REVIEW

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.2021-168
Cyprus J Med Sci 2022;7(3):287-302

Therapeutic Interventions Implemented During the First Year of the COVID-19 Pandemic: A Systematic Review of Evidence

Özen Aşut, Şanda Çalı

Department of Public Health, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

The aim of this study was to review the knowledge and evidence on the therapeutic effectiveness of some agents currently utilized for treating coronavirus disease-2019 (COVID-19).

The literature search was performed using the databases PubMed, Scopus, Google Scholar, and the Cochrane Library. The publications identified were screened to select cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews. End points displaying the results of epidemiological and statistical methods were evaluated to specify the strength of evidence.

Eleven randomised controlled trials, a controlled trial, five cohort studies, four reviews, two systematic reviews, a systematic review-meta-analysis, and a meta-analysis were included. These 25 studies covered treatments with antimalarials, anticoagulation, antivirals, corticosteroids, interferons, monoclonal antibodies, and convalescent plasma. The outcomes assessed included all-cause and in-hospital mortality, death or mechanical ventilation within 28 days, mean or median day to viral clearance, median and day-28 recovery time, and improvement in oxygen support class.

The results showed evidence for the efficacy of remdesivir and corticosteroids in critically ill patients. Only corticosteroids showed efficacy regarding reduced mortality. Favipiravir, anticoagulation, interferons and monoclonal antibodies were agents with weaker evidence of therapeutic efficacy.

The key findings of this review highlight evidence regarding the efficacy of remdesivir and corticosteroids for hospitalised patients.

Keywords: COVID-19, coronavirus disease 2019, therapeutic alternatives, antivirals, remdesivir, favipiravir, corticosteroids, immunomodulators

INTRODUCTION

Coronavirus disease-2019 (COVID-19) was officially announced by the World Health Organisation (WHO) on December 31, 2019,[1] and declared a global pandemic by the WHO on March 11, 2020.[2,3] COVID-19 is predominantly self-limited while up to 20% will progress to severe disease. Early treatment to prevent disease progression and complications is pronounced currently as an urgent need.[4-8]

Antimalarial medications, chloroquine and hydroxychloroquine were among the first drugs introduced for treatment and prophylaxis.[9,10] Although countries continued keeping these drugs in their treatment protocols, the WHO cautioned against administering these unproven treatments.[11-14]

Basically, therapeutics for COVID-19 fall into three categories: Antiviral, immune-based, and adjunctive therapies. Some antiviral medications,

To cite this article: Aşut Ö, Çalı Ş. Therapeutic Interventions Implemented During the First Year of the COVID-19 Pandemic: A Systematic Review of Evidence. Cyprus J Med Sci 2022;7(3):287-302

ORCID IDs of the authors: Ö.A. 0000-0002-9604-4037; Ş.Ç. 0000-0001-9929-2637.

Address for Correspondence: Özen Aşut
E-mail: ozen.asut@neu.edu.tr
ORCID ID: orcid.org/0000-0002-9604-4037

Received: 26.06.2021
Accepted: 19.12.2021

antibiotics and immuno-therapeutics have been introduced for COVID-19 based on the experiences of previous coronavirus diseases and in-vitro findings.[15-19] The therapeutics investigated in trials include ivermectin,[16,17] melatonin,[18,20] and monoclonal antibodies.[15,19]

The National Institutes of Health (NIH) COVID-19 Treatment Guidelines panel has outlined evidence-based statements on primary therapeutics for COVID-19 according to the available research.[17,21,22]

Antiviral medications including remdesivir and favipiravir; immunomodulators such as interferons, corticosteroids, monoclonal antibodies, and anticoagulation and convalescent plasmas are the subjects of this review as well as research on some therapeutics under investigation with insufficient or no evidence to highlight the multidimensional progress on this issue. There are more than 60 thousand COVID-19 publications available on PubMed. It is important that the choice of therapeutic agents by the medical professionals should rely on the best possible evidence currently available.[23]

Objective of the study

The aim of this study was to establish the current knowledge and evidence on the therapeutic efficacy of some prominent agents utilized in the treatment of COVID-19 through a review of the existing evidence-based medical literature universally. Since information on this issue is evolving rapidly, the content within this review intends to serve as a reference for the information available at the time of publication.

Methods

Information Sources and Criteria of Eligibility

The literature search was performed as recommended for systematic reviews[24] through the databases PubMed, Scopus, Google Scholar and the Cochrane Library, only in English, using the keywords COVID-19 therapy and treatment. Additional studies were identified through other means (such as Medscape, references of articles, and press releases).

Article Search

There was no time limit set regarding the study period and publication dates. Starting on 20 June, 2020, an online search was performed until November 10, 2020. Newly appearing articles and other data were covered by continuing the literature search until January 30, 2021.

Study Selection and Recruitment of Articles

The publications identified were screened by the researchers based on title and abstract in order to find the relevant articles. Cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews were recruited into the study list. Pre-print articles, case reports and case series other than those in the review studies were excluded.

Subsequently, 59 full articles were assessed in order to eliminate any articles with study types and content other than those in the inclusion criteria and to select those articles containing a strength of evidence. Some articles were excluded due to the insufficient quality of the research methods, analyses of the data or interpretation of the findings (Figure 1).

Data Collection Process

Data were collected using a data extraction form which covered the following features of the articles: The database, journal name and issue, authors and title; time, setting and the universe of studies; the number of participants, the number of studies (for reviews); and the aim, type, methods, results and outcomes of the studies. The data extraction and assessment were carried out by the two researchers independently. Decisions were made after discussion and by consensus based on the evidence.

Data Items

Data items included the following variables:

Participants: COVID-19 patient groups of differing ages and severity (mild, moderate, severe), hospitalised and non-hospitalised patients, need of oxygen supplementation

Interventions: Therapies applied in COVID-19: Pharmacotherapeutics such as antivirals, chloroquine and hydroxychloquine, anticoagulation, monoclonal antibodies, interferons, convalescent plasma, corticosteroids etc.

