Original Article -2

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Title: Efficacy of Colchicine in moderate COVID-19 patients: A double-blind, randomized, placebo controlled trial.

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Introduction

- SARS-CoV-2 causes life-threatening disease (ARDS) due to cytokine storms.
- The mortality rate in severe disease- 40% to 50%.
- The effective treatment of this wide spread release of acute inflammatory mediators due to hyperactive and inappropriate immune response is very limited.

Introduction

- Colchicine inhibits IL-1β and its subsequent inflammatory cascade principally by blocking pyrin and nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 (NLRP3) activation.
- Cheap, widely available, oral drug to combat the cytokine storm.
- Objective: to determine whether adding colchicine to SOC reduce disease progression.

Study design:

- Prospective, double blind, randomized, placebo controlled trial.

Study Type :	**Interventional (Clinical Trial)**
Enrollment :	300 participants
Sample Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (participant and investigator)
Comparator: **Primary Purpose:**	placebo Treatment and prevention of the development of severe disease.
Study Start Date :	June , 2020
Study Duration :	6 months from start date

Study Populationon

- Laboratory confirmed COVID-19 patients with clinical signs and symptoms of moderate disease
- Time: from June 2020 to November 2020

Selection criteria

Inclusion criteria:

- Competent patents of 18 years or more and can swallow tablets
- COVID-19 infection with positive RT-PCR within the last 3 days
- Patients with moderate symptoms-fever or history of fever, cough and /or shortness of breath, oxygen saturation 94% or more, pneumonia -less than 50% of lungs in chest imaging

Exclusion criteria:

- Pregnancy and breast-feeding, known hypersensitivity
- Known chronic illness - HF,CKD, (eGFR<30ml/min), long QT syndrome
- Patient with IBD, chronic diarrhea or malabsorption
- Patient currently taking colchicine for other indications
- Patient undergoing chemotherapy for cancer

Individual blinded	Information withheld	Method of blinding	Blinding maintained
Person assigning participants to groups	Group assignment	opaque envelops	Yes
Participants	Group assignment	Placebo medications	Yes
Care providers	Group assignment	Placebo medications	Yes
Data collectors and managers	Group assignment	Not informed of group assignment	Yes
Statisticians			No

Interventions

Active drug group

- The treatment group received a starting dose of 1.2 mg of Colchicine (2 tablets of 0.6 mg) 12 hourly divided doses on day 1 then colchicine 0.6 mg daily for 13 days. Additionally, patient were also given with standard of care.

Placebo group

- The placebo group received the standard of care, as well as placebo tablets that appeared and tasted like colchicine.

Experimental Procedures

- The baseline demographic and clinical characteristics were collected. All patients received their initial treatment dose on day 1.
- Follow up- day 1 through day 28 or until discharge from hospital due to clinical recovery and thereafter at post COVID-19 clinic run by the hospital or over telephone.
- Laboratory tests were performed on day 1-CBC,RBS, Creatinine, ALT, CRP, feritin, LDH, chest imaging.
- CBC -repeated on day 3, 7, 10, 14 and RBS, creatinine, RBS, ALT- repeated on day 7 and 14.

Study outcomes

Primary:

