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Colchicine and high-intensity rosuvastatin in the treatment of non-critically ill patients hospitalised with COVID-19: a randomised clinical trial

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ABSTRACT

Objective To evaluate the effect of colchicine and high-intensity rosuvastatin in addition to standard of care on the progression of COVID-19 disease in hospitalised patients.

Design A pragmatic, open-label, multicentre, randomised controlled trial conducted from October 2020 to September 2021. Follow-up was conducted at 30 and 60 days. The electronic medical record was used at all stages of the trial including screening, enrolment, randomisation, event ascertainment and follow-up.

Setting Four centres in the Yale New Haven Health System.

Participants Non-critically ill hospitalised patients with COVID-19.

Interventions Patients were randomised 1:1 to either colchicine plus high-intensity rosuvastatin in addition to standard of care versus standard of care alone. Assigned treatment was continued for the duration of index hospitalisation or 30 days, whichever was shorter.

Primary and secondary outcome measures The prespecified primary endpoint was progression to severe COVID-19 disease (new high-flow or non-invasive ventilation, mechanical ventilation, need for vasopressors, renal replacement therapy or extracorporeal membrane oxygenation, or death) or arterial/venous thromboembolic events (ischaemic stroke, myocardial infarction, deep venous thrombosis or pulmonary embolism) evaluated at 30 days.

Results Among the 250 patients randomised in this trial (125 to each arm), the median age was 61 years, 44% were women, 15% were Black and 26% were Hispanic/Latino. As part of the standard of care, patients received remdesivir (87%), dexamethasone (92%), tocilizumab (18%), baricitinib (2%), prophylactic/therapeutic anticoagulation (98%) and aspirin (91%). The trial was terminated early by the data and safety monitoring board for futility. No patients were lost to follow-up due to electronic medical record follow-up. There was no significant difference in the primary endpoint at 30 days between the active arm and standard of care arm (15.2% vs 8.8%, respectively, p=0.17).

Conclusions In this small, open-label, randomised trial of non-critically ill hospitalised patients with COVID-19, the combination of colchicine and rosuvastatin in addition to standard of care did not appear to reduce the risk of progression of COVID-19 disease or thromboembolic events, although the trial was underpowered due to a lower-than-expected event rate. The trial leveraged the power of electronic medical records for efficiency and improved follow-up and demonstrates the utility of incorporating electronic medical records into future trials.

Trial registration NCT04472611.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised, multicentre clinical trial enrolled a diverse group of patients in a large health system.
⇒ All events were adjudicated by an independent clinical events committee.
⇒ The trial was open-label and hence healthcare providers and subjects were not blinded.
⇒ Patients on prior statins were not excluded, limiting the effect size of the intervention.
⇒ The trial was underpowered due to a lower-than-expected event rate.

INTRODUCTION

COVID-19 continues to spread worldwide, with significant morbidity and mortality in hospitalised patients despite improvements in in-hospital standard of care (SOC).[1–5] This is driven by COVID-19-mediated hyperinflammatory response,[6] including activation of the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome (implicated in lung injury),[7 8] ACE2 downregulation (implicated in lung and cardiac injuries),[9] coagulopathy[10 11] and endothelial damage/inflammation.[12 13] These mechanisms all

contribute to lung and cardiac injuries as well as arterial and venous thromboses seen in these patients.

Both colchicine and statins are widely available medications that could potentially mitigate the pathological effects of COVID-19. Colchicine has multiple anti-inflammatory effects, including downregulation of the NLRP3 inflammasome[14–17] and reduction in endothelial inflammation.[18 19] Similarly, statins also mitigate inflammation, reduce thrombotic risk and endothelial dysfunction and upregulate ACE2.[9 20–25] Despite these potential benefits, there has been mixed evidence on the efficacy of colchicine[26–31] and statins[32–36] in the treatment of patients with COVID-19.

In addition to their individual benefits, both colchicine and statins have been found to work synergistically to improve vascular inflammation in both animal models[37] and clinical trials.[18 19] In addition, both medications have been used together successfully with minimal adverse events[18 19] and were thus deemed promising candidate to be used in combination. Here we report the results of the Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) trial, a pragmatic, open-label, multicentre, randomised controlled trial studying the effect of the combination of colchicine and high-intensity rosuvastatin for the treatment of non-critically ill patients with COVID-19.