Comparisons: Therapies applied to control groups: Usual care, antivirals (lopinavir/ritonavir, oseltamivir, umifenovir), antibiotics and placebos.

Outcomes: 28-day all-cause mortality, in-hospital mortality, death or mechanical ventilation (MV) within 28 days, lethality, improvement of radiologic findings, days to viral clearance, mean or median days to viral clearance, recovery at day 28, time to recovery measured as discharge from hospital, improvement in oxygen support class, organ-support free days, improvement and clinical recovery rate, and median recovery time.

Study design: Cohort studies, randomised controlled trials, meta-analyses, narrative and systematic reviews.

Funding sources: Studies with conflicts of interest

Risk of Bias in Individual Studies

Assessment of the risk of bias included methods of randomisation, treatment allocation and blinding. The novel and urgent nature of COVID-19 therapeutic interventions resulted in weaknesses in preventing bias, as a lack of controls, randomisation or blinding were declared in the method sections of the studies and these were used in assessing the strength of the evidence.

Summary Measures

Principal summary measures included hazard ratios, relative risks, odds ratios, their confidence intervals, risk differences, lethality, other epidemiological measures, statistical tests and their *p* values.

Limitations

Since COVID-19 has a short history of only one year, the results of the studies selected have limitations due to the infection's novel nature, time restrictions, low participant sizes, the lack of sufficient previous experience, and the uncertain nature of future advances. Furthermore, the rapid progress in the treatment of COVID-19 limits the comprehensiveness of a review due to the time needed to finalise studies.

The fact that only English publications have been covered in this study may be considered a bias regarding publication language.

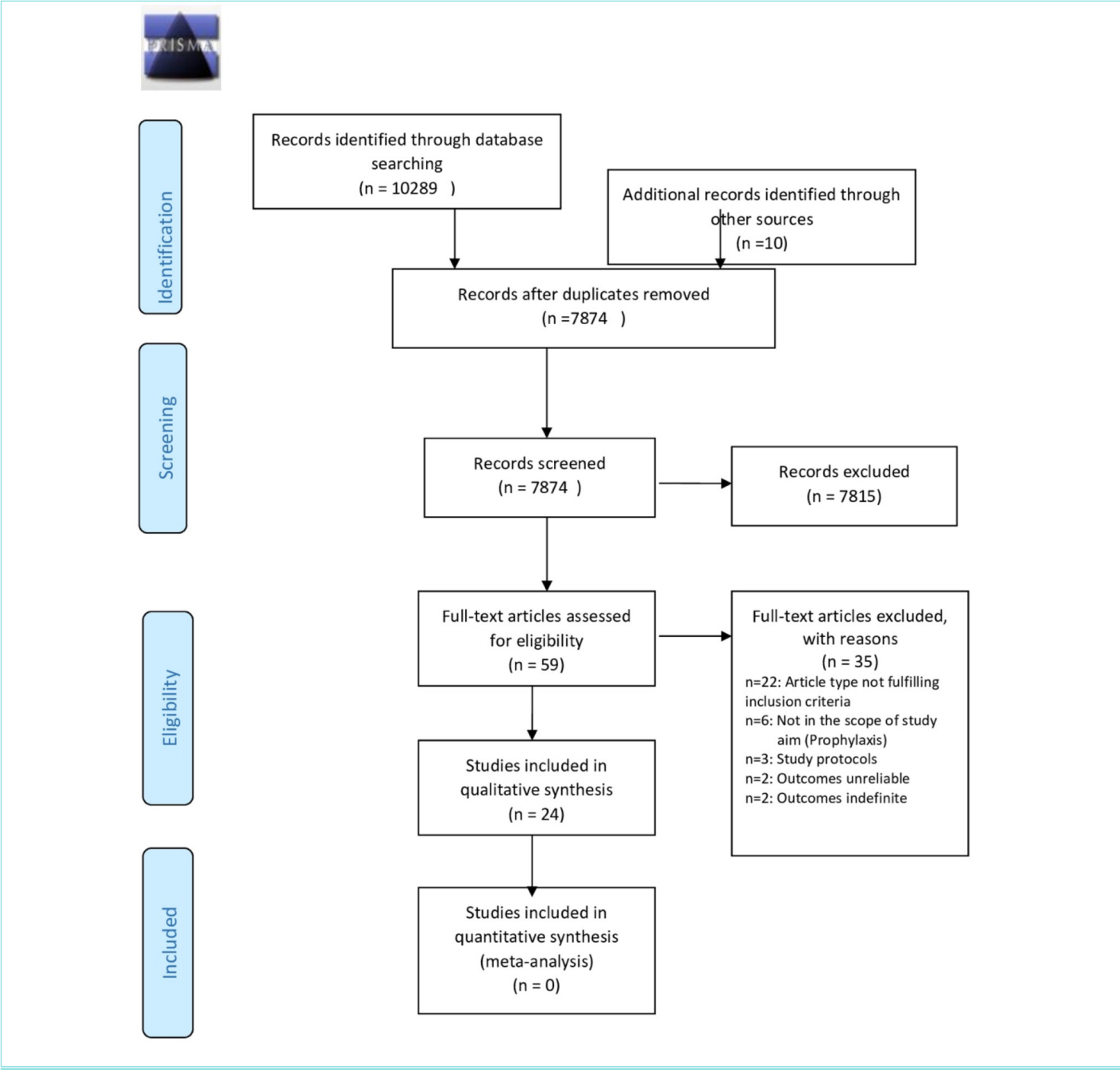

Figure 1. Prisma flow diagram of the search results.

Results

In this study, the selection of the research articles was based on the quality of the evidence in the studies. The number of studies screened, assessed and included are displayed in the flow diagram (Figure 1).

Randomised controlled trials, systematic reviews and meta-analyses comprised 15 of the total 25 studies selected. Eleven randomised controlled trials, one controlled trial, five cohort studies, four reviews, two systematic reviews, one systematic review and meta-analysis, and one meta-analysis were included. Some preliminary research other than these was also covered in the main text of the article, although not included in the tables.