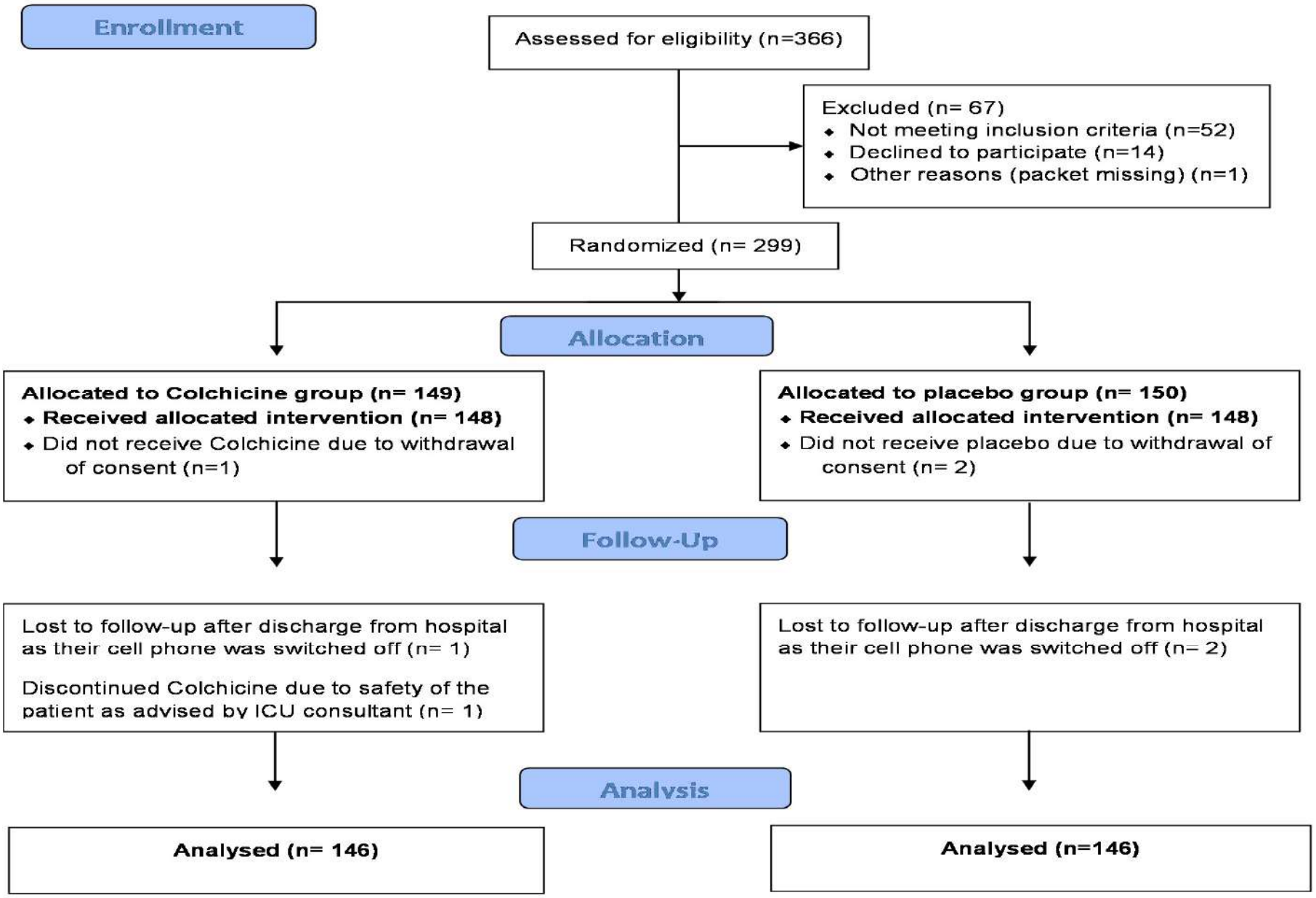
- Outcome Name: Time to develop clinical deterioration, defined as the time from randomization to a deterioration of two points on a Seven-category ordinal scale.

- Metric/method of measurement: Seven-category ordinal scale.

- Time point: 14 days following randomization

Secondary:

- Length of hospital stay
- Number of participant requiring increased amount of supplemental oxygen
- Number of participants requiring mechanical ventilation
- Number of participants who die
- Time frame: 14 days post randomization


Enrollment
Assessed for eligibility (n=366)
Excluded (n= 67)
Not meeting inclusion criteria (n=52)
Declined to participate (n=14)
Other reasons (packet missing) (n=1)
Randomized (n= 299)
Allocation
Allocated to Colchicine group (n= 149)
Received allocated intervention (n= 148)
Did not receive Colchicine due to withdrawal of consent (n=1)
Allocated to placebo group (n= 150)
Received allocated intervention (n= 148)
Did not receive placebo due to withdrawal of consent (n= 2)
Follow-Up
Lost to follow-up after discharge from hospital as their cell phone was switched off (n= 1)
Discontinued Colchicine due to safety of the patient as advised by ICU consultant (n= 1)
Lost to follow-up after discharge from hospital as their cell phone was switched off (n= 2)
Analysis
Analysed (n= 146)
Analysed (n=146)

Baseline characteristics

- Equal in each group.

