Consensus statement and recommendations on the treatment of COVID-19: 2021 update

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Abstract: Many treatments including antiviral and non-antiviral drugs, and critical care are considered for the management of coronavirus disease 2019 (COVID-19). Practice recommendations need to be updated and graded according to the critical evaluation of rapidly emerging literature. In June 2020, Research Center for Epidemic Prevention—National Yang Ming Chiao Tung University formed a task group comprising infectious disease clinicians, pulmonologists, and intensivists with varied areas of expertise. The steering committee prioritized questions and outcomes. The keywords for the searches were COVID-19 and prone position, extracorporeal membrane oxygenation (ECMO), noninvasive positive pressure ventilation (NIPPV), remdesivir, lopinavir, hydroxychloroquine/chloroquine (HCQ/CQ), azithromycin, corticosteroid, tocilizumab, convalescent plasma therapy, and intravenous immunoglobin (IVIG). A systematic review of peer-reviewed literature was performed by the consensus panel. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used in assessing the certainty of evidence and making recommendations. The effects of COVID-19 treatments on mortality and clinical improvement were summarized in 11 tables, and GRADE was presented to define the strength and quality of evidence for recommendation. The consensus recommended that prone position implanted in COVID-19 patients with hypoxic respiratory failure (IIC), careful selection for the support of ECMO (IIB), NIPPV being feasible but a risk of staff contamination (IIC), remdesivir generally administered in mild-to-moderate COVID-19 patients (IA), the use of dexamethasone in critically ill COVID-19 patients (IA), and the use of tociliziumab in hospitalized severe/critical COVID-19 patient with elevated markers of systemic inflammation (IA). The consensus recommended against the use of lopinavir/ritonavir (IB), HCQ/CQ (IA), azithromycin (IA), convalescent plasma therapy (IA), and IVIG (IA). The inception of the consensus and task group has provided much-needed evidence of the efficacy and safety of various therapies for the management of COVID-19 patients, and make a description about the benefits and harms for most treatments.

Keywords: Antiviral agents; Coronavirus disease 2019; Critical care; Non-antiviral drugs; SARS-CoV-2

1. EPIDEMIOLOGY

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China in December 2019. In Taiwan, the first case of COVID-19 infection was a 55-year-old woman who worked in Wuhan, China and arrived at Taiwan Taoyuan International Airport on January 20, 2020.[1–3] Well-trained and experienced teams of officials in Taiwan were quick to recognize the crisis and activated emergency management structures to address the emerging outbreak and effectively reduced the risk of transmission.[3,4] The Taiwan Centers for Disease Control reported two locally acquired cases on April 23, 2021, and the number of cases rapidly increased from 1090 on April 23, 2021 to 15 478, including 778 deaths, on July 21, 2021.[5] Infected persons who remain asymptomatic play a significant role in the ongoing pandemic. Oran and Topol[6] reported asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and can transmit the virus to others for an extended period, perhaps longer than 14 days.

2. CLINICAL PRESENTATIONS

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 days (interquartile range [IQR] 2-7). The median days from the onset of symptoms to dyspnea, acute respiratory distress syndrome (ARDS), and discharge/death were 8 days (IQR 4-9 days), 12 days (IQR 8-15 days), and 21 days (IQR 17-25 days).[7,8]

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Guan et al[7] extracted the data of 1099 patients with laboratory-confirmed COVID-19 and reported that fever was the most common symptom, which developed in 88.7% of these patients during hospitalization, followed by cough (67.8%), dyspnea (18.7%), myalgia (14.9%), headache (13.6%) nausea or vomiting (5.0%), and diarrhea (3.8%). Moreover, 15% had hypertension, 7.4% had diabetes, 2.5% had coronary artery disease, and 1.1% had chronic obstructive pulmonary disease. Yang et al[8] reported that underlying comorbidities, such as hypertension, respiratory system disease, and cardiovascular disease are risk factors for severe patients compared with nonsevere patients. The clinical characteristics of the first 100 cases of COVID-19 in Taiwan were reported by Tsou TP, and the initial symptoms were fever (54%), cough (54%), sore throat (35%), rhinorrhea (27%), and anosmia/dysgeusia (8%). Underlying conditions included cardiovascular disease (17%), diabetes (8%), chronic lung disease (4%), and asthma (3%).[9]

Approximately 81% of COVID-19 cases (n = 72 314) in China were mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, SpO_2 ≤93%, PaO_2/FiO_2 <300 mmHg, and/or lung infiltrates >50% within 24–48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[10] Meanwhile, the Taiwan Centers for Disease Control reported 1184 confirmed cases in Taiwan, 83% of whom were diagnosed as asymptomatic infection or mild, 11% with pneumonia, 6% with severe pneumonia and ARDS, and the mortality rate was 1%. Abnormalities observed in the chest X-rays varied, and bilateral multi-focal opacities were the most common. The abnormalities observed through the computed tomography (CT) of the chest also varied.

3. LABORATORY FINDINGS

Laboratory results from 1994 patients showed that lymphopenia (64.5%), increases in the levels of C-reactive protein (44.3%), lactic dehydrogenase (28.3%), and leukopenia (20.3%) were more common.[11] Many patients showed increased levels of D-dimer, creatine kinase, alanine aminotransferase, aspartate aminotransferase, serum ferritin, and interleukin-6 and erythrocyte sedimentation rate. Elevated levels of procalcitonin, troponin I, and creatinine were uncommon.[12]

4. DIAGNOSTIC TOOL

A laboratory-confirmed case with SARS-CoV-2 infection was defined as a positive result in the high-throughput sequencing real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay for SARS-CoV-2.[13] If there is a high clinical suspicion for infection by SARS-CoV-2, then serial testing is recommended to reduce the false-negative rate. Moreover, waiting 1 to 3 days after symptom onset can lessen the chances of false-negative results. The duration of viral RNA shedding is variable and depends on disease severity; prolonged viral RNA shedding of SARS-CoV-2 is detected with RT-PCR in patients recovering from COVID-19 infection. Thus, the detection of viral RNA does not necessarily reflect the presence of infectious virus, and prolonged viral RNA detection following recovery does not necessarily indicate infectiousness.[14]