The studies reviewed were conducted in the following countries: China, the Netherlands, Italy, France, the United States of America (USA), Columbia, Iran, Mexico, Denmark, the United Kingdom (UK), Korea, Singapore, India, Greece, Germany, Spain, Japan, Hong Kong, Taiwan, Australia, Brazil, Canada, New Zealand, Ireland and Thailand. The details of the publications selected are presented in Tables 1–5. The contents of the articles are presented under the headings relevant to the therapeutic agents.

Prophylactic Dose/Treatment-Dose Anticoagulation

Increased venous and arterial thromboembolic events have been reported previously. In a cohort study of 2773 patients, the association

of treatment dose anticoagulation (AC) and in-hospital survival was investigated. The mortality rate of the intervention group was significantly lower than the control group among patients who required MV (Table 1) ($p<0.001$).[25]

On the other hand, the results of an interim analysis released on January 28, 2021, based on three international randomised open-label trials on the use of anticoagulation from 17 countries revealed contrasting findings to this cohort study. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV-4a) conducted at 60 international sites), Randomised embedded multi-factorial adaptive platform trial at 290 international sites (REMAP-CAP) and Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC at 58 international sites) compared the effectiveness of therapeutic and prophylactic doses of anticoagulation in reducing the need for organ-support. The intervention was heparin treatment versus usual care pharmacologic venous thromboembolism (VTE) prophylaxis. The enrolment of severe state patients requiring intensive care unit (ICU)-level care were paused after an interim analysis demonstrated that therapeutic heparin did not improve organ-support free days at day 21. However, therapeutic dose anticoagulation treatment was superior to usual care pharmacologic VTE prophylaxis for moderate state patients (hospitalised, not on ICU organ support).[26]

Currently, the NIH COVID-19 Treatment Guidelines Panel recommends prophylactic dose anticoagulation for hospitalised patients.[27]

Chloroquine-Hydroxychloroquine

A study on the association of hydroxychloroquine use and intubation or death revealed no significant association between hydroxychloroquine use and intubation or death (Table 1).[28]

A randomised controlled trial (RCT) of 150 patients investigated virus elimination by high dose hydroxychloroquine, which showed no significant difference from the current standard care (Table 1).[29]

A systematic review by Hernandez et al.[30] disclosed further data on hydroxychloroquine or chloroquine use in COVID-19 (Table 1). Four randomised controlled trials and 10 cohort studies assessed its treatment effects. The evidence on the benefits and harms of hydroxychloroquine or chloroquine were depicted as very weak and conflicting.[30]

In a later update of the systematic review, five new randomised trials and 4 cohort studies revealed no new evidence regarding its therapeutic efficacy (Table 1).[31] In addition, there was now a low strength of evidence that hydroxychloroquine had positive effect on all-cause mortality and the need for MV.[31] In the RECOVERY trial, an RCT comparing a range of treatments with usual care in hospitalised patients, the primary outcome was 28-day mortality. The enrolment of patients in the hydroxychloroquine group was closed after an analysis determined a lack of efficacy (Table 1).[32] Furthermore, a randomised study from Brazil revealed increased lethality with higher doses of chloroquine (Table 1).[33] The large SOLIDARITY-WHO and ORCHID-NIH trials were prematurely discontinued, with press releases announcing a lack of efficacy.[31]

Convalescent Plasma

The efficacy and safety of convalescent plasma has been appraised as uncertain due to a lack of RCTs.[34]

The data from several small observational studies demonstrated improvements of symptoms (Table 2).[35-38] The strength of evidence is assessed as very low.

Convalescent plasma is under investigation in 11 studies registered in clinical trials (a total of 1106 patients). The ongoing trials are taking place in China, Italy, the USA, Columbia and Iran.[36]

Monoclonal antibodies-Bamlanivimab and Tocilizumab

Monoclonal antibodies are biotherapeutics for passive immunotherapy against viral infections similar to convalescent plasma. In animal models, there is evidence that antibody therapy may reduce viral load.[19,39-43]

Bamlanivimab

Bamlanivimab, one of the monoclonal antibodies, was studied in a phase II RCT for treating ambulatory mild or moderate COVID-19 patients. Patients were randomised for treatment by one of three doses, or a placebo. The 2800 mg dose resulted in a significant decrease of viral load in the intervention group.[41] In addition, bamlanivimab demonstrated a lower relative risk of hospitalisation (Table 2).[41]

The NIH Guidelines Panel announced in its February 11, 2021, update that bamlanivimab and the combination of casirivimab and imdevimab are available through the FDA's emergency use authorisations (EUAs) for the treatment of mild to moderate outpatients at high risk of progressing to severe disease and/or hospitalisation.[17,40]

Tocilizumab

Non-randomised studies have suggested mortality benefit with tocilizumab, a humanized monoclonal antibody in COVID-19 patients.[15]

In a randomised clinical trial studying the effect of early tocilizumab administration, hospitalised patients with severe COVID-19 requiring oxygen but not ICU-level care were investigated. The trial was stopped early after initial analyses showed no evidence of improvement in primary outcomes.[43]

In the STOP-COVID study of the USA, the treatment of critically ill patients with tocilizumab was investigated by time to death and 30-day mortality. Tocilizumab treated patients had a lower risk of death compared to the others (Table 2).[42] In contrast to the findings from STOP-COVID and multiple observational studies, none of the tocilizumab RCTs reported mortality benefit at 28 or 30 days, and only two of these trials reported outcomes meeting predefined thresholds for efficacy (Table 2).[23]

An update of NIH Panel on February 11, 2021 pointed out that there is insufficient evidence to recommend either for or against the use of tocilizumab or sarilumab for patients within 24 hours of ICU, requiring MV or NIV. For patients not requiring ICU-level care, the panel recommended against the use of these agents except in a clinical trial.17

Interferons

Interferons are cytokines with antiviral properties. Hence, they have been suggested as a potential treatment for COVID-19 due to their antiviral activity.[44] Interferon studies covered in this review include one cohort study, one RCT and the preliminary results of an ongoing RCT.

