Supplementary Appendix. 2.

The characteristics of included studies

Variable	Studies[REF]											
	Altay O et al., 2021[30]	de Alencar JCG et al., 2021[31]	Delic N et al., 2022[32]	Gusdon AM et al., 2022[33]	Mousapour P et al., 2022[34]	Panahi Y et al., 2023[35]	Rahimi A et al., 2023[36]	Taher A et al., 2021[37]	Atefi N et al., 2023[38]	Eslami Ghayour A et al., 2024[39]	Gamarra-Morales Y et al., 2023[40]	Sherkawy SM et al., 2023[41]
Country	Turkey	Brazil	Croatia	USA	Iran	Iran	Iran	Iran	Iran	Iran	Spain	Egypt
Design, Clinical trial registry	• Openlabel, placebo-controlled, phase-2 RCT • Double-blinded, placebo-controlled, phase-3 RCT • NCT04573153	• Double-blind, randomized, placebo-controlled, single-center trial • Brazilian Registry of Clinical Trials (REBEC): U1111-1250-356	• Single-center RCT • NCT04755972	• Multicenter, double-blind, placebo-controlled, adaptive phase 2a single sequential, ascending-dose RCT • NCT04458298	• Double-blinded, placebo-controlled RCT • IRCT20210726051995N1	• Single-center, prospective, open-labeled RCT • IRCT20080901001165N55	• Two-arm parallel single-blinded, phase III RCT • IRCT20200509047364N3	• Single-centre, prospective, phase 2, double-blind, placebo-controlled and pilot RCT • IRCT20120215009014N355	• Single-centre, double-blind RCT • IRCT20200623047897N1	• Single-centre, double-blind RCT • IRCT20220302054167N1	• Single-centre, RCT • Trial registration information not available.	• Single-centre, RCT • NCT04792021

Study Setting, IEC approval	• Umraniye Training and Research Hospital, University of Health Sciences, Istanbul, Turkey • ethics committee of Istanbul Medipol University, Istanbul, Turkey	• Emergency Department of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo in São Paulo, Brazil • The Institutional Ethics Committee approved this trial under #30420720.4.0000.0068 • 10 April 2020 to 25 May 2020	• ICU of the Clinic of Anaesthesiology and Intensive Care of the University Hospital of Split, Croatia • Ethical Committee of the University Hospital of Split (no. 2181-147-01/06/M.S.-20-02).	• At five clinical institutions across the US[$] • approved by a central, western, local institutional IRBs, Copernicus Group • August 2020 and March 2021	• Department of Anesthesiology and Intensive Care, AJA University of Medical Sciences, Tehran, Iran • IEC approval information is not clear	• Baqiyatallah hospital, Tehran, Iran • Ethics Committees of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1399.123) • May 2021 until August 2021	• Shahid Mohammadi Hospital's ICU, Bandar Abbas, Iran • IEC approved under the ethical code of IR.HUMS.REC.1399.539	• Tertiary referral hospital, Hamadan University of Medical Sciences, Hamadan, Iran • Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.153) • June 2020 until February 2021	• Rasool Akram Medical Complex, Tehran, Iran. • Ethics Committee of Iran University of Medical Sciences ((ethical code #IR.IUMS.REC.1399.206)	• Dibaj Therapeutic Center, Hamadan City, Iran. • IEC of Hamadan University of Medical Sciences (Approval No: IR.UMSHA.REC.1400.957)	• Virgen de las Nieves Hospital in Granada (Spain). • IEC of University of Granada (Ref. 149/CEIH/2016).	• El-Asema Hospital, Cairo, Egypt
Participants (Total n)	**Mild-moderate COVID-19**	**Severe COVID-19 (140)** • Total assessed for	**Severe COVID-19 treated with mechani**	**Severe COVID-19 (24)**	**Severe COVID-19 (83)** • Total assessed for	**Symptomatic adult patients with a positive COVID-19**	**Severe COVID-19** • ICU admitted patients (40)	**Mild-to-moderate COVID19 (92)** • Total assessed for	**Stable non-severe cases of COVID-19** • Patients screened for	**Symptomatic COVID-19 patients.** • PCR-positive (225)	**Critically ill COVID-19 patients.**	**Moderate COVID-19** • Hospitalized