METHODS

Trial design

The COLSTAT trial randomised patients 1:1 to colchicine and high-intensity rosuvastatin plus SOC versus SOC alone. The design and rationale of this trial have been detailed previously.[38] The trial was conducted in four hospitals in the Yale New Haven Health System (YNHHS) and was coordinated by using the system's electronic medical record (EMR; Epic Systems) at all stages including screening, randomisation, intervention and follow-up.

Participants

Participants were eligible for the trial if they were 18 years or older, had a documented positive SARS-CoV-2 PCR test and were being admitted to a non-intensive care unit (ICU) for COVID-19. Participants were only eligible if they were admitted to the hospital within 72 hours of enrolment for COVID-19. There was no limitation on enrolment based on days since symptom onset. Written informed consent of the subjects or their legal decision-makers was obtained from all participants, sometimes electronically. Patients were excluded if they required ICU admission before enrolment, had an allergy to colchicine or statins, were on colchicine prior to enrolment, had severely reduced glomerular filtration rate (GFR) <30 mL/min, severe QTc prolongation, elevated creatine kinase, transaminitis or a severe cytopaenia. Notably, patients with antecedent statin use were not excluded. Further details can be found in the study protocol (online supplemental material).

Randomisation

This was an open-label trial given its pragmatic nature. Trial participants were randomised in a 1:1 ratio to the active or SOC arm using simple randomisation through an internal random number generator of the EMR.

Interventions

Patients randomised to the active arm were started on colchicine (0.6 mg two times daily for 3 days followed by 0.6 mg daily) and high-intensity rosuvastatin (40 mg daily) for the duration of hospitalisation or 30 days, whichever was shorter. All other treatments for patients in both the active and control arms were based on SOC as guided by the YNHHS COVID-19 treatment algorithm, which was updated throughout the pandemic as new evidence became available. Patients in the active arm who were on statins prior to enrolment were switched to rosuvastatin 40 mg daily and then transitioned back to their home dose on discharge or at 30 days, whichever was shorter. In the control arm, patients were continued on their home statin dose throughout hospitalisation. Doses for both colchicine and rosuvastatin were adjusted based on GFR and concomitant medications as detailed in the study protocol. Study drugs were discontinued if there was a concern for treatment-related adverse events after discussion with the study investigator.

Outcomes

The primary efficacy endpoint was the progression of COVID-19 disease or arterial/venous thromboembolic complications at 30 days. Progression of COVID-19 disease was classified by the WHO ordinal scale of clinical improvement as detailed previously[38] and included new requirements for high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) (WHO score 5), mechanical ventilation (WHO score 6), pressors, renal replacement therapy or extracorporeal membrane oxygenation (WHO score 7) or death (WHO score 8). Arterial/venous thromboembolic complications included imaging-confirmed deep venous thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction (MI)[39] and ischaemic stroke.[40] All imaging tests were left to the discretion of the primary team. The secondary powered efficacy endpoint was the 30-day composite of new mechanical ventilation requirement, any myocardial injury (ie, 1 troponin >99th percentile of upper reference limit, a greater than or equal to twofold increase if troponin elevated at baseline or a reduction in left ventricular ejection fraction by >10%) or death.

Trial oversight

The study was exempt from investigational new drug application by the Food and Drug Administration, was approved by Yale Institutional Review Board (IRB Protocol ID: 2000027950) and was registered with