Table 1. Trials on therapeutic measures utilized in COVID-19: Insufficient or conflicting evidence, needing further investigations; or evidence for no therapeutic efficacy (anticoagulation, hydroxychloroquine or chloroquine)

Title of article and authors	Type of research	Participants/number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
Association of treatment dose anticoagulation with in-hospital survival among hospitalised patients with COVID-19. **Paranjpe I et al.** [25]	Cohort study	2773 hospitalised patients **786** patients received anticoagulation (AC) therapy **395** of patients requiring mechanical ventilation	New York (NY) city, USA	Treatment dose anticoagulation therapy (AC) (oral, sc, iv)	**1.Overall: In- hospital mortality** Treatment group: 22.5% (median survival 21 days) Control group: 22.8% (median survival 14 days) **2. Patients requiring mechanical ventilation (395 patients)** **In-hospital mortality:** Treatment group: **29.1%** (median survival 21 days) **Control group: 62.7**% (median survival of 9 days) Longer duration of AC treatment associated with a reduced risk of mortality Adjusted **HR: 0.86 per day** (95% **confidence interval** [CI] 0.82−0.89, p<0.001)
Observational study of hydroxychloroquine in hospitalised patients with COVID-19. **Geleris J et al.** [28]	Cohort study	1376 hospitalised COVID-19 patients	NY city, USA	HydroxychloroquineDay1:600 mg × 2 400 mg/day for a median of 5 days **End points:** Death or intubation Median follow -up 22.5 days	25.1% reached one endpoint: 180 intubated patients, of whom 66 died 166 deaths without intubation No significant association between treated and untreated groups **Hazard ratio: 1.04, 95% CI 0.82 − 1.32**
Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. **Tang W et al.** [29]	Randomised controlled trial (RCT) 11-29 Feb. 2020	150 mild to moderate patients in 16 governmen-tal COVID-19 treatment centers	China 3 provinces: Hubei, Henan and Anhui	Hydroxychloroquine 1200 mg/ day for 3 days 800 mg/day up to 2 weeks **Primary outcome**: Negative seroconversion in 28 days	**No significant difference from current standard of care** regarding virus elimination No deaths Adverse events more in trial group
Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19. A living systematic review. **Hernandez AV et al.**[30]	Systematic review Evidence through 1 July 2020	4 RCTs, 10 cohort studies, 9 case series assessed treatment effects, no study on prophylaxis	-	Hydroxychloro-quine or chloroquine **Outcomes:** All-cause mortality Severe disease Virologic clearance	Evidence conflicting and insufficient on: all-cause mortality, progression to severe disease, clinical symptoms and upper respiratory virologic clearance with antigen testing
Update Alert 2: Hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. **Hernandez AV et al.**[31]	Letter (Update of living systematic review) Evidence through 1 Aug. 2020	5 RCTs 4 Cohort studies Placebo or standard care controlled	-	Chloroquine Hydroxychloroquine **Outcomes:** All-cause mortality Need for mechanical ventilation Reductions in hospitalization	No new evidence regarding chloroquine therapy **Low strength of evidence** from RCTs and cohort studies that HCQ has **no positive effect on all-cause mortality** **and need for mechanical ventilation** No benefit or reductions in hospitalization **Low strength of evidence** for "no positive effect" on intubation or death and discharge from the hospital
Effect of hydroxychloroquine in hospitalised patients with COVID-19 **The RECOVERY Collaborative Group.**[32]	Randomised controlled, open-label platform trial	Hospitalised COVID-19 patients 1561 hydroxy chloroquine (HCQ) 3155 usual care		HCQ 800mg twice: Day 1 400mg-twice for 9 days **Primary outcome** Death within 28 days	**Death within 28 days:** No significant difference between trial and control groups 421 patients (27.0%) in the HCQ group 790 (25.0%) in the usual-care group **Rate ratio: 1.09;** 95% CI **0.97 to 1.23,** p=0.15 **Discharge from hospital alive** in 28 days: 59.6% for HCQvs. 62.9% for usual care; rate ratio, 0.90; 95% CI, 0.83 to 0.98 HCQ group had a **higher frequency of invasive mechanical ventilation or death:** 30.7% vs. 26.9%; risk ratio **1.14;** 95% CI, 1.03 to 1.27

Table 1. Continued

Title of article and authors	Type of research	Participants/number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
Effects of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalised with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: A randomised clinical trial. **Borba MGS et al.**[33]	Randomised double blind trial	440 adult hospitalised patients receiving cephtriaxone and oseltamivir: 81 were randomised as 40: 41 patients	Brazil	Chloroquine diphosphate 450mg versus 600mg **End points:** Primary: Lethality by day 13 Secondary: Lethality by day 28	Results: Low dose lethality 11/73 :**15.1%** **High dose** chloroquine diphosphate**:** Increased lethality for patients: **27.2%** **Lethality odds ratio: 3.6** (95% CI: **1.2 to10.6**)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Interferon Beta-1b

The first interferon RCT was a phase 2 clinical trial utilising interferon beta-1b for therapy (Table 3).[45] In the trial group, hospitalised patients were randomised into triple therapy (interferon beta-1b, lopinavir/ritonavir, and ribavirin) or double therapy (lopinavir/ritonavir and ribavirin). The control group received only lopinavir/ritonavir therapy. The median time to negative nasopharyngeal swab was 7 days in the total combination therapy group and 12 days in the control group (hazard ratio: 4.37, p=0.001). Further analyses revealed that the shortening of the time to viral clearance was due to the effect of the interferon beta1b group.[45]

Interferon Alfa-2b

A cohort study investigated the efficacy of nebulized interferon alfa 2b among 77 hospitalised patients. Three patient groups received either umifenovir, interferon alfa 2b or both agents. The end point was viral clearance. Interferon accelerated viral clearance by 7 days.[46] However, this study had limitations and a low strength of evidence (Table 3).

Interferon Beta-1a

The results of an RCT from the UK evaluating the effects of inhaled interferon beta-1a among hospitalised patients was reported on July 20, 2020 (Table 3).[47] Compared to the control group, the intervention group patients were more likely to recover by day 28 [odds ratio (OR): 3.86, p=0.017]. In addition, the intervention group had decreased odds of developing severe disease.[47]

The interferon studies covered in this review have several limitations including low patient size (total 305) and display a low strength of evidence.