	• Phase-2 cohort (100); hospitalized (2), dropped (5), randomized & analysed (93) • Phase-3 cohort (309); hospitalized (1), dropped (4), randomized & analysed (304)	eligibility (612) • Randomized (140) • Lost-to follow up (5): due to misadministration and loss of drug packs • Final analysis (135) Patients with positive • RT-PCR for SARCoV-2 (128)	**cal ventilation (175)** • Total assessed for eligibility (188) • Total enrolled for study (175) • Randomized and allocated (91) • Lost-to follow up (0)		eligibility (101) • Randomized (83) • Lost-to follow up (0)	• Total assessed for eligibility (260) • Randomized (250) • Lost-to follow up (0)		eligibility (175) • Randomized (92) • Lost-to follow up (0) • Excluded from analysis (0)	enrollment (74) • HospitalizedCOVID-19 patients randomized (60)		• PCR-Positive, ICU patients randomized (140)	PCR-positive patients (60)
Severity criteria	NA	• Using the 7-category ordinal scale proposed by the WHO	Based on the Berlin criteria (PaO_2/FiO_2 is ≤100 mmHg	Based on the WHO's seven-point ordinal scale (a	Based on six-category ordinal scale of clinical status	Symptomatic adult patients with a positive RT-PCR for COVID-19	Platelet count >100,000/µL, respiration rate <30/min,	• Based on the WHO Master Protocol using an 8-point ordinal scale (V.3.0,	• According to national protocol. • According to the	• COVID-19- PCR patients with oxygen saturation >92%	• Chinese Clinical Guideline for COVID-19	• Protocol of the Egyptian Ministr

		• SaO_2 <94% or respiratory rate >24 breaths/min	on ventilator settings that include PEEP ≥5 cm H2O)	score of ≥5)			LDH ≤245 U/L, CPR <+2, oxygen saturation >93%, and average lymphocyte count or modified lymphopenia	3 March 2020) • Berlin criteria for mild-moderate (oxygen saturation <94% with no supplemental oxygen or PaO_2/ FiO_2 ratio <300 and >100 mm Hg, and <48 h from hospital admission	opinion of the treating physician,based on clinical signs and PCR or paraclinical or laboratory findings.		classification	y of Health and Population
Inclusion criteria	• age of ≥18 • Covid-19 confirmation by PCR within the previous 24 h, and were in stable conditi	Patients aged 18 years or older diagnosed with severe COVID-19 (suspected or confirmed) by RT-PCR	• Adult patients with COVID-19 who were treated with mechanical ventilation • Covid-19 confirmation by RT-PCR	• Male and nonpregnant females aged ≥18 • Laboratory-confirmed SARS-CoV-2 infection • WHO 7OS score of 5 to 7	Severe COVID-19 based on the six-category ordinal scale of clinical status	• age of ≥18 • positive result on RT-PCR • CT results that confirmed COVID-19 infection and <7 days since the symptoms onset	• Covid-19 confirmation by PCR • Respiratory rate >30 beats per minute • hypoxemia ≤93% or PaO2 ratio <300, progressive lymphopenia, pulmonary infiltration (more	• age of ≥18 • either the positive RT-PCR and/or clinical and radiological findings compatible with COVID-19	• Fever >39°C, respiratory distress, retractions, respiratory rate >30/min, heart rate >120 bpm, O2 saturation <93%, underlying conditions (DM, HT, COPD, and smoking)), age >50	• PCR-positive, Symptomatic COVID-19 patients.	• Aged ≥18 years, Previously hospitalized for over 48 hours, ICU admission stay of at least 3 days, Positive PCR test	• Aged ≥18 years, PCR-positive PCR test