Other diagnostic methods for COVID-19 include (1) point-of-care diagnostics and Xpert Xpress SARS-CoV-2 test,[15] (2) loop-mediated isothermal amplification and clustered regularly interspaced short palindromic repeats, (3) antigen detection testing, and (4) molecular and serology testing.[14] Novel molecular and serological tests can complement RT-PCR. Current active infection is detected with RT-PCR, and serology tests are used in detecting the presence of SARS-CoV-2 antibodies produced by the humoral immune system for later stages. IgA and IgM antibodies can be detected as early as 5 days after infection, and high levels are detected in the second and third week.[16,17] The peak of IgM level in the third week may correspond to a negative RT-PCR test result. The clinical performances of available tests should be assessed.[18] Notably, low titers of antibodies may be correlated with high viral load in the second week or delayed antibody development.[19]

Clinical presentation with acute olfactory impairment is an early symptom of the disease in hospitalized COVID-19 patients with a high specificity of 97%, sensitivity of 65%, positive predictive value of 63%, and negative predictive value of 97% for COVID-19 infection.[20,21]

5. VACCINATION

The first and complete genome sequence of SARS-CoV-2 provides the key to determining the structures and glycosylation patterns of viral proteins. The modes of association with a host cell have been recently reported on January 25, 2020.[22] This procedure is essential to SARS-CoV-2 vaccine development. Most vaccines target the surface-exposed spike (S) glycoprotein or S protein, mainly inducing neutralizing antibodies. S-protein based vaccines should induce antibodies that block not only viral receptor binding but also virus genome un-coating.[23]

(1) Moderna's mRNA-1273 produced through the collaboration between the National Institute of Allergy and Infectious Diseases and Moderna is a nucleotide-based vaccine containing synthetic lipid nanoparticle that carries mRNA templates into host cell and has a co-opt host machinery to express antigens of interest. The vaccine trains the immune system to recognize SARS-CoV-2's spike protein. Two doses of Moderna's mRNA-1273 provide 94.5% (90.3%-97.6%) protection against COVID-19 in persons 18 years of age or older. Pfizer and BioNTech sponsored a safety and efficacy of mRNA COVID-19 vaccine (BNT162b2) and a total of 43 548 participants (16 years of age or older) were enrolled and randomized in a 1:1 ratio to receive two doses, 21 days apart of either placebo or the BNT162b2.[24] The authors reported that a two-dose regimen of BNT162b2 mRNA COVID-19 vaccine conferred 95% (90.3%-97.6%) protection against COVID-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (2) The University of Oxford and AstraZeneca have embraced the recombinant vaccine AZD 1222 by engineering a chimpanzee adenovirus to carry DNA for the spike protein (ChAdOx1 nCoV-19). WHO 2021 Interim recommendation for the AZD 1222 reported that two doses, 12 weeks apart from AZD 1222 confer 82.4% (62.7%-91.7%) protection against COVID-19 in persons 18 years of age or older. The Janssen vaccine is based on the adenovirus serotype 26 (Ad26) which expresses the stabilized prefusion SARS-CoV-2 S protein. A phase 3 RCT trial of the single-dose Ad26. COV2.S in approximately 40 000 participants demonstrated a vaccine efficacy of 66.9%.[25] (3) Sanofi and GlaxoSmithKline are working together on a protein subunit approach, in which the spike protein antigen itself is combined with an immunogenic adjuvant to trigger a strong immune response. The vaccine developed by Novavax Company (NVX-CoV2373) is a protein subunit constructed from pre-fusion SARS-CoV-2 S-glycoprotein and adjuvanted by saponin-based Matrix M1. In the British trial, the NVX-CoV2373 vaccine had an efficacy rate of 89%.[25] (4) A few companies are focusing on whole-virus approaches, in which weakened or killed SAES-CoV-2 (inactivated virus) is used to trigger the immune system.[26]

In Taiwan, Medigen Vaccine Biologics Corp., United Biomedical Inc. Asia, and Adimmune Corp. develop COVID-19 vaccine, and the Medigen vaccine used the technology of CpG-adjuvanted stable prefusion SARS-CoV-2 spike antigen as a subunit vaccine against COVID-19 (MVC-COV1901, SP + CpG 1018). Both of companies get the approval by TFDA to conduct Phase 2 study. The Medigen Vaccine Biologics Corp. enrolled 3700 subjects since the end of February 2021 and get the approval of Emergency Use Authorization by TFDA on July 17, 2021. Recently, large numbers of emerging SARS-CoV-2 variants have appeared in the United Kingdom (variant 20I/501Y.V1, lineage B.1.1.7, alpha variant), South Africa (variant 20H/201Y.V2, lineage B.1.351, beta variant), Brazil (variant 20J/501Y.V3, lineage P.1, gamma variant), and India (variant 21A/478K, lineage B 1.617.2, delta variant). The common feature of these variants shares the N501Y mutation involving the SARS-CoV-2 spike protein which is precisely the target of most COVID-19 vaccines. The latest studies concern the impact of S protein variants on COVID-19 vaccine and report that the efficacy of Moderna's mRNA-1273 vaccine, AZD 1222 vaccine, and NVX-CoV2373 vaccine against UK variant are 95%, 74.6%, and 85.6%. For South Africa variant, NVX-CoV2373 vaccine showed a 49.4% of efficacy, but AZD 1222 vaccine did not show protection against mild to moderate COVID-19 due to South Africa variant.[27] For India variant, the efficacy of BNT162b2 vaccine, and AZD 1222 vaccine are 88% and 60%.[25] The emergence of SARS-CoV-2 variants must be examined to allow effective preventive and curative control strategies to be developed.

6. PANEL COMPOSITION AND PROCESS OF CONSENSUS DEVELOPMENT

A field verification task group, Research Center for Epidemic Prevention—National Yang Ming Chiao Tung University, was established for consensus preparation in June 2020. The working group for field verification comprised two components: a steering committee and a consensus panel. The steering committee included two infectious disease specialists, two pulmonologists, and one secretary. The tasks of the steering committee defined the purpose, scope, and target audience of the consensus and invited the members of the consensus to attend meetings. The consensus panel comprised eight pulmonologists and one secretary. The four experts provided critical review and suggestions during consensus preparation. The working group developed the consensus during six face-to-face meeting from June 2020 to March 2021.

7. LITERATURE REVIEW

The working group performed comprehensive literature searches on two electronic databases (Medicine and Cochrane library). The keywords for searches were COVID-19 and prone position, extracorporeal membrane oxygenation (ECMO), noninvasive positive pressure ventilation (NIPPV), remdesivir, lopinavir, hydroxychloroquine/chloroquine (HCQ/CQ), azithromycin, corticosteroid, tocilizumab, convalescent plasma therapy, and intravenous immunoglobin. The searches were limited to articles published in English and from December 1, 2019 to June 30, 2021. High-quality studies including randomized controlled trials and observational studies were included for evidence rating and analysis. Important epidemiological reports on COVID-19 in Taiwan were carefully interpreted and described. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) were defined as follows: (1) quality of evidence for recommendation I (one or more randomized trials with clinical outcomes and/or validated laboratory endpoints), II (one or more well-designed, nonrandomized trials or observational cohort studies), and III (expert opinion), (2) strength of recommendation A (strong recommendation for statement), B (moderate recommendation for the statement), and C (optional recommendation for the statement).