Remdesivir

Remdesivir is an antiviral known to have inhibitory activity against SARS-CoV and MERS-CoV. *In vitro* studies revealed the efficacy of remdesivir in inhibiting SARS-CoV-2 as well.

The therapeutic effectiveness of remdesivir was investigated in a multicentre randomised, controlled trial covering 10 countries with 1063 hospitalised patients. The primary outcome was the time to recovery (Table 4).[48]

The final report was published in October, 2020.[48,49] Patients in the remdesivir group had a shorter time to recovery (median 10 days, compared with 15 days; rate ratio for recovery 1.29; p<0.001).[49] Those patients who received remdesivir were found more likely to have clinical improvement on day 15 (OR: 1.5) (Table 4).[49] The strength of evidence was appraised as high for this study.

A double-blind controlled trial of 237 patients from China found no significant differences in favour of the trial group (Table 4).[50]

In a multinational cohort study of 53 hospitalised severely ill patients, remdesivir therapy improved the oxygen support class in 68% of the patients and 47% were discharged. Of those receiving MV, 57% were extubated. The overall mortality rate and mortality among MV patients were lower than previously reported (Table 4).[51]

A multi-country RCT of 397 patients with severe disease but without the need for MV were randomised into therapy with remdesivir to receive either 5 or 10-day treatments. There was no significant difference between the two groups on day 14 regarding clinical improvement as assessed on an ordinal scale (Table 4).[52]

Remdesivir has been approved by the FDA for use among hospitalised COVID-19 patients and endorsed globally.[8]

The remdesivir studies in this review cover some earlier and later research. Three RCTs and one cohort study included 1749 hospitalised cases covering multiple countries. The results have consistently manifested the efficacy of remdesivir, as shown by the assessments of relevant studies with moderate to high strengths of evidence.

Table 2. Trials on therapeutic measures utilized in COVID-19: Insufficient evidence of therapeutic efficacy, needing further investigations: Convalescent plasma and monoclonal antibodies

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	Transfusion and Apheresis Science Published June, 2020	Treatment for emerging viruses: Convalescent plasma and COVID-19. **Brown BL et al.** [35]	Review Case series	9 patients in 3 case series	China	Convalescent plasma of 1 dose 200 mL with neutralizing antibody titers >1:640	Improved oxygenation Reduced inflammation and C- reactive protein Viral load undetectable in 7 of 9 patients **Limitation:** Study type No controls
2	HemaSphere Published June, 2020	The emerging role of convalescent plasma in the treatment of COVID-19. **Psaltopoulou T et al.** [36] **Ye M et al.** [37] **Shen C et al.** [38]	Narrative Review 6 case series April 2020	34 patients in 6 case studies	China	Convalescent plasma plus other therapies: Antiviral agents such as L/R, umifenovir (Arbidol) and levofloxacin, methyl prednisolone	Reported to suppress viremia and restore coagulation factors Improvement of radiologic findings reported [37] Viral load negative in 12 days, in 5 patients [38] Risks: Transfusion related acute lung injury, antibody dependent enhancement **Limitations:** No information on other outcomes No control groups
3	N Engl J Med **2020** Epub 28 October, 2020	SARS-CoV-2 Neutralizing antibody LY-CoV555 in outpatients with COVID-19. **Chen P et al.** [41]	RCT Phase 2	452 Mild or moderate non-hospitalised COVID-19 patients		Bamlanivimab In one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo **Primary outcome**: Change in viral load on day 11	2800 mg dose resulted in a **significant decrease of viral load** in the intervention group on day 11 (Interim analysis, Sep5, 2020) Bamlanivimab demonstrated a lower relative risk of hospitalisation: **RR: 0.26;** 95% CI: 0.09 to 0.75 **Hospitalization or visit to an emergency department**: **Intervention** group: **1.6%** Placebo group: **6.3%** **Limitation:** Phase 2 trial
4	JAMA Internal Medicine Published online Oct 20, 2020	Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. **Gupta et al. for the STOP-COVID investigators** [42]	Cohort study	Total 3924 patients 433 (11%) intervention group **-younger population**	USA 68 sites	Tocilizumab Given in 2 days of ICU admission **Outcome:** Death at day 27	39.3% of total patients died at 27 days Tocilizumab treated group had a lower risk of death: 27.5% versus 37.1% **Hazard ratio 0.71** (95% CI: 0.56 to 0.92) Risk difference: **9.6%** (95% CI, 3.1% to 16.0%) **Limitation:** Age bias between groups
5	JAMA Internal Medicine Published Oct. 20, 2020	Time to re-assess Tocilizumab's role in COVID-19 pneumonia. **Parr JB** [23]	Editorial Review- 1 Study retrospective cohort 4 Studies randomised controlled trials	Number of patients/sites 3924 68 126 24 450 67 131 9 389 69	**USA** **Italy** Multicountry **COVAC-TA** (Canada, Denmark , France, Germany, Italy, Netherlands, Spain, UK, US) **France** Multicountry **EMPACTA** Trial (Brazil, Kenya, Peru, US, Mexico, S. Africa)	**Tocilizumab** **Primary outcomes**: Mortality at day 28 or day 30 Survival without non-invasive ventilation (NIV) or mechanical ventilation (MV) by day 14 Death or mechanical ventilation at day 28	**1 Retrospective cohort- USA study** Threshold for efficacy of Tocilizumab met: **27.5% versus 37.1%**Risk difference **9.6**% (95% **CI: 3.1 to 16.0%**) **4 Randomised controlled trials** Threshold for efficacy of Tocilizumab for the first two primary outcomes not met in any of the 4 studies Threshold for efficacy of Tocilizumab for **survival without NIV or MV by day 14 met** for the France study : **HR 0.58 (95% CI 0.33 to 1.00)** Threshold for efficacy of Tocilizumab for **death or mechanical ventilation at day 28** met in EMPACTA Trial **HR 0.56 (95% CI 0.32–0.97)** Reduced need for mechanical ventilation **Mortality at day 28 or 30: No effect:** 10.4% vs 8.6%, ARD 2.0%, (95% CI, -5.2 to 7.8)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Favipiravir

In the light of *in vitro* studies, research in China, Japan, and Russia have introduced favipiravir as a promising agent with its advantage of being an oral formulation utilized on an outpatient basis.[53] Recently, treatment guidelines from multiple countries have included favipiravir in their treatment protocols.[53,54]

The studies on favipiravir treatment covered in this review include a controlled trial and a review of observational studies.