	on not requiring hospitalization			(severe COVID-19).			than 50% involvement of the lung field in 24 to 48 h), LDH >345 U/L		with symptoms, and ≥1/3 lung involvement.			
Exclusion criteria	• partial oxygen saturation below 93% and required hospitalization after diagnosis • Pregnant or breastfeeding • HF, SLD, PKA, T1DM/T2DM • Allergy, alcoho	Known allergy or hypersensitivity to NAC, signs of the imminent need for orotracheal intubation (increased respiratory effort, decreased level of consciousness, SaO2 <90% with supplemental oxygen), pregnancy, or refusal to sign the written consent.	• Recent polytrauma; pregnancy; severe hemodynamic instability defined as a need for vasopressor/inotropic therapy or mechanical circulatory support; cardiogenic pulmonary edema or edema due to fluid overload; ICU stay	• patients on ECMO, • expected survival <24 hrs • NMD, CLD requiring mechanical ventilation at baseline • severe liver failure (Childs-Pugh score >12) • MI, CHF, dialysis for CRF • WHO class III or IV PH, and	NR	• Any allergy or hypersensitivity to NAC • signs of the imminent need for intubation or the need for ICU admission due to increased respiratory effort, decreased level of consciousness, and SpO_2 <90% with supplemental oxygen • being a participant in another clinical trial at the same time • pregnancy or	NR	• Severe ARDS (PaO_2/ FiO_2 ratio < 100 mm Hg and need for mechanical ventilation at the time of enrollment, on chronic home oxygen therapy, hepatic failure or CRF • concurrent treatment with other agents outside the standard of care; using any other anti-inflammatory agents or antioxidant supplements	• Minors, individuals with unstable vital signs, intubation (required or ongoing), reduced consciousness, respiratory rates >24, blood pressure <90/60 mmHg, multilobular infiltration on imaging, persistent hypoxia, pregnancy or breastfeeding, and prior hypersensitivity to NAC or glutathione-containing	• Pregnant or who received a COVID-19 vaccine	• Data on patients with mild symptoms were not available	• < 18 years, pregnancy or lactation, allergic to NAC, critically ill, or mechanically ventilated patients.

	l consumption, receipt of any experimental treatment for COVID-19 within the prior 30 days		<3 days; and verified bacterial infection prior to ICU admission	active malignancy or recent trauma. • Patients receiving other trial immunomodulatory agents		breastfeeding • unwilling to participate or unable to give informed consent		outside the institutional protocol treatment; prior hypersensitivity to NAC; the occurrence of any adverse effect leading to the patients' intolerance or complications; pregnancy and lactation	medications.			
Randomization, allocation, blinding	• Using randomization codes entered into the electronic case report form • 3:1 (CMAs standard therap	• Randomization was done by the chief pharmacist using QuickCalcs random-number calculators • 1:1 (in individually numbered packs)	• Using an online platform (www.random.org, Randomness and Integrity Services Ltd., Dublin, Ireland) • 1:1 • The radiologist was blinded (interpretation of	• Block randomization (block size of 4) using Suvoda Interactive Response Technology (Conshohocken, PA) (third party), and a compute	• Randomization process (not clear) • 1:1 • Double-blinded	• Block randomization r in permuted blocks of 6, using the sealed envelope technique and computer-generated random numbers by Random Allocation Software© (RAS; Informer	• Permuted block randomization method using online web-based tools • 1:1 • Single-blinded (patients were unaware, whereas the principal investigators, medical staff, data collectors, and result	• Block randomisation by independent statistician • (1:1) • The researchers, ICU nurses, physicians, and patients were blinded	• Stratified blocked randomization • 1:1 • Double-blinded RCT (The secondary assessor and the data analyst were blinded to the treatment regimens).	• Patients were randomly assigned to three groups; NAC (75), Bromhexine (75), Control group (75)	• Except for a statement 'Randomized, controlled clinical trial', no further details available.	• Simple randomization • 1:1