8. CLINICAL PRACTICE AND CRITICAL CARE OF COVID-19

8.1. Prone position

The main physiological effects of prone position are as follows: (1) improvement of oxygenation; (2) improvement of respiratory mechanics, including respiratory rate; (3) improvement of ventilation-perfusion mismatch; and (4) facilitation of secretion drainage. The prone position improves oxygenation and reduces mortality in patients with ARDS. For patients with COVID-19 and hypoxic respiratory failure, using the prone position can improve oxygenation and decrease the requirement of invasive mechanical ventilation. Furthermore, the use of the prone position is relatively safe and feasible outside the critical care units (Table 1).[26,28–33] Given the beneficial effects of the prone position and its low cost and easy implementation during the intervention. The prone position could be implanted in patients suffering from COVID-19 and hypoxic respiratory failure requiring invasive or NIPPV (GRADE IIC).

8.2. Extracorporeal membrane oxygenation

Despite insufficient data of the prognoses and clinical outcomes, ECMO in patients with COVID-19 and refractory hypoxemia, the World Health Organization (WHO) recommended that expert centers with sufficient ECMO volume to maintain proficiency and consider ECMO support in COVID-19-related ARDS with refractory hypoxemia if lung-protective mechanical ventilation is insufficient to support patients. Barbaro et al presented the largest cohort of COVID-19 patients requiring ECMO for respiratory or cardiac support and reported that the in-hospital mortality was 37% and the estimated mortality 90 days after ECMO was less than 40%. The complications of ECMO include infection, bleeding, and thrombosis formation. Therefore, careful patient selection for ECMO is necessary because patients' ages and comorbidities would influence prognoses and outcomes in critically ill patients with COVID-19 (GRADE IIB) (Table 2).[26,34–36]

8.3. Noninvasive positive pressure ventilation

Franco et al presented the largest cohort of COVID-19 patients with hypoxic respiratory failure requiring NIPPV support outside ICUs and reported that in-hospital mortality was 26.7%. NIPPV, including HFNC, CPAP, and NIPPV, are preferred over conventional oxygen therapy for the reduction of the need for intubation in COVID-19 patients with hypoxic respiratory failure. The application of NIPPV outside ICUs is feasible but is associated with a risk of staff contamination (GRADE IIC) (Table 3).[37–40]

9. POTENTIAL ANTIVIRAL DRUGS FOR THE TREATMENT OF COVID-19

The antiviral agents included were remdesivir, lopinavir/ritonavir, HCQ/CQ, and add-on azithromycin. Notable, most reports on antiviral treatment defined enrolled patients as having mild-to-moderate COVID-19 (room air oxygen saturation

Table 1

Effect of the prone position on oxygenation

Studies	Study design	Patients	Intervention	Comparison	Effect on oxygenation	Comments
			Prone position	Standard care	Prone position	
Xu et al, 2020[28]	Case series	P/F ratio < 300 mmHg, mild respiratory alkalosis and no alkalemia	N = 10	None	Improve oxygenation	Prone position improved oxygenation and avoid intubation
Coppo et al, 2020[29]	Prospective uncontrolled noncomparative study	O_2 supplement or noninvasive CPAP	N = 56	None	Improve oxygenation 13 (23%) patients required intubation and invasive mechanical ventilation.	Prone position improved oxygenation and was feasible outside of the critical care unit in most patients.
Thompson et al, 2020[30]	Case series	RR ≥ 30/min, SpO_2 ≤ 93% while O_2 supplement 6 L/min via and 15 L/min via NRM.	N = 25	None	Improve oxygenation 12 (48%) patients required intubation.	Prone position improved oxygenation and decreased the risk of intubation.
Elharrar et al, 2020[31]	Case series	O_2 supplement	N = 24	None	25% of patients improved oxygenation. 5 (21%) patients required invasive mechanical ventilation.	Prone position improved oxygenation and was feasible outside of the critical care unit in most patients.
Garcia et al, 2020[26]	Retrospective cohort study	Added-on VV-ECMO use	N = 14	N = 11	Improved oxygenation. Higher mortality in prone position compared with supine position. (78.6% vs 27.3%, $p = 0.02$)	Prone position improved oxygenation. The higher mortality indicated greater illness severity in prone position group.
Sartini et al, 2020[32]	Case series	Noninvasive ventilation use	N = 15	None	Improved oxygenation. 1 (7%) patient required invasive mechanical ventilation. 1 patient passed away.	Prone position improved oxygenation and was feasible outside of the critical care unit. Whether intubation was avoided or delayed remains to be determined.
Damarla et al, 2020[33]	Case series	O_2 supplement	N = 10	None	Improved oxygenation. 2 (20%) patients required invasive mechanical ventilation.	Prone position improved oxygenation and decreased the risk of intubation

ECMO = extracorporeal membrane oxygenation.

Table 2

Effect of extracorporeal membrane oxygenation on mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality		Comments
			ECMO placement				
Barbaro et al, 2020[34]	Prospective uncontrolled noncomparative observation study	ICU patients	N = 1035	None	N = 380 (37%)		For ARDS salvage treatment, ECMO placement reduced mortality.
Huette et al, 2020[35]	Case series	ICU patients	N = 12	None	N = 4 (33%)		For ARDS salvage treatment, ECMO placement reduced mortality.
Zeng et al, 2020[36]	Case series	ICU patients	N = 12	None	N = 5 (42%)		For COVID-19 ARDS patients, the mortality remained height after ECMO placement.
Garcia et al, 2020[26]	Case series	ICU patients	N = 25	None	N = 14 (56%)		For COVID-19 ARDS patients, the mortality remained height after ECMO placement.
Studies	Study design	Patients	Intervention ECMO	Comparison	Effect on complications		Comments
Barbaro et al, 2020[34]	Prospective	In-patient	1035	None	N = 56 (6%) N = 48 (5%)	CNS Hemorrhage Hemolysis	

ARDS = acute respiratory distress syndrome; CNS = central nervous system; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

of >94% or only needing use of ≤4 L/minute of supplemental oxygen)[41,42] or severe COVID-19 (a SaO_2 of ≤94% while breathing ambient air and a PaO_2/FiO_2 of <300 mmHg and needing to use >4 L/minute of supplemental oxygen, HFNC, and NIV or IMV).[43,44] Regarding outcome measurements, most of the reviewed literature focused on mortality and clinical improvement assessed by different ordinal scales and adverse effects.