An early controlled trial published in March 2020 announced that favipiravir treatment resulted in a shorter viral clearance time compared to lopinavir/ritonavir treatment ($p<0.001$). Favipiravir treatment was associated with significant improvement rates in chest imaging (91.43% vs. 62.22%, $p=0.004$). (Table 4).[53] The study was non-randomised and open-label. The strength of evidence is accordingly evaluated as low.

A recent review of observational favipiravir interventions has highlighted its therapeutic effectiveness in terms of recovery rates and clinical improvements among mild to moderate patients. The findings demonstrated high recovery rates at days 7 and 14 for both mild and moderate cases in one study. Clinical improvement was reported for 66.7% overall in another study. The Japan observational registry revealed similar results for mild and moderate COVID-19 cases (Table 4).[54] However, although the number of patients is high, the quality of evidence is appraised as very low due to study type and the lack of control groups.

A pre-print publication regarding favipiravir efficacy should be mentioned, even though the study is not within the inclusion criteria of our review. In this prospective randomised controlled, open-label multicentre trial involving 240 patients with mostly moderate COVID-19 from China, the therapeutic effectiveness of favipiravir *versus* umifenovir was studied. The clinical recovery rate on day 7 was significantly higher ($p=0.019$) for the favipiravir group (71.4%) than the umifenovir group (55.8%). However, there was no difference between the groups regarding ICU admission and all-cause mortality.[55]

Favipiravir is widely used across many highly populated communities of middle income countries in Asia. However, more RCTs are mandatory for higher evidence-based results.

Corticosteroids

Corticosteroids were not advised for COVID-19 treatment unless needed for other conditions according to WHO, US CDC and IDSA early recommendations.[2,39]

The approach for treating patients with COVID-19 changed dramatically when the results of the UK-based RECOVERY trial were reported in June, 2020. This was an RCT of 6425 patients receiving dexamethasone or usual care. Treatment with dexamethasone reduced mortality by one-third in those patients receiving MV (rate ratio: 0.64) and by one-fifth in patients receiving oxygen (rate ratio: 0.82) compared with usual care. However, there was no benefit for those patients not receiving respiratory support (Table 5).[56]

The WHO REACT Working group studied the results of the current data on corticosteroid therapy on COVID-19 in a meta-analysis. A total of 1703 patients were randomised in seven trials for a prospective meta-analysis (Table 5).[57]

There were 222 deaths in the trial group and 425 deaths in the control group; 28-day all-cause mortality was lower among those patients receiving corticosteroids (OR=0.66, $p<0.001$). The association was similar for dexamethasone and hydrocortisone suggesting a general benefit for glucocorticoids.[57]

Following this, a systematic literature search and meta-analysis of RCTs and observational studies on adults was performed from December, 2019 to October, 2020 comprising a total of 20,197 patients in 37 retrospective observational studies and five RCTs. The findings confirmed the previous findings. The primary outcomes were short-term mortality (including 28-day, 30-day) and the secondary outcomes were MV, length of hospital stay, and secondary infections. The findings have confirmed a beneficial effect of corticosteroids on short-term mortality and a reduction in the need for MV. The overall risk estimate was 0.72, suggesting a beneficial effect of steroid use on the mortality of patients hospitalised with moderate or severe respiratory failure. Fewer patients required MV in the corticosteroids group [relative risk (RR): 0.71] (Table 5).[58]

The relevant research indicated in this review highlighted the efficacy of corticosteroids in reducing mortality among critically ill patients requiring oxygen. The trials on this topic cover more than 28 thousand (28,325) patients and the results indicate high evidence. Corticosteroids are the only therapeutics which are currently shown to be effective in reducing mortality in COVID-19.

The details of the presented articles of this review are illustrated in tables: Table 1,[25,28-33] Table 2,[23,35-38,41-42] Table 3,[45-47,59] Table 4,[48-54] and Table 5.[56-58]

Discussion

New findings from recent research draw attention to the urgent need for new approaches and agents for managing COVID-19, including in mild and moderate cases. A prospective cohort study with patients recovering from COVID-19 displayed evidence of ventricular dysfunction and signs of myocardial inflammation in 78% of the patients.[60,61] In addition, post-mortem research has shown inflammation is ongoing in the heart muscle weeks after recovery. These findings may be precursors of a considerable burden of heart failure in the coming years.[62]

In this review, we aimed to contribute to the collection and dissemination of the new evidence for COVID-19 therapy regarding all forms of the disease. We shall discuss our findings together with expert opinions and global statements about this issue.

A considerable number of studies on the therapeutic efficacy of various treatments for COVID-19 have weaknesses regarding the study sample and research methods utilized. Currently, evidence comes mostly from those studies conducted among hospitalised patients, while more research is essential for the therapy of mild and moderate forms.[8,53]

The results of studies in this review show evidence for the efficacy of the antiviral remdesivir and also corticosteroids. The efficacy of therapeutic dose anticoagulation has been demonstrated among

Table 3. Trials on therapeutic measures utilized in COVID-19: Insufficient or conflicting evidence, needing further investigations; or evidence for no therapeutic efficacy: Interferons and antivirals