	y or placebo + standard therapy) • All participants, clinical staff were blinded		chest radiographs)	r-generated serial number • 3:1 (OP-101 to placebo) • All patients, care providers, investigators, all site and study staff (Sponsor, designee, central laboratories, biostatistician) are blinded		Technologies, Inc.) 1:1	evaluators were aware of patient grouping					
NAC treatment (n), M/F, Mean/Median Age	• NAC in the form of CMAs [#] • Oral doses of CMA, one in the	• High dose intravenous NAC 21 g (~300 mg/kg) for 20 hours • Divided into 2 doses: 14 g in the first 4 hours	• NAC inhalation therapy given twice daily at 12 h intervals. • The first inhalation was	• OP-101 supplied as a lyophilized powder (500 mg per vial) was reconstituted	• One gram NAC was administered intravenously every 12 hours for 7 days • (42) • M/F (31/11)	• NAC inhaler spray (@sinadarou.co) one puff (200 µg per puff) every 12 h for 7 days • (125) • M/F (64/61)	• Single dose intravenous NAC (300 mg/kg) upon admission to the ICU on the first day in addition to standard	• NAC at a dose of 40 mg/kg/day diluted in 5% dextrose as a continuous intravenous infusion for 3 consecutive days	• 600 mg of NAC, orally every 8 h for 14 days. • Kaletra + HCQ + NAC (15) • Atazanavir/ ritonavir + HCQ + NAC (15)	• NAC (75) • No additional details available.	• Intravenous (3 days). • Loading dose: 150 mg/kg in 100 mL saline	• 1800 mg in 3 divided doses (600 mg sachets) • (30) • M/F (17/13)

	morning and one in the evening • Phase-2: • (71) • M/F (31/40) • Mean Age (35y) • Phase-3: • (229) • M/F (136/93) • Mean Age (36.7y)	and 7 g in the next 16 hours • NAC was diluted in 500 mL dextrose 5%, and divided into 2 doses: 14 g in the first 4 hours (28 mg/mL) and 7 g in the next 16 hours (14 mg/ mL) • The volume received for each patient was 1000 mL over 20 hours • (70): 67 completed and 3 discontinued the intervention • M/F (43/24)	applied within 12 h of the patient's admission to the ICU. • (39) • M/F (28/11) • Mean Age (68.5y)	with sterile water and added to a 100-ml intravenous saline bag • The 100-ml saline bag (with active drug or saline placebo) was administered as a single intravenous infusion over 60 min. • (12) • M/F (12/5) • Min-Max Age (45-86y)	• Mean Age (63.6y)	• Mean Age (57.25y)	drug treatment • (20) • M/F (12/8) • Mean Age (58.75y)	• (47) • M/F (15/32) • Mean Age (59.4y)	• M/F (29/31) • Mean Age (57.82y)		over 15 minutes, followed by 50 mg/kg in 100 mL saline over 4 hours. • Maintenance dose: 50 mg/kg in 250 mL saline at 10 mL/h for 72 hours. If PaO2/FiO2 > 200 after 72 hours, 600 mg IV every 12 hours. • (72) • M/F (56/16)	• Mean Age (56.3y)

		• Mean Age (59y)									• Mean Age (61.4y)	
Control/placebo (n)	• placebo (equal amounts of lactose • Phase-2: • (22) • M/F (6/16) • Mean Age (32.5y) • Phase-3: • (75) • M/F (39/36) • Mean Age (35.2y)	• placebo (equal amounts of dextrose 5% in water (1000 mL in total) Intravenously • (70): 68 completed and 2 discontinued intervention • M/F (37/31) • Mean Age (58y)	• (52) • M/F (40/12) • Mean Age (68y)	• placebo (saline) • (7) • M/F (5/2) • Min-Max Age (43-76y)	• placebo (equal volume of 0.9% sodium chloride) • (41) • M/F (26/15) • Mean Age (60.5y)	• (125) • M/F (74/51) • Mean Age (52.77y)	placebo (20) • M/F (10/10) • Mean Age (58.30y)	• placebo (equal volume of 5% Dextrose for 3 consecutive days) • (45) • M/F (24/21) • Mean Age (55.5y)	• Kaletra (lopinavir/ritonavir)+ HCQ (15) • Atazanavir/ritonavir + HCQ (15)	• Standard care (75)	• Standard care (68) • M/F (50/18) • Mean Age (62.2 y)	• Standard care (30) • M/F (15/15) • Mean Age (59.5 y)
Standard care/Treatments	• either HCQ or FP (HCQ	• Based on the institutional	• Based on the local ICU protocol, a	• Remdesivir use was common	Based on the institutional protocols,	• Based on the latest version of the Ministry	• Based on the treatment protocol of the national	• Based on the institutional protocol treatment, all	• Kaletra + HCQ • Atazanavir/	• Standard care as per the local protocols with no	• Standard care	• (azithromycin, linezoli