Table 3

Effect of NIPPV on mortality

Studies	Study design	Patients	Intervention	Comparison NIV use	Effect on Mortality	Comments
Franco et al, 2020[37]	Multi-centers observational study	Hospitalized patients with SaO_2 <94%, RR >20[a]	HFNC, N = 163 CPAP, N = 330 NIV, N = 177	None	Crude 30 d mortality: HFNC: 26 (15.9%) CPAP: 100 (30.3%) NIV: 54 (30.5%) Crude endotracheal intubation rate: HFNC: 47 (28.8%) CPAP: 82 (24.8%) NIV: 49 (27.7%)	Noninvasive respiratory support is feasible in patients with COVID-19 and acute hypoxic respiratory failure treated outside the intensive care units The contamination rate was 11.4% among healthcare workers treating the infected patients.
Burns et al, 2020[38]	Case series Retrospective observational study	Hospitalized patients SpO_2 ≥94% with FiO_2 <40%	N = 28 CPAP: 23 (82.1%) NIV: 5 (17.9%)	None	Mortality: CPAP: 2 (8.6%) NIV: 12 (52.2%)	NIPPV should be considered as a treatment option in an integrated escalation strategy for COVID-19 patients with hypoxic respiratory failure.
Nightingale et al, 2020[39]	Case series retrospective observational study	Hospitalized patient with hypoxic respiratory failure	N = 24	None	Overall mortality N = 5 (20.8%) Died on CPAP: 1 Died on IMV: 4 Requirement of IMV use N = 9 (37.5%)	With careful selecting and close monitoring of COVID-19 patients with hypoxic respiratory failure, CPAP could be a successful treatment strategy outside the intensive critical units.
Duca et al, 2020[40]	Retrospective observational study	Hospitalized patients with ARDS	CPAP, N = 71 NIV, N = 7	None	Overall mortality CPAP: 54 (76.1%) NIV: 4 (57.1%) Intubation: CPAP: 26 (36.6%) NIV: 0	For COVID-19 ARDS patients, the strategy of NIV use outside the intensive care unit was feasible and did not lead to higher mortality rates compared to other studies.

ARDS = acute respiratory distress syndrome; CPAP = Continuous positive airway pressure; HFNC = High-flow nasal cannula; IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation; NIV = Noninvasive ventilation.

[a]Denoted poor response to 10–15 L/min oxygen requiring CPAP/NIV with very high FiO_2.

9.1. Remdesivir

We identified four randomized control trials in the literature from May 2020 to October 2020. In one study, for patients with moderate COVID-19 (n = 397), a 5-day course of remdesivir was correlated to statistically significant improvement in clinical status at 11 days after the initiation of treatment compared with standard care, but the difference between a 10-day course of remdesivir and standard care was not observed.[42] In the largest scale study, most patients with severe COVID-19 (n = 1062, 15.0% mild-to-moderate and 85.0% severe disease), a 10-day course of remdesivir was superior to placebo in terms of effectiveness in shortening recovery time and was associated with increased odds in day-15 clinical improvement.[45] However, in the other two studies, in patients with severe COVID-19 (n = 397 and 237), no significant difference in clinical improvement was observed between the 10-day course and 5-day courses of remdesivir and between a 10-day course and placebo.[43,46] Nevertheless, a network meta-analysis of four randomized control trials concluded that remdesivir compared with standard care was associated with a significantly higher clinical improvement rate.[47] Accordingly, in patients with mild-to-moderate COVID-19, the use of remdesivir for 5 days may lead to clinical improvement and is thus generally recommended (GRADE IA). However, the use of remdesivir in patients with severe COVID-19 remains uncertain (Table 4).[42,43,45–47]

9.2. Lopinavir/Ritonavir

We identified two randomized control trials of lopinavir/ritonavir treatment for COVID-19. One study, in patients with severe COVID-19 (n = 199), found that there was no benefit in mortality and clinical improvement associated with lopinavir–ritonavir treatment beyond standard of care.[48] One study comparing the 14-day combination of lopinavir/ritonavir plus ribavirin therapy and lopinavir/ritonavir alone in patients with mild to moderate COVID-19 (n = 127).[49] Although the study reported that ribavirin is highly effective in shortening the duration of virus shedding and facilitating hospital discharge, the effect of lopinavir/ritonavir remains unknown. Thus, no strong evidence of the routine use of lopinavir/ritonavir in treating patients with COVID-19 (GRADE IB) (Table 5).[48,49]

9.3. Hydroxychloroquine/Chloroquine

We identified two randomized control trials comparing the COVID-19 treatment effects of HCQ/CQ versus lopinavir/ritonavir (n = 22).[50] The studies showed that HCQ/CQ was associated with lung improvement based on CT image on day 14 (rate ratio = 2.21, 95% confidence interval [CI], 0.81-6.62) and decreased hospital length of stay. However, one larger randomized control trial found that the use of HCQ alone did not improve clinical status compared with standard of care in patients with mild-to-moderate COVID-19 (n = 439).[41] In addition, one retrospective cohort study comparing HCQ/CQ and placebo found that HCQ administration was not associated with greatly lowered or increased risk of the composite end point of intubation or death.[51] One randomized control trial in asymptomatic adults who had household or occupational exposure to someone with confirmed COVID-19 compared the postexposure prophylaxis effect of HCQ and