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	The Lancet Published online May 8, 2020	Triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin in the treatment of patients hospitalised with COVID-19: An open-label, randomised, phase 2 trial. **Hung IFN et al.**[45]	Randomised controlled trial (RCT) Phase 2 trial	127 patients: **Trial group** 86: Disease onset <7 days **52** patients Disease onset ≥7days **34** patients **Control group** **41** patients	Hong Kong 6 hospitals	**Combination therapy** Trial group -Lopinavir-ritonavir -**ribavirin** -**interferon beta-1b** 8 million units every other day up to 7 days (1-3 times) **Control group** Lopinavir-ritonavir **Outcome: Median time to negative nasopharyngeal and all specimen swab**	**Time (days) to negative nasopharyngeal swab**: Combination therapy group (All trial group) vs. all control group: Significantly shorter median time from therapy to negative swab: **7 days (5−11days) vs 12 days (8−15 days) p=0.0010** **Hazard ratio: 4.37**(95% CI: 1.86−10.24) **Interferon group** (52) patients vs. control: 6.5 (4.0−8.0) vs 12.5 (8.0−14.8), **p<0.0001** Ribavirin group (34 patients) vs. control: 10.5 (8.0-12.3) vs. 12.0 (8.0-17.0), p=0.10 **Conclusion:** Early triple therapy was safe and superior to control in shortening virus shedding, relieving symptoms and facilitating discharge of patients **Limitations:** Open-label study, low number of patients, phase 2 study
2	Frontiers in Immunology Published May 16, 2020	Interferon alfa-2b treatment for COVID-19. **Zhou Q et al.**[46]	Cohort study Jan16 – Feb 20, 2020	77 COVID-19 patients	Wuhan China	3 groups: 1.Umifenovir 200mg 2.Interferon α2b 5mU 3.Interferon α2b + Umifenovir **End point**: Mean days to viral clearance	**End point:** Mean days to viral clearance Umifenovir : 27.9 days, Interferon α2b: 21.1 days, Interferon α2b + Umifenovir : **20.3 days** **p= 0.002** Interferon accelerated viral clearance by **7 days** and reduced elevated blood levels for inflammatory markers IL-6 and CRP **Limitations**: Age and comorbidity differences between the intervention and control groups, low patient size
3	Press release July 20, 2020	Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients **Synairgen**[47]	Double blind placebo- controlled trial March 30- May 27, 2020	101 non-ventilated patients	UK 9 hospitals	Interferon beta 1a (inhaled) -14 days **End point**: Recovery at day 28 Odds of developing severe disease	**Recovery at day 28 : OR= 3.86** (95% CI: 1.27−11.75) , p=0.017 Decreased odds of developing severe disease: **OR=0.21** (95% CI: 0.04−0.97) p=0.046 **Limitations:** Pre-publication, low patient size, conflict of interest
4	The New England Journal of Medicine Published Mar. 18, 2020	A trial of lopinavir-ritonavir in adults hospitalised with severe COVID-19. **Cao Bet al.**[59]	RCT Jan 18-Feb 3, 2020	199 hospitalised patients:	Wuhan, China	Lopinavir-ritonavir versus standard care	No benefit beyond standard care

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Table 4. Trials on therapeutic measures utilized in COVID-19 with promising evidence of efficacy: Antivirals

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
1	The New England Journal of Medicine Published May 22, 2020	Remdesivir for the treatment of COVID-19 - Preliminary Report **Beigel JH et al.**[48]	RCT Feb 21-April 19, 2020 Double blind, placebo- controlled trial	1063 hospitalised COVID-19 patients	Trial sites/ patients USA 45 Denmark 8 UK 5 Greece 4 Germany 3 Korea 2 Mexico 2 Spain 2 Japan 1 Singapore 1	Remdesivir 200 mg iv-day 1 100 mg-days 2-10 **Primary outcome**: Time to recovery (discharge from hospital) **Key secondary outcome**: Clinical status at day 15, as assessed on an eight-category ordinal scale	Time to recovery shortened by remdesivir **Median recovery time:** **Remdesivir 11 days** (95% CI: 9–12) **Placebo 15 days** (95% CI: 13–19) (Rate ratio for recovery, 1.32, 95% CI: 1.12 to 1.55) **p <0.001**
2	The New England Journal of Medicine Published Oct. 8, 2020	Remdesivir for the treatment of COVID-19 — Final Report **Beigel JH et al.**[49]	RCT Feb 21-Apr 19, 2020 Double blind, placebo- controlled trial	1062 COVID-19 patients in 60 sites & 13 subsites in USA	Trial sites /patients USA 45 Denmark 8 UK 5 Greece 4 Germany3 Korea 2 Mexico 2 Spain 2 Japan 1 Singapore 1	Remdesivir 200 mg iv-day 1 100 mg-days 2-10 Total 1062 patients Remdesivir-541 Placebo- 521 **Primary outcome**: Time to recovery **Secondary outcome**: Clinical status at day 15 as assessed on an eight-category ordinal scale	Patients completing the study: Trial group 391 Control group 340 Time to recovery shortened by remdesivir: **Median recovery time** **Remdesivir group 10 days (95% CI: 9–11)** **Placebo group 15 days (95% CI: 13–18)** **Rate ratio for recovery: 1.29**(95% CI: **1.12–1.49), p<0.001** **Clinical improvement on day 15 better in therapy group:** **OR 1.5, 95% CI: 1.2 to 1.9** The Kaplan–Meier **estimates of mortality: By day 15**: Remdesivir group 6.7% placebo group 11.9% (hazard ratio, 0.55; 95% CI: 0.36 to 0.83) **By day 29**: Remdesivir group 11.4%, placebo group15.2% (hazard ratio, 0.73; 95% CI: 0.52 to 1.03)
3	The Lancet Published online April 29, 2020	Remdesivir in adults with severe COVID-19. **Wang Y et al.**[50]	RCT Double blind, placebo controlled Feb 6- March 12, 2020	237 severe hospitalized patients (2:1 ratio) 158 intervention, 79 controls	Hubei China Multicenter- 10 hospitals	200 mg day1 100 mg days 2-10, infusion Concomitant use of lopinavir-ritonavir, interferon, cortico-steroid in all patients **Primary end point:** Clinical improvement in 28 days based on 6-point ordinal scale or discharge from hospital	Faster time to clinical improvement, although not significant: **Hazard ratio: 1.52** (95% **CI: 0.95 to 2.43**) **Limitations:** Concomitant use of multiple other drugs, small patient size
4	The New England Journal of Medicine Published April 10, 2020	Compassionate use of remdesivir for patients with severe COVID-19. **Grein J et al.**[51]	Cohort study Jan 25-March 30, 2020	61 hospitalised patients with severe COVID-19 (defined as oxygen saturation of ≤94% or need of oxygen support)	22 patients from USA, 21 from European countries 1 Canada 9 Japan **Total 53 patients evaluated**	Remdesivir iv 200 mg on day 1-100 mg for 9 days **Outcome:** Improvement in oxygen support class Median follow up: 18 days	36 patients **(68%)** had **improvement in oxygen support class** **Worsening in 15%** 17 of 30 (**57%**) receiving mechanical ventilation were extubated 25 patients (47%) discharged Overall mortality **13%** (7 patients) **Mortality 18%** (6/34) among patients under invasive ventilation **Limitation:** No control group, low patient size