	initial oral-dose of 800 mg/day followed by 400 mg/day for a total of 5 days, FP 1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days)	protocol that oxygen supplementation, invasive ventilation, and antibiotics • All patients received ceftriaxone 2 g/day and azithromycin 500 mg/day	standard dose of intravenous dexamethasone (8 mg) during the first 10 days, along with the same broad-spectrum, empirical antibiotics	• Antithrombotic medications • All subjects were treated with corticosteroids as per standard of care	remdesivir for a total of 5 days	of Health of Iran protocols for COVID-19	COVID-19 committee • HCQ/CQ pills: 200 mg of HCQ or 250 mg of CQ (equivalent to 150 mg base dose) on the first day, two pills every 12 h, then one pill every 12 h for a minimum of one week and maximum of two weeks • One of these drugs at treating physician's discretion: Kaletra pills (lopinavir/ritonavir) 200/50 mg every 12 h twice a day for at least one week and up to two	patients received supportive and/or COVID-19 standard treatments (HCQ, Antiviral & Azithromycin) • corticosteroids administration if the need for supplemental oxygen was 6-8 L/min or more • vitamin C (1000 mg bid), vitamin D3 (1000 IU bid), and Zinc (50 mg daily) • 70.21% (in NAC group) and 68.9% (in control group) received dexamethasone. • None received ECMO	ritonavir + HCQ	NAC or Bromhexine		d, ceftazidime, levofloxacin), corticosteroids (dexamethasone 8 mg once daily), and remdisivir (200 mg IV administrated on day 1 followed by 100 mg IV every day since day 2 for 5 days) as well as supplementary vitami

							weeks; Atazanavir/ Ritonavir 300/100 mg pills: One daily with food or 400mg daily atazanavir for a minimum of one week and a maximum of two weeks					ns and minerals; as Vitamin C (1000 mg p.o once daily), Zinc (50 mg p.o once daily), Vit D3 (42000 IU every week)
Follow-up/Study treatment duration/lost to follow-up	14 days	Followed till the end of study (duration was not mentioned)	28 days?	60 days	7 days	7 days	Until their discharge or for a maximum of 14 days	28 days	14 days	Follow-ups on days 7 and 14, with hospitalized patients monitored for one month post-hospitalization	Admission (first day) and on the follow-up (third day), 28-day mortality.	A maximum of 2 weeks or until Discharge from the hospital, intolerance to the medication, or death

Matching /confounder adjustment	Baseline characteristics, age, sex, comorbidities, HCQ and FP standard treatments	Age, sex, comorbidities, medicines taken, disease severity, laboratory & HRCT findings	Age, blood pressure, heart rate, comorbidities, disease duration upon intubation, immunosuppressive or antibiotic treatment. Multivariate analysis for age, sex, duration of hospitalization, ventilator therapy, smoking and charlson comorbidity index.	Age, sex, BMI, comorbidities. The small sample size precluded correction for potential confounders.	Age, sex, comorbidities, clinical status & laboratory parameters except CRP	Sex, BMI, comorbidities, smoking status, and frequency of symptoms at preintervention	Age, gender, baseline laboratory & clinical parameters	Baseline characteristics, including general condition, use of concomitant treatments, comorbidities, vital signs, disease severity, and median time from COVID-19 symptom onset to enrolment (7 days)	Sex, PCR-positivity, comorbidities like DM, lung disease, kidney disease, dialysis, malignancy, and immunodeficiency.	• No additional details available.	Age, Sex, MBP, ICU stay, SOFA score, APACHE II score, PaO2/FiO2.	Age, Sex, Comorbidities, presenting symptoms, kidney function and laboratory parameters like ferritin, LDH, D-Dimer, IL-6, CRP and TNF-α.
Outcomes/endpoints	• clinical efficacy	• Primary endpoint was the need for intubation	• The primary outcome was the	• Risk for the composite outcome	• Liver function on day 3, 5 & clinical outcomes	• Hospital length of stay	• Primary endpoint was the combined endpoint of	• Clinical Status & 28-day overall mortality	• Primary outcomes (Mortality and discharge)	• Hospitalization rate, ICU admission rate,	• Mortality at 28 days	• Primary outcomes