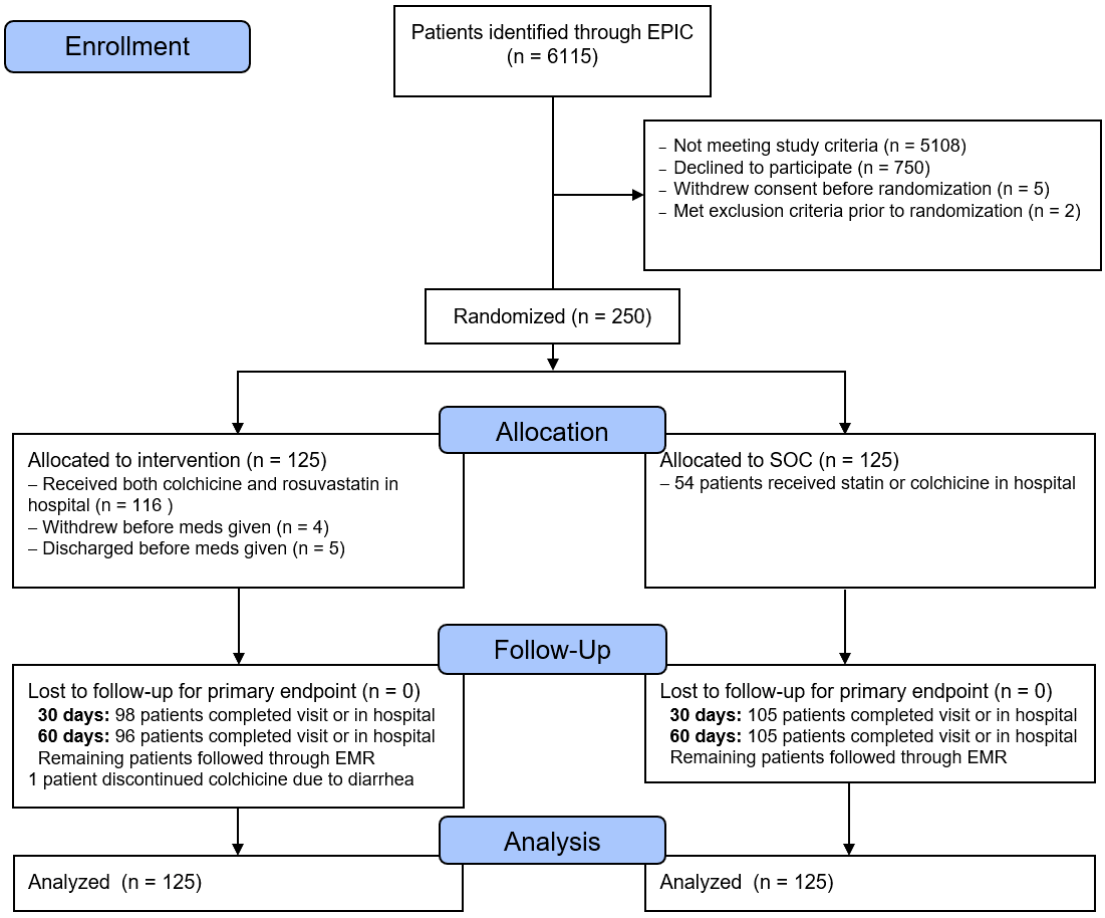

Figure 1 Patient flow diagram of the COLSTAT trial. COLSTAT, Colchicine/Statin for the Prevention of COVID-19 Complications; EMR, electronic medical record; SOC, standard of care.

ClinicalTrials.gov (NCT04472611). An independent data and safety monitoring board (DSMB) was responsible for the oversight of the study. An independent clinical events committee (CEC) adjudicated all primary and clinically significant secondary events potentially meeting endpoint criteria during and after trial completion. Adverse events were screened for remotely through patients' charts while patients were in hospital, and the primary teams for each patients were notified about potential adverse events that would warrant trial medication discontinuation through a note placed in the chart. Significant adverse events were also categorised based on their severity and relationship to trial medications. Given the novelty of using the EMR to extract data on demographics, comorbidities, laboratory values and outcomes, a subset of the data regarding patient baseline characteristics and laboratory values was validated manually.

Patient and public involvement

No patient involved.

Protocol amendments

In March 2021, in light of slower than excepted enrolment and lower than expected event rate per the DSMB, the inclusion/exclusion criteria and primary endpoint were amended as detailed elsewhere.[38] The primary changes were to allow for enrolment within 72 hours of hospital admission, rather than 48 hours and to allow for enrolment of patients on HFNC and NIV which was not allowed initially. Similarly, the primary endpoint was expanded to include venous and arterial thromboembolic complications.

Statistical analysis

Details regarding the trial's sample size and power calculations have been presented previously.[38] Briefly, the planned sample size was 466 subjects (233 in each arm) which would have provided ≥80% power to detect an assumed 30% relative difference in the primary endpoint at an alpha level of 0.05. The rate of loss to follow-up at 30 days was expected to be 10%. The primary analysis was done in the intention-to-treat population. A secondary analysis was done in the per-protocol (PP) population where patients in the active arm were excluded if they did not receive at least one dose of both trial medications in hospital and patients in the SOC arm were excluded if they received a dose of colchicine during the index hospitalisation. Prespecified sensitivity analyses were done excluding patients in the SOC arm who received statins and also comparing patients who received any statin in the hospital with those who did not. For all group