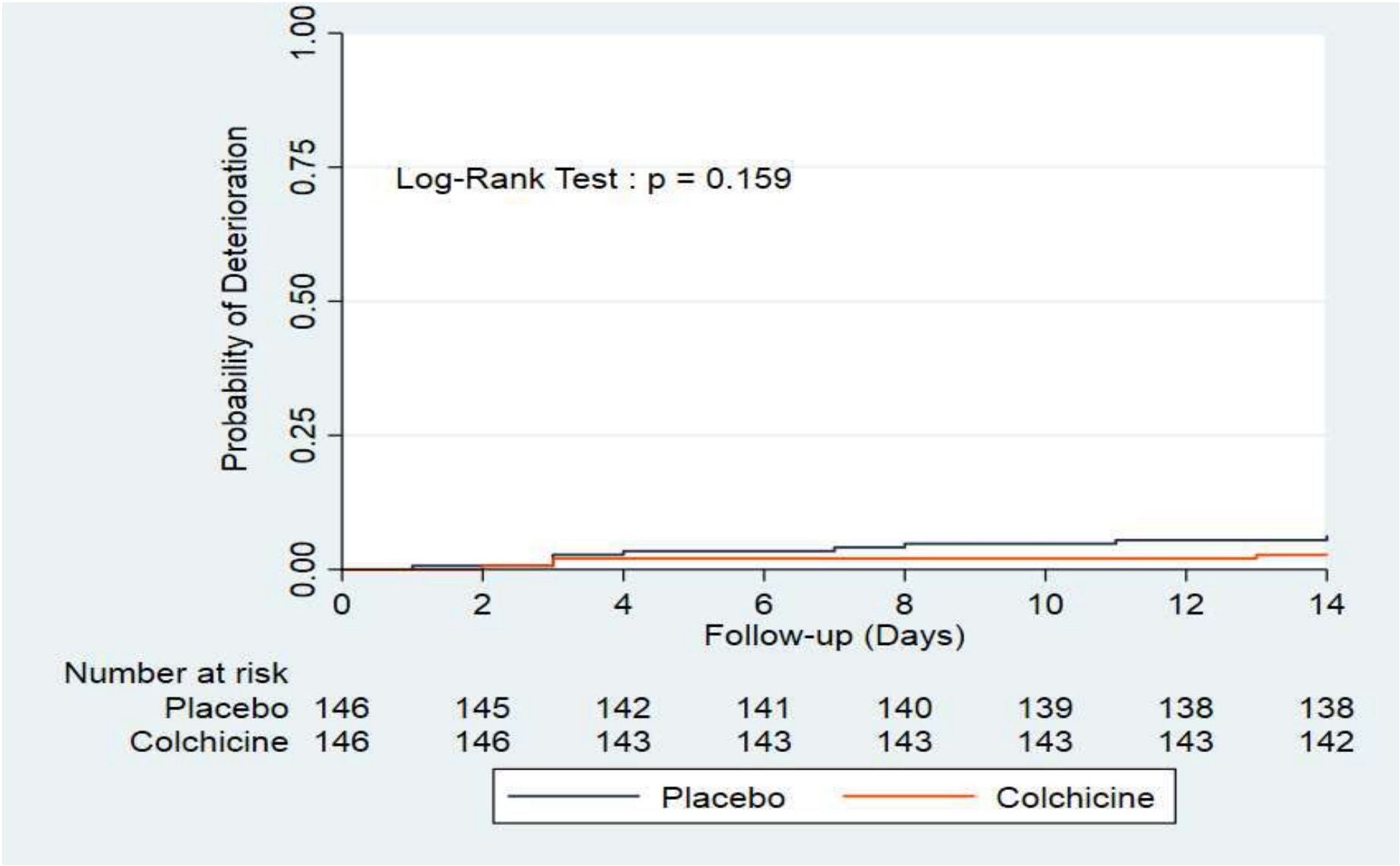
Characteristics	Total (n=296) N (%)	Colchicine (n=148) N (%)	Placebo (n=148) N (%)
Age (Years)			
18-40	109 (36.8)	57 (38.5)	52 (35.1)
41-60	154 (52.0)	75 (50.6)	79 (53.4)
≥61	33 (11.2)	16 (10.8)	17 (11.5)
Gender			
Female	106 (35.8)	53 (35.8)	53 (35.8)
Male	190 (64.2)	95 (64.2)	95 (64.2)
Duration (Day) of symptoms before enrolment Median (IQR)	9 (7-12)	9 (7-11)	9 (6.25-12)
Clinical features			
Fever	287 (97.0)	143 (96.6)	144 (97.3)
Cough	177 (59.8)	96 (64.9)	81 (54.7)
Shortness of breath (SOB)	134 (45.3)	64 (43.2)	70 (47.3)
Sore throat	104 (35.1)	48 (32.4)	56 (37.8)
Diarrhea	26 (8.8)	13 (8.8)	13 (8.8)
Anosmia	1 (0.3)	0 (0.0)	1 (0.7)
Duration (Day)of symptoms before admission Median (IQR)	6 (4-8)	6 (4-8)	6(3-9)
Duration (Day) of fever At the time of Enrolment Median (IQR)[$]	9 (6-11)	9 (7-11)	8(6-12)
Presence of Co-morbidity	148 (50.0)	69 (48.6)	79 (51.3)
Diabetes mellitus	100 (33.8)	52 (35.1)	48 (32.4)
Hypertension	79 (26.7)	32 (21.6)	47 (31.8)
COPD/Bronchial asthma	23 (7.8)	12 (8.1)	11 (7.4)
CKD	3 (1.0)	0 (0.0)	3 (2.0)
Ischemic heart disease	14 (4.8)	4 (2.7)	10 (6.8)
CLD	2 (0.7)	0 (0.0)	2 (1.3)