Table 4

Effect of remdesivir on mortality and clinical improvement

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality and clinical improvement		Comments
				Non-remdesivir	Relative (95% CI)	Absolute (95%CI)	
Goldman et al, 2020[43]	Randomized, open-label, phase 3 trial	Inpatients with COVID-19, $SpO_2 \leq 94\%$ on room air, and evidence of pneumonia.	IV remdesivir for 5 d. N = 200. (200 mg on day 1 then 100-mg once daily)	IV remdesivir for 10 d. N = 197. With a worse clinical status at baseline.	Clinical status at day 14 was similar between the 10 d group and the 5 d group ($p = 0.14$).	A clinical-scale improvement by day 14: 64% in the 5 d group vs 54% in the 10 d group.	This trial (without a placebo control) did not show a significant difference between a 5 d and a 10 d course of remdesivir.
Wang et al, 2020[46]	Randomized, double-blind, placebo-control trial	In patients with $SpO_2 \leq 94\%$ on room air or a P/F ratio ≤ 300, and pneumonia.	IV remdesivir (200 mg on day 1, 100 mg once daily for 10 d, N = 158, Permitted use of other drugs. [a]	Same volume of placebo infusions for 10 d, N = 79, permitted use of other drugs.	(1) No difference in time to clinical improvement (HR 1.23 [0.87–1.75])[b]. (2) In subgroup with symptoms of ≤10 d: a faster time to improvement than placebo (HR 1.52 [0.95–2.43]).	Adverse effect: 102 (66%) in remdesivir group versus 50 (64%) in placebo	In this inpatient study, remdesivir was not associated with statistically significant clinical benefits.
Spinner et al, 2020[42]	Randomized, open-label trial	Inpatients with COVID-19 and moderate pneumonia (pulmonary infiltrates and $SpO_2 > 94\%$ on room air	10 d course of remdesivir (N = 197), or 5 d course of remdesivir (N = 199), 200mg on day 1, then 100mg once daily.	Standard care (N = 200).	On day 11, a better clinical status in 5 d group than standard care (OR 1.65 [1.09–2.48; $p = 0.02$), but no difference between 10 d group and standard care.	By day 28, 9 patients had died: 2 (1%) in the 5 d remdesivir group, 3 (2%) in the 10 d group, and 4 (2%) in the standard care group.	For moderate COVID-19, a 5 d course of remdesivir was related to a significant difference in a clinical status scale compared with standard care, but its clinical importance was uncertain.
Beigel et al, 2020[45]	Double-blind, randomized, placebo-control trial	1062 inpatients with COVID-19 and lower respiratory tract infection. 85.0% severe disease; 15.0% mild-to-moderate.	Remdesivir (200 mg on day 1, 100 mg daily for up to 9 additional days), N = 541	Placebo for up to 10 d, N = 521	(1) day-15 clinical improvement (OR 1.5 [1.2-1.9], after adjustment for disease severity). (2) Less mortality (HR 0.73 [0.52-1.03]).	Median recovery time, 10 d ([95% CI, 9-11]) vs 15 [13-18]), Serious adverse effect: 24.6% in Remdesivir vs 31.6% in placebo.	Remdesivir was superior to placebo in shortening the time to recovery in adult inpatients with COVID-19
Yokoyma et al, 2020[47]	A network meta-analysis	4 randomized control trials	5 d and 10 d courses of remdesivir	Standard care	ORs for clinical improvement in 5 and 10 d groups vs standard care: 1.89 (1.40-2.56) and 1.38 (1.15-1.66).		Remdesivir was associated with the significantly higher clinical improvement rate compared with standard of care alone.

HR = hazard ratio with (95% CI); IV = Intravenous; OR = odds ratio with (95% CI); P/F ratio = the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage); SpO_2 = oxygen saturation.

[a]Other drugs included lopinavir–ritonavir, interferons, and corticosteroids.

[b]Clinical improvement was defined as the time (in days) from randomization to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1 = discharged to 6 = death).

placebo and found that HCQ did not prevent infection.[52] In summary, no strong evidence to support the use of HCQ/CQ for the treatment or prophylaxis of COVID-19 was found (GRADE IA) (Table 6).[50–52]

9.4. Add-on azithromycin

We identified three randomized control trials, one nonrandomized trial and two retrospective cohort studies, which compared HCQ treatments with or without add-on azithromycin in patients with COVID-19. Although one small randomized trial showed that HCQ plus azithromycin treatment was beneficial for COVID-19 patients without prior cardiac diseases (n = 111),[53] the other two larger trials found that the use of HCQ with azithromycin did not improve clinical status as compared with HCQ alone in patients with mild-to-moderate or severe COVID-19 (n = 439 and 397).[41,44] The positive finding of virological cure from the nonrandomized trials (N = 36) was limited by nonrandomized nature and small sample size.[54] The reports from the two retrospective cohort studies were inconsistent with each other with regard to the treatment effect of HCQ plus azithromycin treatment on mortality reduction.[55,56] Again, according to the results of the randomized control trials, the use of HCQ with azithromycin for COVID-19 treatment is not generally recommended (GRADE IA) (Table 7).[41,44,53–56]

In summary, the use of remdesivir for 5 days may lead to the clinical improvement of mild-to-moderate disease and this regimen is recommended for patients with mild-to-moderate COVID-19 (GRADE IA). However, the use of remdesivir in patients with severe COVID-19 remains uncertain. In addition, no evidence supports the routine use of lopinavir/ritonavir, HCQ/CQ, or HCQ plus azithromycin treatments for patients with COVID-19 (GRADE IA).

Table 5

Effect of lopinavir-combined regimen on mortality and clinical improvement

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality and clinical improvement: Relative (95% CI)	Effect on mortality and clinical improvement: Absolute (95% CI)	Comments
Cao et al, 2020[48]	Randomized, controlled, open-label	Inpatients with $SpO_2 \leq 94\%$ on room air or a P/F ratio ≤ 300.	Standard care plus lopinavir–ritonavir (400 mg/100 mg) twice a day for 14 d, N = 99	Standard care alone, N = 100	HR for clinical improvement: a 1.24 (0.90–1.72).	28 d mortality was similar: 19.2% vs 25.0%	No benefit was observed with lopinavir–ritonavir treatment beyond standard of care.
Hung et al, 2020[49]	Multi-center, prospective, open-label, randomized, phase 2 trial	In-patients with mild to moderate	14 d of lopinavir 400 mg/ritonavir 100 mg every 12 h, combined with ribavirin 400 mg every 12 h, 3 doses of interferon β-1b on alternate days, N = 86	14 d of lopinavir 400 mg/ritonavir 100 mg every 12 h (control group), N = 41	Time to providing a nasopharyngeal swab negative for SARS-CoV-2 RT-PCR: 7 d (IQR 5–11) in combined group vs 12 d (8–15) in control; HR 4·37 (1.86–10.24, $p = 0.0010$).	Duration of hospital stay, Combination: 9.0 (7.0–13.0) d vs control: 14.5 (9.3–16.0), $p = 0{\cdot}016$	Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.

HR = hazard ratio with (95% CI); IQR = interquartile range; P/F ratio = the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage); RT-PCR = real-time reverse-transcriptase polymerase-chain-reaction; SpO_2 = oxygen saturation.

[a]Clinical improvement was defined as an improvement of two points on a seven-category ordinal scale or discharge from the hospital.