Table 1 Patientcharacteristics by treatment group

	Colchicine+rosuvastatin	Standard of care	P value
Age, years	59.0 (49.0, 71.0)	62.0 (50.0, 74.0)	0.24
Male sex	69/125 (55.2%)	70/125 (56.0%)	1.00
Race			
African American/Black	24/125 (19.2%)	13/125 (10.4%)	0.07
Asian	0/125 (0.0%)	2/125 (1.6%)	0.50
Caucasian/White	76/125 (60.8%)	81/125 (64.8%)	0.60
Native Hawaiian/Pacific Islander	0/125 (0.0%)	1/125 (0.8%)	1.00
Other	26/125 (20.8%)	27/125 (21.6%)	1.00
Unknown	1/125 (0.8%)	2/125 (1.6%)	1.00
Ethnicity			
Hispanic or Latino	34/125 (27.2%)	31/125 (24.8%)	0.77
Not Hispanic or Latino	90/125 (72.0%)	93/125 (74.4%)	0.78
Unknown	1/125 (0.8%)	1/125 (0.8%)	1.00
Comorbidities			
Smoker (current/former)	53/125 (42.4%)	53/125 (42.4%)	1.00
Hypertension	79/125 (63.2%)	84/125 (67.2%)	0.60
Hyperlipidaemia	74/125 (59.2%)	71/125 (56.8%)	0.80
Coronary artery disease	24/125 (19.2%)	24/125 (19.2%)	1.00
Congestive heart failure	13/125 (10.4%)	17/125 (13.6%)	0.56
Chronic kidney disease	40/125 (32.0%)	32/125 (25.6%)	0.33
Cerebrovascular disease	16/125 (12.8%)	11/125 (8.8%)	0.42
Diabetes mellitus	49/125 (39.2%)	57/125 (45.6%)	0.37
Chronic obstructive pulmonary disease	19/125 (15.2%)	17/125 (13.6%)	0.86
Hospitalisation characteristics			
Initial SOFA score			
Median (IQR)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.08
Mean (SD)	1.88±1.09 (124)	1.60±0.98 (125)	–
Initial high-sensitivity C reactive protein	74.6 (34.5, 113.1)	63.5 (36.1, 122.4)	0.70
Supplemental oxygen on enrolment	105/125 (84.0%)	95/125 (76.0%)	0.15
Nasal cannula or facemask	95/125 (76.0%)	89/125 (71.2%)	0.47
HFNC/NIV	10/125 (8.0%)	6/125 (4.8%)	0.44
Duration of hospitalisation before enrolment, days	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.34
Colchicine given	116/125 (92.8%)	4/125 (3.2%)	<0.0001
Time on colchicine, days	4.0 (3.0, 5.5)	3.0 (2.5, 3.0)	0.12
Rosuvastatin given*	123/125 (98.4%)	54/125 (43.2%)	<0.0001
Time on rosuvastatin, days	4.0 (3.0, 6.0)	5.0 (3.0, 9.0)	0.11
SOC COVID-19 treatments			
Fully vaccinated prior to hospitalisation	6/125 (4.8%)	5/125 (4.0%)	1.00
Anticoagulation	121/125 (96.8%)	125/125 (100%)	0.12
Prophylactic/mid-dose	97/125 (77.6%)	104/125 (83.2%)	0.34
Full dose	24/125 (19.2%)	21/125 (16.8%)	0.74
Aspirin	115/125 (92.0%)	113/125 (90.4%)	0.82
Remdesivir	112/125 (89.6%)	106/125 (84.8%)	0.34
Dexamethasone†	120/125 (96.0%)	110/125 (88.0%)	0.03
Tocilizumab	27/125 (21.6%)	19/125 (15.2%)	0.25
Baricitinib	4/125 (3.2%)	0/125 (0.0%)	0.12

Continued

Table 1 Continued

	Colchicine+rosuvastatin	Standard of care	P value

Values are median (first quartile, third quartile) or n/N (%).
*Four patients among 54 listed in the SOC arm received a statin other than rosuvastatin while admitted.
†One patient listed did not receive dexamethasone but received equivalent dosing of hydrocortisone.
HFNC, high-flow nasal cannula; IQR, interquartile range; NIV, non-invasive ventilation; SD, standard deviation; SOC, standard of care; SOFA, sequential organ failure assessment.

characteristics and outcomes, continuous variables were compared using the Wilcoxon rank-sum test and categorical variables were compared using the χ^2 or Fisher's exact tests. Endpoints were compared at 30 days and 60 days.