Other Treatment			
LMWH	260 (87.8)	130 (87.8)	130 (87.8)
Dexamethasone	182 (61.5)	97 (65.5)	85 (57.4)
Ramdesivir	27 (9.1)	13 (8.7)	14 (9.4)
Ceftriaxone	73 (24.6)	37 (25)	36 (24.3)
Meropenem	36 (12.2)	16 (10.8)	20 (13.5)
Baseline blood parameters Median (IQR)			
Hemoglobin*	12.2(11.0-13.5)	12.10(11.00-13.4)	12.25(10.90-13.70)
Total count of WBC*	8.5(6.2-11.8)	8.5(6.4-12.2)	8.4(6.1-11.1)
Neutrophil*(%)	71.70(60.8-83.0)	73.2(61.0-83.7)	70.0(60.5-82.4)
Lymphocyte*(%)	21.7(12.8-30.8)	20.4(12.2-30.0)	24.6(12.8-31.0)
Platelet count*	247.0(188.5-324.0)	245.0(191.5-328.5)	249.0(185.2-315.0)
Serum Creatinine**	1.0(0.8-1.1)	0.93(0.80-1.10)	0.99(0.81-1.12)
RBS$^{\$}$	8.4(6.2-14.0)	8.3(6.3-17.2)	9(6.91-13.7)
ALT$^{\#}$	40.0(24.0-59.0)	49.0(29.0-71.0)	34.5(22.0-60.0)
Serum CRP$^{@}$	12.0(6.0-36.3)	10(6-28.20)	15.24(6.00-25.02)
Serum Ferritin$^{\#}$	297.0(121.5-672.0)	301.0(175.0-758.0)	256.0(95.04-642.0)
LDH$^{\$}$	451.5(351.5-594.5)	483.0(372.0-619.0)	446.0(331.5-583.0)
D-dimer$^{\&}$	0.5(0.3-1.1)	0.43(0.26-0.83)	0.51(0.28-1.50)