Table 6

Effect of hydroxychloroquine/chloroquine on mortality and clinical improvement

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality and clinical improvement: Relative (95% CI)	Effect on mortality and clinical improvement: Absolute (95% CI)	Comments
Huang et al, 2020[50]	Randomized, controlled trial	In hospitalized patients with COVID-19 (36.4% severe disease, 63.6% mild/moderate).	Chloroquine 500 mg orally twice daily for 10 d, N = 10	Lopinavir/Ritonavir 400/100 mg orally twice daily for 10 d, N = 12	Lung improvement on CT scan at day 14: RR 2.21 (95% CI 0.81-6.62).	Hospital length of stay: 100% of the chloroquine cases were discharged vs 50% in the controls.	The sample size was small. The preliminary results may suggest that chloroquine could be an effective and inexpensive option.
Geleris et al, 2020[51]	Retrospective cohort study	COVID-19 patients without death, intubation or discharged within 24 h at emergency room	HCQ (600 mg twice on day 1, then 400 mg daily for a median of 5 d), N = 811	Without HCQ, N = 565	Composite of intubation or death: HR 1.04 (0.82–1.32).		HCQ administration was not associated with the risk of the composite end point of intubation or death.
Boulware et al, 2020[52]	Randomized, controlled trial	Asymptomatic adults with exposure to COVID19 cases at a distance of <6 ft for >10 minutes	HCQ (800 mg once, followed by 600 mg in 6-8 h, then 600 mg daily for 4 additional days), started within 4 d after exposure, N = 414	Placebo, N = 407		Post-exposure new illness compatible with COVID 19: HCQ =11.8% in HCQ vs 14.3% in placebo, absolute difference: 2.4% points ($p = 0.35$).	HCQ did not prevent illness compatible with COVID-19 or confirmed infection when used as postexposure prophylaxis within 4 d after exposure

CQ = chloroquine; HCQ = hydroxychloroquine; HR, hazard ratio with (95% CI).

10. POTENTIAL NON-ANTIVIRAL DRUGS FOR COVID-19 TREATMENT

The clinical efficacy of non-antiviral agents in patients with COVID-19 includes corticosteroid, tocilizumab, convalescent plasma therapy, and intravenous immunoglobulin. The included clinical trials enrolled patients needing hospitalization or intensive care. Notably, several studies[57,58] were not subjected to thorough peer review and were found in the preprint server. Some results were obtained from direct contact with study groups.[59]

10.1. Corticosteroid

We identified four randomized control trials in the literature from May 2020 to December 2020.[59–62] Additional three unpublished clinical trials, such as DEXA-COVID19 (NCT04325061),[63] COVID STEROID (NCT04348305),[63] and Steroids-SARI (NCT04244591)[64] were pooled for meta-analysis on 28-day all-cause mortality among critically ill patients with COVID-19 adapted from reports from WHO.[59] A total of 1703 patients were included in the analysis. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR = 0.66 [95% CI, 0.53-0.82], $p < 0.001$). Small inconsistency was observed among the trial results (I2 = 15.6%; $p = 0.31$ for heterogeneity). The adverse and serious adverse events in the steroid and control groups were similar. Hyperglycemia, neurological side effects, including agitation or confusion, adrenal suppression, and risk of bacterial and fungal infection had been reported in patients treated with corticosteroids.[59–62]

Table 7

Effect of azithromycin plus hydroxychloroquine/chloroquine on mortality and clinical improvement

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
Rosenberg et al, 2020[54]	Retrospective cohort study	Random sample of in-patients with COVID-19 in 25 hospitals in New York State (36.4% severe disease; 63.6% mild/moderate	HCQ plus AZM, N = 735; HCQ alone, N = 271; AZM alone; N = 211	Neither drug, N = 221	HR for in-hospital mortality: 1.35 (0.76-2.40) in HCQ plus AZM, group, 1.08 (0.63-1.85) in HCQ alone, 0.56 (0.26-1.21) in AZM alone	The probability of death: 25.7% in HCQ plus AZM group, 19.9% in HCQ alone, 10.0% in AZM alone, 12.7% in neither drug group.	Treatment with HCQ, AZM, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality
Arshad et al, 2020[55]	Multi-center retrospective cohort study.	Inpatients	HCQ plus AZM, N = 783; HCQ alone, N = 1202; AZM alone, N = 147	Neither drug, N = 409	For in-hospital mortality: HCQ plus AZM showed a 71% HR reduction and HCQ 66% compared to neither treatment ($p < 0.001$).	Mortality: 20.1% in HCQ plus AZM; 13.5% in HCQ alone; 22.4% in AZM alone, 26.4% in neither drug group.	When controlling for risk factors, HCQ plus AZM and HCQ alone was associated with reduction in COVID-19 associated mortality.
Gautret et al, 2020[56]	Open-label nonrandomized clinical trial	French Confirmed COVID-19 inpatients	600 mg of HCQ daily with and without AZM in a hospital setting, N = 20	Untreated patients from another center and cases refusing the protocol, N = 16		Virological cure at day 6: 14/20 (70.0%) in HCQ treated group vs 2/16 (12.5%) in untreated, $p = 0.001$	The study was limited by small sample size, no adjustment for baseline viral load. The result was, inconsistent with other reports.
Cavalcanti et al, 2020[41]	Multi-center, randomized, open-label, controlled trial	Inpatients with suspected or confirmed COVID-19, with SpO_2 ≤ 94% on room air.	Standard care plus HCQ (400 mg twice daily, N = 217, or standard care plus HCQ plus AZM (500 mg once daily for 7 d, N = 221)	Standard care, N = 227	Clinical status at 15 d (1-7 level ordinal scale) OR 1.21 ([0.69-2.11]; $p = 1.00$) or 0.99 ([0.57-1.73]; $p = 1.00$)		Among patients hospitalized with mild-to-moderate COVID-19, the use of HCQ, alone or with AZM, did not improve clinical status at 15th days as compared with standard of care.
Furtado et al, 2020[44]	Open-label, Randomized, controlled trial, in Brazil	In-patients with confirmed COVID-19, with the use of O_2 of > 4 L/min flow, HFNC, NIV, or invasive MV.	AZM (500 mg daily for 10 d) plus standard of care (HCQ 400 mg twice daily, for 10 d), N = 214	Standard of care with HCQ without AZM for 10 d N = 183	HR for mortality 1.08 ([0.79-1.47]; $p = 0{\cdot}63$); OR for worsening clinical status at day 15 1.36 ([0.94-1.97], $p = 0.11$).		In patients with severe COVID-19, adding AZM to standard of care treatment (which included HCQ) did not improve clinical outcomes.
Sekhavati et al, 2020[53]	Open-label, Randomized, controlled trial	In-patients with COVID-19, without prior cardiac disease, in Iran.	AZM in addition to the same regimen of control, N = 56	HCQ and lopinavir/ritonavir, N = 55	No patient in either group experienced arrhythmia or QTc prolongation.	Mortality: 0/56 vs 1/55 ($p = 0.495$; Hospital length of stay: 4.61 vs 5.96 d ($p = 0.02$)	Patients who received AZM in addition to HCQ and LPV/r had a better general condition.