RESULTS

In September 2021, after an interim analysis of the primary endpoint, the DSMB terminated the study for futility due to a lower-than-expected event rate. The trial randomised 250 patients from October 2020 to September 2021, with 125 patients randomised to each arm (figure 1). In the active arm 9 patients (7%) did not receive the trial medications, while in the control arm 54 patients (43%) were on antecedent statins that were continued in hospital and 4 of these patients also received colchicine for other indications while in hospital. The median treatment time with study medications in the active arm was 4 days for both medications with an interquartile range of 3–6 days. Only 203 patients (81%) completed their 30-day follow-up appointment or were in the hospital at 30 days and 201 patients (80%) completed their 60-day follow-up visit or were in the hospital at 60 days. However, all patients were able to be evaluated for the primary endpoint at 30 and 60 days with assistance of EMR review.

Table 2 Primary and secondary endpoints at 30 days in the ITT population

	Colchicine+rosuvastatin	Standard of care	P value
Primary endpoint (30 days)	19/125 (15.2%)	11/125 (8.8%)	0.17
Maximum new WHO score (≥5)	17/125 (13.6%)	8/125 (6.4%)	0.09
5: HFNC/NIV*	5/115 (4.3%)	4/119 (3.4%)	0.75
6: Mechanical ventilation	2/125 (1.6%)	0/125 (0.0%)	0.50
7: Additional organ support	4/125 (3.2%)	1/125 (0.8%)	0.37
8: Death	6/125 (4.8%)	3/125 (2.4%)	0.50
DVT/PE	1/125 (0.8%)	3/125 (2.4%)	0.62
Myocardial infarction	0/125 (0.0%)	0/125 (0.0%)	1.00
Ischaemic stroke	1/125 (0.8%)	0/125 (0.0%)	1.00
Secondary endpoints			
Secondary powered endpoint	11/125 (8.8%)	6/125 (4.8%)	0.32
Mechanical ventilation	6/125 (4.8%)	2/125 (1.6%)	0.28
All stroke	1/125 (0.8%)	0/125 (0.0%)	1.00
Any myocardial injury	3/125 (2.4%)	2/125 (1.6%)	1.00
Acute kidney injury	10/125 (8.0%)	8/125 (6.4%)	0.81
Duration of oxygen therapy†, days	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	0.39
Duration of hospitalisation†, days	4.0 (3.0, 6.0)	4.0 (3.0, 8.0)	0.93
SOFA score peak			
Median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.08
Mean (SD)	3.0±2.6	2.3±1.4	–
C reactive protein peak, mg/L	94.7 (56.7, 136.0)	75.4 (46.2, 127.4)	0.30
D-dimer peak, mg/L FEU	1.0 (0.6, 2.9)	1.0 (0.6, 1.9)	0.46

For categorical variables, values are n/N (%) and for continuous variables, values are median (first quartile, third quartile).
*Only new requirements were counted as meeting primary endpoint. Sixteen patients were already at a WHO score of 5 on enrolment and were hence not included in this category.
†Duration after enrolment.
DVT, deep venous thrombosis; FEU, fibrinogen equivalent units; HFNC, high-flow nasal cannula; IQR, interquartile range; NIV, non-invasive ventilation; PE, pulmonary embolism; SD, standard deviation; SOFA, sequential organ failure assessment.

