMC8811745.
[5] Marques-da-Silva C, Chaves MM, Castro NG, et al. Colchicine inhibits cationic dye uptake induced by ATP in P2X2 and P2X7 receptor-expressing cells: implications for its therapeutic action. Br J Pharmacol. 2011Jul;163(5):912–926. PMID: 21306580; PMCID: PMC3130939.
[6] Bourguiba R, Delplanque M, Vinit C, et al. Clinical course of COVID-19 in a cohort of 342 familial Mediterranean fever patients with a long-term treatment by colchicine in a French endemic area. Ann Rheum Dis. 2020 Nov 2; annrheumdis-2020-218707 doi:10.1136/annrheumdis-2020-218707. Epub ahead of print. PMID: 33139307
[7] Pelechas E, Drossou V, Voulgari PV, et al. COVID-19 in patients with gout on colchicine. Rheumatol Int. 2021Aug;41(8):1503–1507. Epub 2021 Jun 5. PMID: 34089357; PMCID: PMC8178663.
[8] Reyes AZ, Hu KA, Teperman J, et al. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. Ann Rheum Dis. 2021May;80(5):550–557. Epub 2020 Dec 8. PMID: 33293273; PMCID: PMC8491433.

[9] Wagstaff KM, Sivakumaran H, Heaton SM, et al. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443 (3):851–856.

[10] Sim¸sek Yavuz S, Unal S. Antiviral treatment of COVID-19. Turk J Med Sci. 2020;50(SI–1):611–619.

[11] Caly L, Druce JD, Catton MG, et al. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;3:104787.

[12] Kory P, Meduri GU, Varon J, et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. Am J Ther. 2021Apr22;28(3):e299–e318. Erratum in: Am J Ther. 2021 Nov-Dec 01;28(6):e813. PMID: 34375047; PMCID: PMC8088823.

[13] Coronavirus Disease. (COVID-19) treatment guidelines [Internet]. Bethesda (MD): National Institutes of Health (US); 2021 Apr 21 2022 Mar 24 2019. PMID: 34003615

[14] Marshall JC, Murthy S, Diaz J. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020 Aug;20(8):e192–e197.

[15] Scarsi M, Piantoni S, Colombo E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020Oct;79 (10):1286–1289. Epub 2020 Jul 30. PMID: 32732245; PMCID: PMC7509521.

[16] Tardif JC, Bouabdallaoui N, L'Allier PL, et al. COLCORONA investigators. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multi-centre trial. Lancet Respir Med. 2021Aug;9 (8):924–932. Epub 2021 May 27. PMID: 34051877; PMC ID: PMC8159193.

[17] Vrachatis DA, Giannopoulos GV, Giotaki SG, et al. Impact of colchicine on mortality in patients with COVID-19: a meta-analysis. Hellenic J Cardiol. 2021Sep-Oct;62(5):374–377. Epub 2021 Jan 6. PMID: 33421583; PMCID: PMC7833703.

[18] Brunetti L, Diawara O, Tsai A, et al. Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. J Clin Med. 2020 Sep 14; 9(9):2961.

[19] Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD Open. 2021 Feb;7(1):e001455.

[20] López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA. 2021;325(14):1426–1435.

[21] Pascual-Figal DA, Roura-Piloto AE, Moral-Escudero E, et al. COL-COVID investigators. Colchicine in recently hospitalized patients with COVID-19: a randomized controlled trial (COL-COVID). Int J Gen Med. 2021 Sep 11; 14:5517–5526

[22] Lim SCL, Hor CP, Tay KH, et al. Efficacy of ivermectin treatment on disease progression among adults with mild to moderate COVID-19 and comorbidities: the I-TECH randomized clinical trial. JAMA Intern Med. cited 2022 Feb 18 182(4):426.

[23] Karakaş Ö, Erden A, Güven SC, et al. Reducing length of hospital stay with colchicine. J Infect Dev Ctries. 2022 Jan 31; 16(1):57–62.

[24] Karale S, Bansal V, Makadia J, et al. A meta-analysis of mortality, need for ICU admission, use of mechanical ventilation and adverse effects with ivermectin use in COVID-19 patients. medRxiv. 2021. preprint at. doi:10.1101/2021.04.30.21256415.

[25] Diaz R, Orlandini A, Castellana N, et al. ECLA PHRI COLCOVID trial investigators. effect of colchicine vs usual care alone on intubation and 28-Day mortality in patients hospitalized with COVID-19: a randomized clinical trial. JAMA Network Open. 2021 Dec 1; 4(12):e2141328.

[26] Sandhu T, Tieng A, Chilimuri S, et al. A case control study to evaluate the impact of colchicine on patients admitted to the hospital with moderate to severe COVID-19 infection. Can J Infect Dis Med Microbiol. 2020;2020:8865954. Oct 27.

[27] Reis G, Easm S, Silva DCM, et al. TOGETHER investigators. Effect of early treatment with ivermectin among patients with covid-19. N Engl J Med. 2022 Mar 30; 386 (18):1721–1731.

[28] Chiu L, Lo CH, Shen M, et al. Colchicine use in patients with COVID-19: a systematic review and meta-analysis. PLoS One. 2021 Dec 28; 16(12):e0261358.

[29] RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Respir Med. 2021 Dec;9(12):1419–1426.

[30] Abd-Elsalam S, Noor RA, Badawi R, et al. Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: a randomized controlled study. J Med Virol. 2021Oct;93(10):5833–5838. Epub 2021 Jun 7. PMID: 34076901; PMCID: PMC8242425.

[31] Zhao H, Lu L, Peng Z, et al. SARS-CoV-2 omicron variant shows less efficient replication and fusion activity when compared with delta variant in TMPRSS2-expressed cells. Emerg Microbes Infect. 2022 Dec;11(1):277–283.