AZM = azithromycin; HCQ = hydroxychloroquine; HFNC = High-flow Nasal Cannula; HR = hazard ratio with (95% CI); MV = mechanical ventilation; NIV = noninvasive ventilation; OR = odds ratio with (95% CI); SpO_2 = oxygen saturation.

Regarding the choice of corticosteroid, most enrolled critically patients (n = 459, 67.8%) received dexamethasone with an initial dose ranging from 6[60] to 20 mg[59] daily. Among critically ill patients with COVID-19, we recommended the use of corticosteroids, especially dexamethasone rather than not applying steroid treatment (GRADE IA). The definition of critical illness included patients on mechanical ventilation, ECMO, or end-organ dysfunction such as sepsis, septic shock, and ARDS (Table 8).[59–62]

10.2. Tocilizumab

We identified seven randomized control trials of tocilizumab treatment for COVID-19.[57,65–68] RECOVERY trial contributed most participants among other studies with both tocilizumab arm and usual care arm included more than 2000 participants, respectively. In patients with progressive COVID-19 defined as oxygen saturation less than 92% on room air or receiving oxygen therapy and elevated C-reactive protein level ≥75 mg/L, with balanced use of steroids across both treatment arms, they were randomized to receive tocilizumab or usual care. Eighty-two percent of participants in both arms received steroids treatment concomitantly. In tocilizumab group, there was significantly lower 28-day mortality and higher rate of survival to discharge compared with usual care group. Although the RECOVERY trial did not blind participants or healthcare personnel, this would unlikely introduce bias in measurement of mortality. Serious adverse events among patients receiving tocilizumab did not differ from those receiving placebo. However, side effects from treatment with tocilizumab included an increased risk of infection.[57] In addition, cases of

Table 8

Effect of corticosteroid on 28-day mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on 28 d mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
CoDEX[59]	Multi-center, randomized, open-label, clinical trial	Patients with COVID-19 and moderate to severe ARDS	20 mg of dexamethasone intravenously daily for 5 d, 10 mg of dexamethasone daily for 5 d or until ICU discharge, plus standard care N = 151	Standard care alone N = 148	0.97 (0.72–1.31), $p = 0.85$	5.2% (–5.9% to 16.3%)	28 d mortality as secondary outcome.
RECOVERY[60]	Randomized, open-label trial	Patients who were hospitalized with COVID-19	Oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 d N = 2104	Usual care alone N = 4321	0.83 (0.75-0.93)	2.8% (0.6%-5%)	28 d mortality as primary outcome.
CAPE COVID[61]	Multi-center randomized double-blind sequential trial.	Patients admitted to the (ICU for COVID-19–related acute respiratory failure.	Low-dose hydrocortisone (treatment was continued at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 d and 50 mg/d for 3 d, for a total of 14 d), N = 76	Placebo N = 73	0.46 (0.20-1.04)	12.9% (0-25.9%)	Data adapted from WHO working group.[4] 21 d mortality as post-hoc outcome
REMAP-CAP[62]	Randomized, open-label trial	Patients with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support	The corticosteroid domain randomized participants to a fixed 7 d course of intravenous hydrocortisone (50 mg or 100 mg every 6 h) N = 143 Or a shock-dependent course (50 mg every 6 h when shock was clinically evident), N = 152	No hydrocortisone N = 108	0.71 (0.38-1.33)	6.8 (–5.8% to 19.3%)	Data adapted from WHO working group.[4] The primary end point was organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 d.

ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

bowel perforations after the use of tocilizumab for COVID-19 were reported. Considering the currently available evidence, we suggest tocilizumab in hospitalized severe or critical COVID-19 patients with elevated markers of systemic inflammation (GRADE IA) (Table 9).[57,65–69]

10.3. Convalescent plasma therapy

We identified three randomized control trials comparing convalescent plasma therapy plus usual care with usual care alone.[70–72] These trials presented concerns about the risk of bias due to unadjusted potential confounders and variation

Table 9

Effect of tocilizumab on 28-day mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on 28 d mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
COVACTA[57]	Double-blinded, randomized control trial (2:1 randomization)	Patients ≥18 y/o with severe COVID-19 pneumonia with SaO_2 ≤93% or PF ratio <300 mm/Hg.	Intravenous TCZ (8 mg/kg infusion, maximum 800 mg). If clinical signs or symptoms did not improve or worsened (defined as sustained fever or worsened ordinal scale clinical status), a second infusion could be administered 8 to 24 h after the first, N = 294	Placebo, N = 144	1.018 (0.688–1.508)	–0.3% (–8.2% to 7.6%)	Data from preprint manuscript. The primary outcome measure was clinical status on a 7-category ordinal scale at day 28.
BACC[65]	Randomized, double-blind, placebo-controlled trial (2:1 randomization)	Patients 19-95 y/o with confirmed severe acute respiratory syndrome coronavirus 2 infection, hyperinflammatory states + 2 of the following (fever, pulmonary infiltrates, or need of oxygen to keep SpO_2 ≥92%)	Intravenous TCZ (8 mg/kg infusion, maximum 800 mg). N = 161	Placebo, N = 82	1.509 (0.420 to 5.424)	–1.9% (–7.3% to 3.5%)	The primary outcome was intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo, assessed in a time-to-event analysis

(*Continued next page*)

Table 9 (Continued)