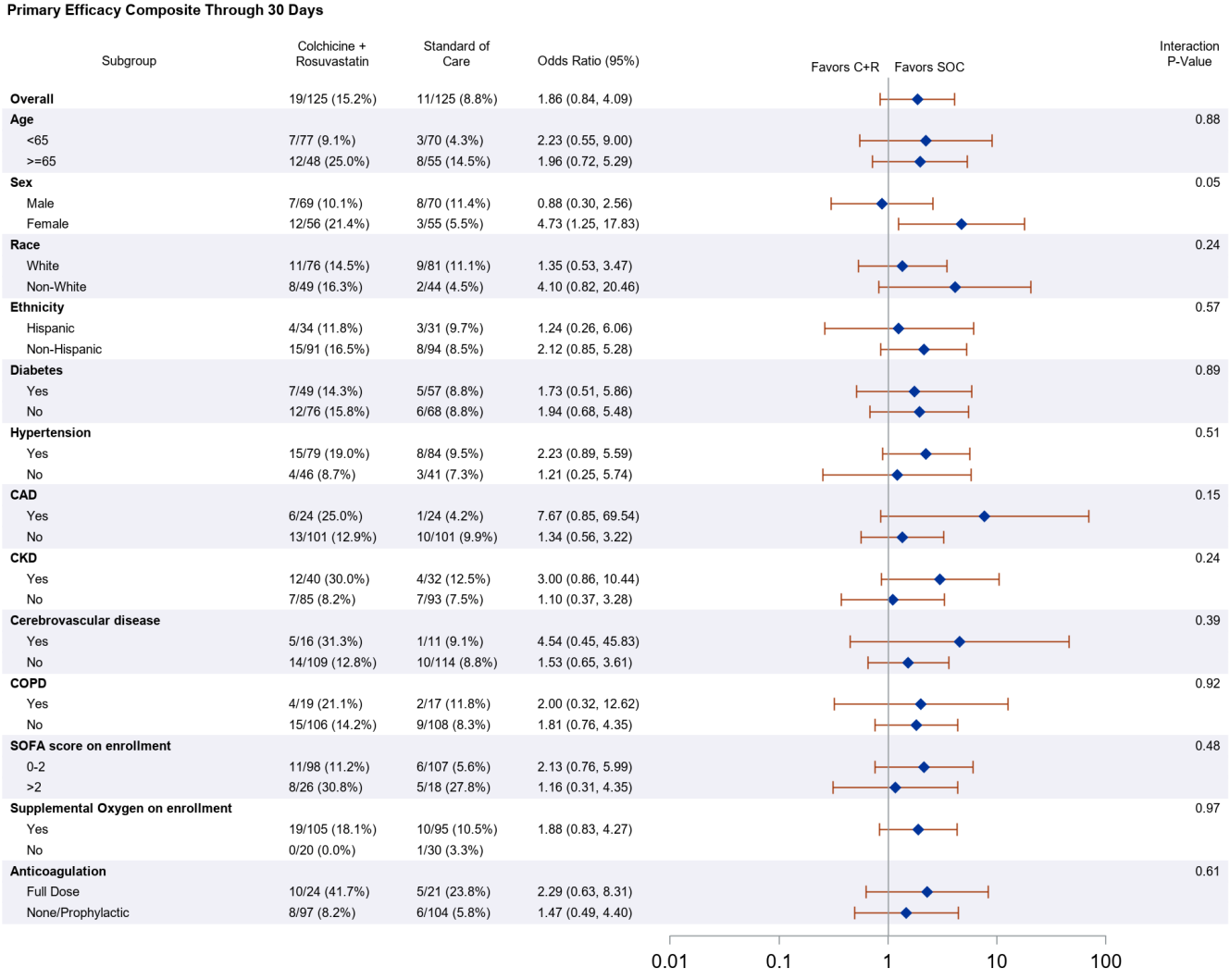

Figure 2 Subgroup analysis for primary endpoint. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment.

Both groups had similar comorbidities and demographics, with a median age of 61 years, 44% women, 15% African American/Black and 26% Hispanic/Latino in the overall cohort (table 1). In total, 42% had diabetes (39% in active arm and 46% in SOC arm). The median time from hospitalisation to enrolment was 1 day for both groups, and on enrolment, the median sequential organ failure assessment (SOFA) score was 2 (out of maximum score of 24). In total, 200 patients (80%) were on oxygen at the time of enrolment and at the time of enrolment 16 patients (10 in active arm and six in SOC arm) were on HFNC or NIV. A total of 11 trial participants (4%) were fully vaccinated on hospitalisation. During hospitalisation, both groups received similar treatments for COVID-19 per SOC as detailed in table 1; however, more patients in the active arm received dexamethasone (96.0% vs 88.0%, p=0.03).

Outcomes

By 30-day follow-up, the primary endpoint occurred in 19 patients (15.2%) in the colchicine plus rosuvastatin arm and in 11 patients (8.8%) in the SOC arm (p=0.17) (table 2). There were no significant differences between the active and SOC arm in any component of the primary endpoint or any other prespecified secondary endpoints including death (4.8% vs 2.4%, p=0.50), mechanical ventilation (4.8% vs 1.6%, p=0.28), DVT/PE (0.8% vs 2.4%, p=0.62), MI (0% both groups) and ischaemic stroke (0.8% vs 0%, p=1.00). One patient in the active arm required extracorporeal membrane oxygenation. There were also no statistically significant differences in outcomes at 60 days (online supplemental eTable 1).