	(symptom-free recovery within the 14 d of the initial diagnosis of COVID-19)	and invasive mechanical ventilation • Secondary endpoints were time of mechanical ventilation, ICU admission, time in ICU, and mortality.	incidence of VAP • The secondary outcome was the all-cause mortality within a 28-day time period	of mechanical ventilation or death at 30 and 60 days after treatment • Survival at 60 days	on days 7, 14 (Discharge-alive, hospital admission requiring supplemental oxygen, non-invasive ventilation, invasive mechanical ventilation & deaths)	• need for ICU admission • mortality	ICU stay length and the patient's clinical status		• Secondary outcomes (drug tolerance and treatment satisfaction) .	Mortality rate		(TNF-α, IL-6, and glutathione peroxidase) • Secondary outcomes (length of hospital stay, the need for oxygen support, the duration of oxygenation, and the mortality rate).
Statistical analyses	• Kaplan-Meier method	• Chi-square test for categorical variables • Wilcoxon test or Student's t	• Chi-square test for categorical variables • Kruskal-Wallis	• Fisher's exact test	• No clear mention of statistical tests	• Chi-square or Fisher's exact tests (categorical variables) • Mann–Whitney u test and Wilcoxon	• Chi-square and Fisher's exact tests (qualitative variables) • Mann-Whitney and	• Chi-squared test, Independent t test and Mann-Whitney U test	• ANOVA And linear regression	• Number of events & %	• Chi-squared test, Correlations	• Frequency and percentage (qualitative data)

		test for continuous variables	test for continuous variables			Ranks test (continuous variables)	independent t-tests (quantitative variables)					• Student t-test or Mann-Whitney test (quantitative data)
Effect sizes	Number of events, hazard ratios and 95% CI	Number of events, median (IQR), Point estimates and 95% CI	Number of events, median (IQR)	Number of events	Number of events, Mean ± SD, & frequency (percent)	Number of events, Mean ± SD, & median (IQR)	Number of events & Mean ± SD	Number of events, Mean ± SD, & median (IQR)	Number of events & Mean ± SD	Number of events & %	Number of events & Mean ± SD	Number of events & Mean ± SD
Important results & conclusions	• CMA intervention lead to a more rapid symptom-free recover in COVID-19 • Administration of CMA is an	• No significant difference between the placebo and NAC groups in the primary outcome (need for invasive mechanical ventilation) or in the secondary outcomes	• Inhalation therapy had no effect on the overall VAP incidence or all-cause mortality	• OP-101, a hydroxyl dendrimer conjugated to NAC, shows promising trends in efficacy and safety after a single intravenous dose with	• Improvement rates at days 7 and 14 were numerically higher in NAC group, with similar mortalities between groups (not significantly different)	• The mortality rate was significantly lower the intervention group • No differences were seen for hospital length of stay or the need for ICU admission • Considering the excellent	• Respiratory rate and D-dimer were significantly lower in the NAC group • The length of ward and ICU stay was shorter with lower morality in the NAC group (s statistically insignificant)	• Better clinical outcomes at day-28 and no differences in mortalities between groups	• NAC may reduce mortality in hospitalized COVID-19 patients and show greater efficacy as a prophylactic or adjunctive therapy in stable, non-severe cases.	• NAC may be effective in COVID-19 , and reduces mortality compared to control group	• NAC administration improves the clinical and analytical response of seriously ill COVID-19 patients with compared to	• Addition of NAC to the institutional treatment protocol has led to a decline in TNF-α and the duration required for