Effect of tocilizumab on 28-day mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on 28 d mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
CT-TCZ–COVID-19[57]	open-label, randomized trial	Patients ≥18 y/o with COVID-19 pneumonia and acute respiratory failure. PF ratio 200-300, an inflammatory Phenotype (temperature > 38 °C during the last 2 d, and/or serum CRP ≥ 10 mg/dL or increased to at least twice the admission measurement	Intravenous TCZ (8 mg/kg infusion, maximum 800 mg) within 8 h from randomization, N = 60	Supportive care. N = 66	2.2 (0.205-23.65)	–1.8% (–7.2% to 3.6%)	The primary composite outcome was defined as entry into the intensive care unit with invasive mechanical ventilation, death from all causes, or clinical aggravation with PF ratio < 150
CORIMUNO-TOCI-1[66]	open-label, randomized trial	Patients with confirmed SARS-CoV-2 infection with moderate, severe, or critical pneumonia (O_2 >3 L/min, WHO Clinical Progression Scale (WHO-CPS) score ≥5	TCZ was administered intravenously (IV) at 8 mg/kg on day 1. Administration of an additional fixed dose of TCZ, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician. N = 64	Usual care alone. N = 67	0.916 (0.353-2.38)	1% (–9.9% to 11.9%)	Primary outcomes were scored higher than 5 on the World Health Organization 10-point clinical progression Scale (WHO-CPS) on day 4 and survival without the need of ventilation (including noninvasive ventilation) at day 14.
REMAP-CAP[67]	Open-label, randomized trial	Patients ≥18 y/o with critically ill COVID-19 admitted to ICU and receiving respiratory or cardiovascular organ support	Intravenous TCZ (8 mg/kg infusion, maximum 800 mg); this dose could be repeated 12-24 h later at the discretion of the treating clinician if clinical improvement was judged insufficient. N = 353	Control. N = 48	30 d mortality: 0.739 (0.588-0.93)	30 d mortality 8.7 (2.2%-15.1%)	The primary outcome was respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death (assigned a value of –1) and days free of organ support to day 21.
Coalition covid-19 Brazil VI[68]	open-label, randomized trial	Patients ≥18 y/o with supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (CRP > 5 mg/dL, D dimer >2.74nmol/L, LDH > ULN, or ferritin>300 ug/L)	Intravenous TCZ (8 mg/kg infusion, maximum 800 mg). N = 65	Standard care. N = 64	2.297 (0.942-5.605)	–12.2% (–24.4% to 0.1%)	The primary outcome was clinical status at 15 d evaluated with the use of a seven-level ordinal scale. The trial was prematurely Interrupted due to higher mortality in tocilizumab group.
RECOVERY[69]	Randomized, open-label trial	Patients who were hospitalized with COVID-19 with hypoxia (SpO_2 <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (CRP ≥75 mg/L)	Intravenous TCZ (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12-24 h later if the patient's condition had not improved, N = 2022	Usual standard of care alone. N = 2094	0.882 (0.808-0.963)	4.1% (1.2%-7%)	The primary outcome was 28 d mortality.

CRP = C-reactive protein; P/F ratio = the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage); SpO_2 = oxygen saturation; TCZ = tocilizumab.

in the timing of convalescent plasma administration during the clinical course. Moreover, these trials failed to show survival benefits in the treatment arm. Considering current evidence, we recommended against the routine use of convalescent plasma therapy in patients with COVID-19 (GRADE IA)(Table 10).[70–72]

10.4. Intravenous Immunoglobulin

We identified two clinical trials comparing intravenous immunoglobulin plus standard of care and standard of care alone.[73,74] Although one trial in Iran found reduction in in-hospital mortality, the trial was predominated by male and

Table 10

Effect of convalescent plasma therapy on mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
Li et al[70]	Open-label, multi-center, randomized clinical trial	Patients with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation).	Convalescent plasma in addition to standard treatment, N = 52	Standard treatment alone, N = 51	0.589 (0.270-1.286)	8.3% (–7.2% to 23.8%)	28 d mortality as secondary outcome. Primary outcome was time to clinical improvement within 28 d, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale (ranging from 1 [discharge] to 6 [death]).
ConCOVID[71]	Multi-center open-label randomized clinical trial	Patients hospitalized for COVID-19	300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at least 1:80, N =43	Without plasma treatment, N = 43	0.472 (0.197-1.132)	11.6% (–5% to 28.3%)	The primary endpoint was day 60 mortality.
PLACID[72]	Multi-center open-label randomized controlled trial	Moderate COVID-19 with P/F ratio between 200 mmHg and 300 mmHg or a respiratory rate of more than 24/min with SpO_2 93% or less on room air	Two doses of 200 mL convalescent plasma, transfused 24 h apart + best standard of care, N = 235	Best standard of care, N = 229	1.069 (0.681-1.679)	–0.9% (–7.2% to 5.4%)	The primary outcome is a composite of progression to severe disease (P/F ratio <100 mmHg) or all-cause mortality at 28 d.

P/F ratio = the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage); SpO_2 = oxygen saturation.

not balanced in baseline demographics.[74] Moreover, the side effect was not reported.[74] In another study, in-hospital mortality did not differ between treatments with and without immunoglobulin.[70] Although the use of intravenous immunoglobulin improved hypoxia and reduces hospital length of stay, co-administration of methylprednisolone in the immunoglobulin treatment group is not balanced. No adverse events were reported in the immunoglobulin arm.[70] Given the lack of evidence, we recommended against the routine use of intravenous immunoglobulin in patients with COVID-19 (GRADE IA) (Table 11).[73,74]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Table 11

Effect of intravenous immunoglobulin on in-hospital mortality

Studies	Study design	Patients	Intervention	Comparison	Effect on in-hospital mortality		Comments
					Relative (95% CI)	Absolute (95% CI)	
Sakoulas et al[73]	Open label, randomized control trial	Adult patients > 18 years of age presenting with COVID-19 infection with moderate to severe hypoxia (SpO_2 <96% on > 4 liters O_2 by nasal cannula) but not on mechanical ventilation.	IVIG 0.5 g/kg/d × 3 d with methylprednisolone 40 mg 30 minutes before infusion plus standard of care, N = 16	Standard of care alone, N = 17	3.214 (0.377 to 27.396)	–11.4% (–33.1% to 10.3%)	Primary endpoint included (1) respiratory failure requiring receipt of mechanical ventilation or (2) death from nonrespiratory causes before receipt of mechanical ventilation
Gharebaghi et al[74]	Randomized placebo-controlled double-blind clinical trial.	Adult patients with confirmed COVID-19 diagnosis, involvement of > than 30% of both lungs (ground-glass opacity) in HRCT, O_2 saturation of <90%, and a lack of adequate response to initial treatment including at least both one antiviral and one chloroquine-class drug	Four vials of 5 g IVIG (human flebogamma 5% DIF GRIFOLS) daily for three consecutive days + their prior initial treatment, N = 30	Placebo + their prior initial treatment, N = 29	0.414 (0.185 to 0.930)	28.3% (5.1% to 51.4%)	Outcome measure was in-hospital mortality

HRCT = high resolution computed tomography; IVIG = intravenous immunoglobulin; SpO_2 = oxygen saturation.

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