Primary outcome

- The primary endpoint occurred in 9 (6.2%) patients in the placebo group and in 4 (2.7%) patients in the colchicine group (P = 0.171), corresponding to a Hazard Ratio (95% CI) of 0.44 (0.13 - 1.43).
- The median (IQR) time of 2 point deterioration in the seven category ordinal scale was found 3(2.2-10.5) days in the placebo group and 4(3.0-9.5) days in the colchicine group (P=0.604).

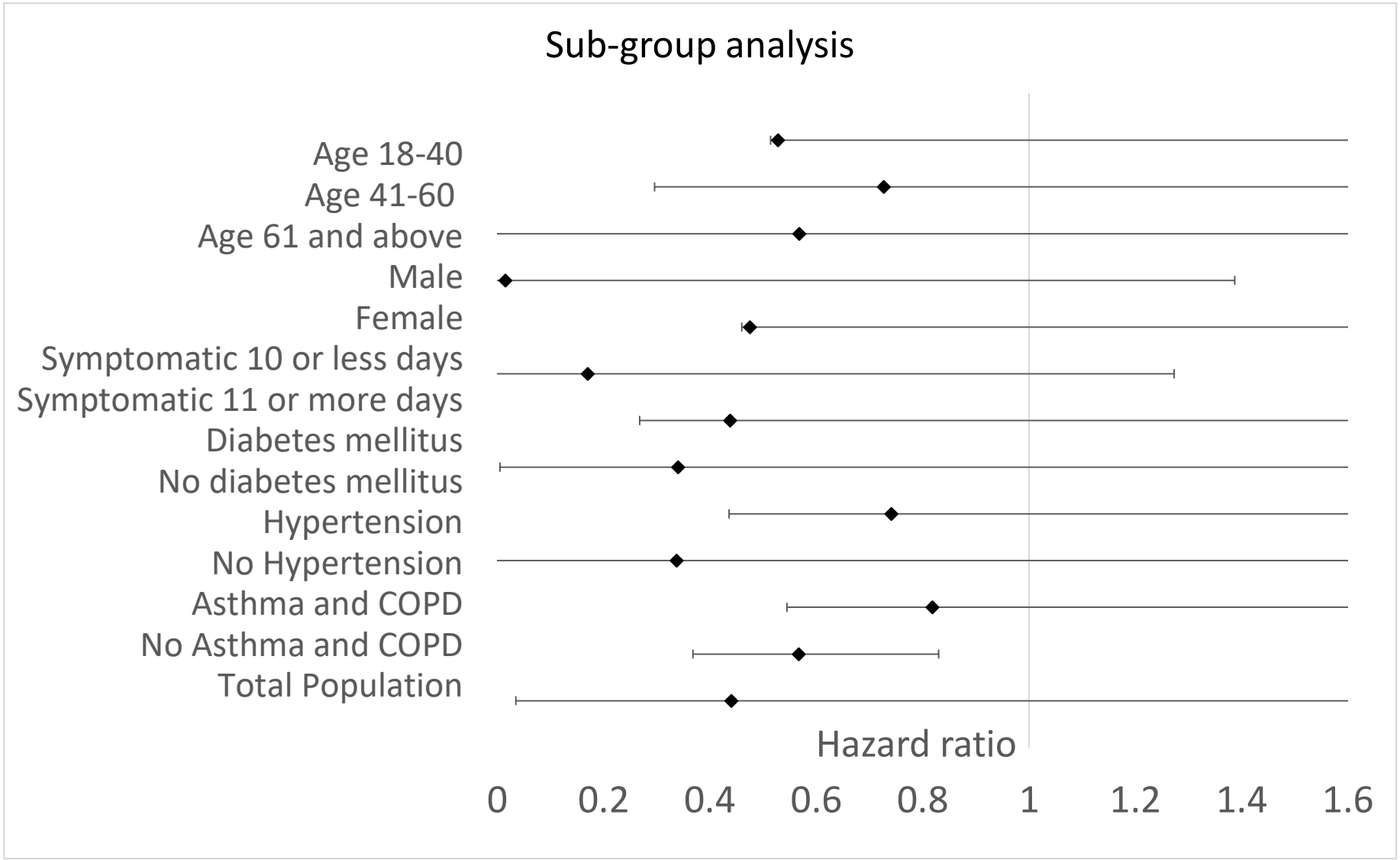
Kaplan-Meier Curves



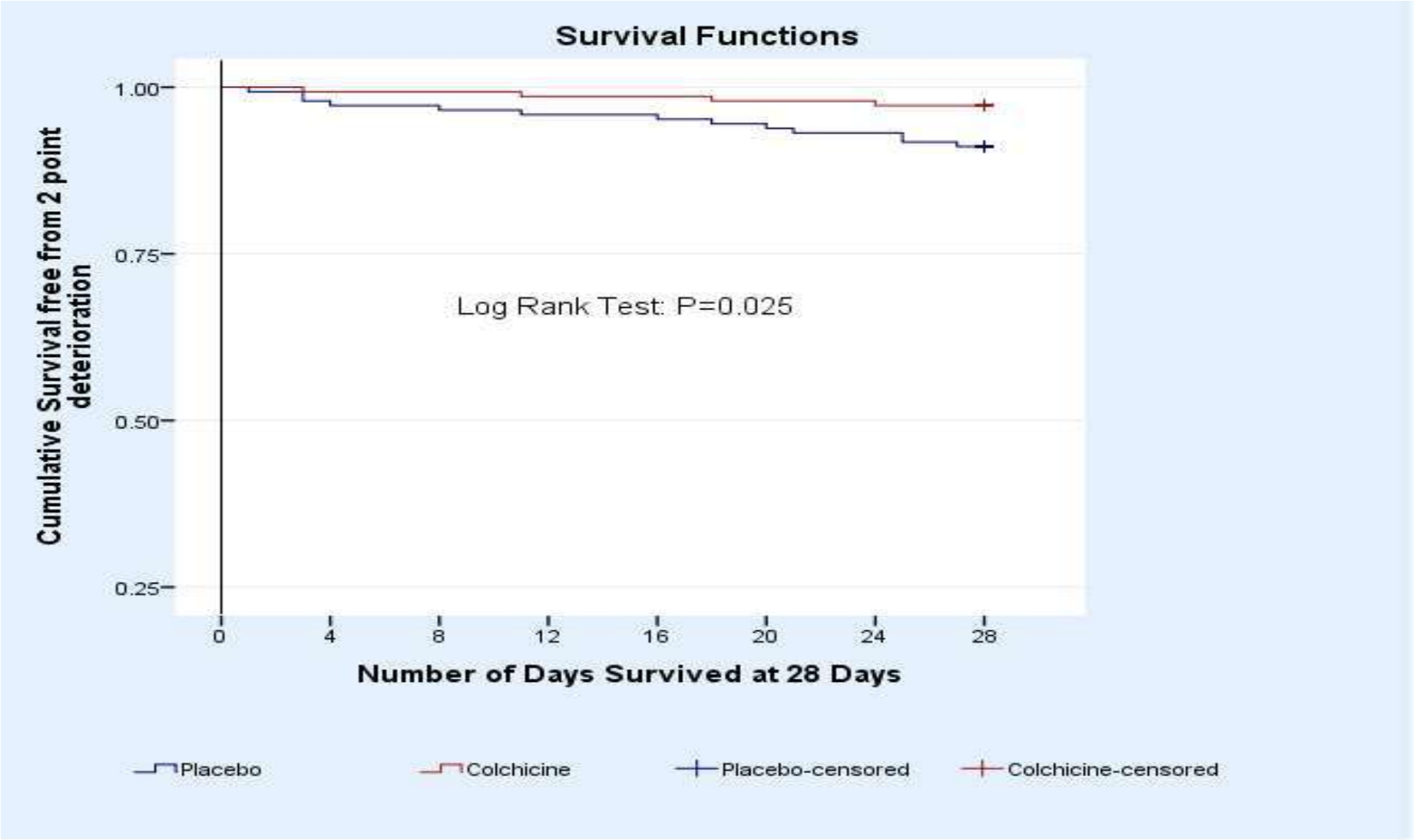
Outcome analysis

Outcomes	Colchicine (N=146) n (%)	Placebo (N=146) n(%)	Hazard Ratio (95% CI)	p-value
Deterioration of 2 or more points in the ordinal outcome	4 (2.7)	9 (6.2)	0.44 (0.13 - 1.43)	0.171
Participants requiring Supplemental oxygen (any device)	7(4.8)	7(4.8)	0.98 (0.34-2.78)	0.96
Participants requiring mechanical ventilation (both non-invasive and invasive)	2(1.4)	4(2.7)	0.49(0.09-2.68)	0.41
Death (all-cause mortality)	2(1.4)	5 (3.4)	0.39(0.08-2.02)	0.26
Length of hospital stay Median (IQR)	10 (7-15)	9 (6-15)		0.59

Subgroup analysis



Kaplan-Meier survival curve at Day 28 follow up with Log-Rank test.



Safety outcomes

Adverse events	Colchicine (n=146)	Placebo (n=146)	p-value