	effective and safe treatment for COVID-19	(Mortality, ICU admission, time of invasive mechanical ventilation)		improvement in survival in COVID-19		safety profile and low cost, NAC use as adjunct therapy in COVID-19 should be considered	• The intubation and mechanical ventilation rates were higher, while oxygen with mask and nasal oxygen rates were lower in the NAC group (s statistically insignificant)				the control group.	oxygen support.
Study limitations	• Possible drug interactions • mid-point analysis (at day 7) was not done	• Sample size • This study was initially proposed as a preparatory stage before a larger multicenter trial; which however was aborted based on the unambiguo	• Limited sample size • The study was not powered to draw conclusions on the secondary findings • No information on blinding • Selection bias	• Small sample size • This study was not powered for efficacy	• Limitations not reported in the study • No details of IEC approval • The randomization process and statistical analyses were not clear	• A drug synergism effect with other components of the standardized care was not ruled out • Therapeutic dose monitoring was not performed	Single-blinded, non-homogeneous evaluation of the endpoint either at 14th day or at discharge	• Limitations not reported in the study • The preliminary results of this pilot study did not support the potential benefits of intravenous NAC	• Low sample size • Heterogeneous baseline characteristics • Limited lab data	• Single centre study with low sample size • Excluded patients with underlying medical conditions and COVID-19 vaccination	• Single centre study • Mild symptomatic patients were not included	• Single centre study with small sample size

		us negative results found in this study										
Adverse events related to NAC treatment	• No severe adverse events occurred • Adverse effects were uncommon and self-limiting • Of CMA group, 2.8% in phase-2, and 0.6% in phase-3 reported adverse events	• No adverse effects in patients who received NAC • All patients tolerated the drug and the fluid dosing • Safety analyses were based on the patients' actual treatment exposure	No significant adverse events except for bronchospasm in one patient, who fully recovered spontaneously or shortly after bronchodilator inhalation therapy	• No significant differences in AEs between the placebo and OP-101 groups • 70.5% in OP-101 group (47% had serious TEAEs) • 71.4% in the placebo group (57.1% had serious TEAEs)	None reported	No adverse drug reaction occurred in any of the study subjects treated with NAC	None reported	No intolerable or severe adverse events were reported due to NAC infusion	None reported	• No additional details available.	None reported	None reported. Only one patient refused to keep taking the NAC due to unpleasant taste.

	(mild rash and skin redness) and decided to complete the study											

CQ: chloroquine phosphate, HCQ: hydroxychloroquine, NA: not available, NR: not reported, SaO_2: Oxyhemoglobin saturation, RT-PCR: reverse transcriptase–polymerase chain reaction, CI: confidence intervals, WHO: World Health Organization, CRP: C-reactive protein, RR: respiratory rate, SpO2: blood oxygen saturation, VAP: ventilator-associated pneumonia, IQR: interquartile range, IRCT: iranian registry of clinical trials, AEs: adverse events, TEAEs: treatment-emergent adverse events, US: United States, Egfr: estimated glomerular filtration
Rate, ECMO: extracorporeal membrane oxygenation, NMD: neuromuscular disorders, CLD: chronic lung disease, MI: myocardial
infarction, CRF: chronic renal failure, CHF: congestive heart failure, PH: pulmonary hypertension, FP: favipiravir, HF: heart failure, SLD: severe liver disease, PKA: phenylketonuria, T1DM/T2DM: uncontrolled Type 1 or type 2 diabetes, CMAs: combined metabolic activators

SOFA score: Sequential Assessment of Organ Failure, APACHE II: score Acute Physiology and Chronic Health Assessment II, MBP: Mean Blood Pressure, PaO2/FiO2: Partial Oxygen Arterial Pressure/Fraction of Inspired Oxygen.

[$](Johns Hopkins School of Medicine, Maryland; Emory University School of Medicine, Georgia; Memorial Hermann Hospital System, University of Texas Health Science Center at Houston, Texas; Broward Health Medical Center, Florida; and Avera McKennan Hospital and University Health Center, South Dakota)

[#](Powder form dissolvable in water. Each dose of CMA contained 2.55 g NAC, 3.73 g l-carnitine tartrate, 1 g nicotinamide riboside chloride, and 12.35 g serine)