In the PP population, nine patients were excluded from the active arm and four patients were excluded from the control arm. There were again no significant differences in the primary (14.7% vs 9.1%, p=0.23) or secondary endpoints between the active and SOC arms (online supplemental eTable 2). None of the patients in the SOC arm who received colchicine had a primary event. Sensitivity analyses excluding patients in SOC who received a statin (leaving 71 patients in SOC

Table 3 Treatment-related adverse events within 60 days

	Colchicine+rosuvastatin	Standard of care	P value
Self-reported symptoms			
Diarrhoea	4/125 (3.2%)	0/125 (0%)	0.12
Myalgias	3/125 (2.4%)	0/125 (0%)	0.25
Laboratory abnormalities			
AST change from baseline (IU/L)	6.0 (0.0, 26.0)	0.0 (0.0, 9.0)	0.0005
ALT change from baseline (IU/L)	17.0 (4.0, 55.0)	9.0 (0.0, 30.0)	0.01
AST or ALT >5× ULN	0/125 (0.0%)	0/125 (0.0%)	1.00
Creatine kinase >5× ULN	0/58 (0.0%)	0/45 (0.0%)	1.00
Cytopaenias			
Leucopenia (WCC <2.5×10^9/L)	0/125 (0.0%)	0/125 (0.0%)	1.00
Anaemia (Hgb <80 g/L)	0/125 (0.0%)	0/125 (0.0%)	1.00
Thrombocytopaenia (platelets <100×10^9/L)	6/125 (4.8%)	5/125 (4.0%)	1.00

For categorical variables, values are n/N (%) and for continuous variables, values are median (first quartile, third quartile).
ALT, alanine transaminase; AST, aspartate aminotransferase; Hgb, haemoglobin; IU, international units; ULN, upper limit of normal; WCC, white cell count.

arm) and comparing patients who received a statin in hospital with those who did not regardless of original arm of randomisation (177 received statin compared with 71 who did not) also revealed no differences with regard to primary or secondary endpoints (online supplemental eTables 3 and 4). In the prespecified subgroup analyses, the lack of treatment effect was consistent across all subgroups including patients with diabetes. The one exception was sex, for which there was a trend toward a significant interaction (p=0.053) (figure 2). While men in the active or SOC arm met the primary endpoint at a similar frequency (OR, 0.88; 95% CI, 0.30–2.56), women met it significantly more frequently in the active arm (OR, 4.73; 95% CI, 1.25 to 17.83).

Adverse events

Selected potentially treatment-related adverse events within 60 days are reported in table 3. There were numerically more cases of self-reported diarrhoea (3.2% vs 0%) and myalgias (2.4% vs 0%) in the active arm. Patients in the active arm had significantly higher increases in their aspartate aminotransferase and alanine transaminase levels; however, no patients in either arm had elevations greater than five times the upper limit of normal. There were no significant differences in creatine kinase levels or cytopaenias between the two groups. Only one patient had their trial medications discontinued due to an adverse event (diarrhoea).

DISCUSSION

In this randomised controlled trial, the use of colchicine and high-intensity rosuvastatin did not provide any benefit above contemporary SOC in the treatment of non-critically ill hospitalised patients with COVID-19. In fact, in the overall cohort, the primary endpoint occurred numerically more frequently in the active arm (15.2% vs 8.8%; p=0.17), but the gap narrowed in the PP population (14.7% vs 9.1%; p=0.23) given that two of the nine patients who did not receive any doses of the trial medications despite being in the active arm developed severe COVID-19 requiring mechanical ventilation. The trial was not adequately powered to definitively identify if the active arm actually derived harm from the treatment. However, that trial did demonstrate that it is highly unlikely that this combination would have provided benefit even if more patients were enrolled.

Notably, there was a trend toward significant interaction between the primary endpoint and sex (figure 2). The only subgroup with a significant treatment effect was women who did significantly worse in the active arm compared with SOC (OR, 4.73; 95% CI, 1.25 to 17.83). The significance of this result remains unclear and should be interpreted with caution given the interaction is only trending toward significance (p=0.053) and could be the result of multiple testing. Still, sex differences among patients with COVID-19 have been widely reported and hypothesised to be the result of differences in various pathways including innate immunity and ACE2 expression,[41] both of which could be affected by colchicine and rosuvastatin.[9 14–25] These results warrant further study.

Overall, the lack of treatment effect in the overall cohort is consistent with multiple recent randomised trials. One other randomised trial has studied the effect of the combination of colchicine and high-intensity rosuvastatin on patients with COVID-19 and found no benefit with regards to mortality (HR, 0.78; 95% CI, 0.44 to 1.36).[31] This trial enrolled mostly ICU-level patients and had a 2×2 factorial design comparing emtricitabine/tenofovir to SOC and colchicine and rosuvastatin to SOC. It found