Diarrhoea, n(%)	27 (18.5)	6 (4.1)	<0.001
Nausea/ vomiting, n(%)	12 (8.2)	4 (2.7)	0.040
Abdominal pain or burning, n(%)	11 (7.5)	6 (4.1)	0.211

Discussion:

- Al-though there is a 56% reduction of deterioration to the need for mechanical ventilation and death at day 14, it was not statistically significant.
- There was no difference in the length of hospital stay among groups.
- However the colchicine treated patient deteriorated 1 day later than placebo.
- At day 28, Colchicine significantly reduced the primary outcome and all-cause mortality.

- The open leveled GREECO trial suggested a significant clinical benefit where 105 patients were hospitalized with severity category 3 to 5.

- In the COLCORONA trial the outcome in 30 days showed a significant reduction of composite outcome of hospitalization and death.

- The result of our study is different when we compare with the outcome at day 14 but is similar to these studies when we compare with the outcome in 28 days follow up.

- This finding revealed that we may have measured the primary outcome early and the beneficial effect of the Colchicine use during cytokine storm may continue through the next two to three weeks.

- A recent meta-analysis of three RCTs concluded that the result suggests a direction toward benefit in mortality that is not statistically significant among patients receiving colchicine versus non-colchicine regimens.
- In our study, we have found the same trends in 14 day follow up but in 28 day follow up Colchicine showed significant benefit.

Limitations:

- It was a single centered study over a short period of time.
- Patients were not hospitalized throughout the observation period. So it required telecon follow up which has its own inherited drawbacks.
- Due to the limitated investigation facilities, we could not do the follow up RT-PCR in all participants in scheduled time.
- Follow up investigation of the patient after discharges was not possible in most of the instance.

Conclusion

- Significant beneficial effect of colchicine in reducing mortality and deterioration to the point of needing mechanical ventilation was not found in treating hospitalized moderate COVID-19 disease.
- A significant late beneficial effect was observed. We recommend further study with evaluation of late outcome.

Acknowledgment

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THANK YOU