that the combination of the four medications reduced 28-day mortality compared with SOC (HR, 0.53; 95% CI, 0.29 to 0.96), but neither the emtricitabine/tenofovir nor colchicine/rosuvastatin alone improved mortality. A different trial showed that colchicine alone does not improve outcomes in hospitalised patients with COVID-19.[29] Similarly, another trial showed that moderate-intensity atorvastatin does not improve outcomes in patients with COVID-19 admitted to the ICU, although there was a trend toward benefit in patients with an onset of symptoms ≤7 days prior to hospitalisation (OR, 0.60; 95% CI, 0.37 to 0.99).[34] This suggested that perhaps patients earlier in their COVID-19 disease course may derive a benefit from statins; however, our study enrolled non-ICU patients soon after hospital admission (median 1 day), who were presumably early in their COVID-19 disease course and did not find a benefit from high-intensity statins on any clinical endpoint.

It should be noted that none of the prior trials found a trend toward harm with treatment, and the reasons for the higher event rate in the active arm in our study remain unclear. It is possible that the difference is due to chance and that the patients enrolled in the active arm were somewhat sicker. For example, patients in the active arm were more frequently admitted on HFNC or NIV, had numerically higher SOFA scores (table 1) and were more likely to receive dexamethasone, tocilizumab and baricitinib (although this may have also been because they became sicker after being started on trial medications). Another potential explanation is that in all the above trials the SOC did vary somewhat while our trial used the most contemporary SOC. It is possible that the use of more potent anti-inflammatory medications in hospitalised patients with COVID-19 including dexamethasone, tocilizumab and baricitinib, along with prophylactic anticoagulation and aspirin overpowered any potential benefit colchicine or statins could provide. This could have resulted in some patients experiencing adverse effects from these medications without added benefit. This is consistent with the fact that unlike the more recent trials discussed above, multiple earlier trials and observational studies conducted before even dexamethasone was part of the SOC found that colchicine[26 27] and statins[32 33] benefited inpatients with COVID-19. In fact, colchicine continues to show a benefit in multiple more contemporary trials in outpatients with COVID-19 who do not receive any other anti-inflammatory medications or anticoagulation.[28 30]

Finally, it is important to note that this was one of the first trials to use EMR at all stages of the trial.[38] The use of the EMR allowed for the rapid initiation of this trial across the YNHHS in the early stage of the pandemic with a rapidly changing clinical landscape and SOC and reduced the necessary resources for screening, consenting, randomisation, data collection, monitoring and follow-up. For example, 19% of patients in this trial would have been lost to traditional follow-up (figure 1); however, loss to follow-up for the primary endpoint was reduced to 0 patients due to EMR usage. This clearly demonstrates that EMRs are powerful tools that can be adopted to improve efficiency and resource usage in future clinical trials.

Limitations

This trial had several limitations. First, this was an open-label trial and both participants and treating physicians were non-blinded; however, the ascertainment of the primary outcome was unlikely to be affected given the nature of chosen events, and all potential events were adjudicated by an independent CEC. Second, the estimated event rate for SOC based on early studies available at the time of trial initiation[38] was far higher than the observed event rate (40%–50% vs 9%, respectively), which significantly lowered the statistical power of this study. This issue, which was also seen in many other published COVID-19 trials,[42–44] likely resulted from a combination of rapid improvements in SOC since the onset of the pandemic (including steroids tocilizumab and baricitinib), evolving COVID-19 variants, and regional trends in which patients are hospitalised and which patients are managed outpatient. Still, while SOC did change during the course of this trial, most patients received a contemporary SOC, with all patients having access to remdesivir and dexamethasone, and tocilizumab being added to SOC within 2 months of the initiation of the trial. Third, the trial did not exclude patients on antecedent statins, limiting the potential effect size of the intervention. This was done because excluding patients on statins prior to hospitalisation would exclude many higher-risk patients who would also be most likely to benefit from intervention.

CONCLUSION

In this randomised controlled trial, the use of colchicine and high-intensity rosuvastatin did not provide any benefit above contemporary SOC in the treatment of non-critically ill hospitalised patients with COVID-19.

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Contributors AL, TS and HP designed the study. TS and AL managed and conducted the study and drafted the manuscript. HH and HP analysed the data. MM, IN, HA, ER, JK, NK, CP, PP, JL, PK, CS, MK, FUH, RA, CH, BC, GL, MC and CDC made contributions to data acquisition and interpretation and revised the manuscript critically for important intellectual content. AL is the guarantor and accepts full responsibility for the work and the conduct of the study.

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Ethics approval This study involved human participants and was approved by Yale Institutional Review Board (IRB Protocol ID: 2000027950). Participants gave informed consent to participate in the study before taking part.

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