Table 4. Continued

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention-Treatment and primary end point	Outcome/Results
5	The New England Journal of Medicine Published May 27, 2020	Remdesivir for 5 or 10 days in patients with severe COVID-19. **Goldman JD et al.**[52]	RCT March 2020 Phase 3 trial	397 hospitalised COVID-19 patients	Trial sites: USA Italy S.Korea Singapore Spain Germany Hong Kong Taiwan	Remdesivir 200 mg on day 1 and 100 mg subsequently **End point:** Clinical status on day 14 assessed on an ordinal scale	Patients not needing mechanical ventilation received remdesivir for 5 or 10 days No significant difference between 5 and 10- day therapies regarding clinical improvement based on clinical status on day14 **Limitation:** No placebo group
6	Engineering Published March18, 2020	Experimental treatment with favipiravir for COVID-19: An open-label control study. **Cai Q et al.**[53]	Controlled trial Jan 30-Feb14, 2020	Treatment group: 35 patients received Favipiravir and interferon alfa Control group: 45 patients received Lopinavir/ Ritonavir (LPV/ RTV) and interferon alfa	Shenzhen, China People's hospital	**Favipiravir** 1600 mg x 2 on day 1 600 mg x 2 on 2-14 days **LPV/RTV** 400/100 mg x 2 on 1-14 days **End points:** Viral clearance time Chest CT improvement	Favipiravir group had **shorter viral clearance time:** Median (interquartile range, IQR: 4 (2.5–9) days vs. 11 (8–13) days **p< 0.001** Significant improvement rate in chest imaging (CT) (**91.43% vs. 62.22%) p=0.004** Higher improvement rates of chest CT for viral clearance within 7 days of treatment Multivariable Cox regression: Favipiravir treatment was significantly associated with faster viral clearance (**p=0.026**) **Limitations:** Non-randomised and open -label trial Low patient number
7	International Journal of Infectious Diseases Published Oct. 29, 2020	Role of favipiravir in COVID-19. **Joshi S et al.**[54]	Review of favipiravir interventions **Limitations:** Observa-tional studies, No control groups	Mild to moderate COVID-19 patients	China Thailand Japan	Favipiravir 1800×2 on day 1 800×2 up to 14 days **Outcome:** Clinical recovery or improvement	**1.Clinical recovery rates** (Doi Y et al) **Outcome at day 7** Mild patients:73.8%, Moderate patients: 66.6% **Outcome at day 14** Mild:87.8%, Moderate:84.5% **2.Clinical improvement rates** (Rattanaumpawan et al) Overall:66.7% , patients not needing oxygen supply: 92.5% **3.Clinical improvement rates** (Japan observational registry-2158 cases) Mild:73.8%, moderate:66.6%,severe 40.1%

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

Table 5. Trials on therapeutic measures utilized in COVID-19 with evidence for efficacy on mortality of severely ill patients: Corticosteroids

No	Journal name and date	Title of article and authors	Type of research	Participants/ number of studies	Country - region	Intervention- Treatment and primary end point	Outcome/Results
1	RECOVERY Trial Press release June 16, 2020 JAMA Oct 6, 2020	Corticosteroids in COVID-19 ARDS. Evidence and hope during the pandemic. Editorial. **Prescott HC et al.**[56]	Open – label randomised controlled trial **Limitation:** Open-label study	6425 patients Trial 2104 patients: Dexametha-sone Control 4321 patients: Usual care	United Kingdom	Dexamethasone 6 mg /day for 10 days **Primary outcome:** Mortality in trial and control groups	**Mortality rates** Mechanical ventilation patients: **Trial Control** 29.3% 41.4 % **Rate ratio 0.64** (95%CI 0.51 to 0.81) Patients needing oxygen supply: **Trial Control** 23.3% 26.2% **Rate ratio 0.82** (95% CI 0.72 to 0.94) No benefit observed for patients not receiving oxygen support (rate ratio 1.19, 95% CI 0.91 to 1.55)
2	The Journal of the American Medical Association (JAMA) Published online Sep 2, 2020	Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19-A meta-analysis. **The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group**[57]	Prospective meta-analysis Feb 26-June 9, 2020 Final follow-up July 6, 2020	7 trials: RECOVERY, REMAP-CAP, CoDEX, CAPE COVID +3other 1703 patients randomised Corticosteroid **678** patients Usual care or placebo: **1025** patients	Australia Brazil Canada China Denmark France Ireland Netherlands New Zealand Spain UK USA	**Corticosteroid groups included dexamethasone at low and high doses:** low-dose hydrocortisone, and high-dose methyl-prednisolone compared with others who received usual care or placebo Critically ill patients End point: Mortality at 28 days	**Total 647 patients died** **222** deaths among 678 patients randomised to corticosteroids **425 deaths** among 1025 patients randomised to usual care or placebo **28-day all-cause mortality** was lower among patients who received corticosteroids compared with those who received usual care or placebo **Summary odds ratio= 0.66** (95% CI 0.53-0.82) **p<0.001** Based on a fixed-effect meta-analysis, patients receiving systemic corticosteroids were **34% less likely to die over 28 days**
3	Critical Care (Crit Care) December 2020	Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. **Van Paassen J et al.**[58]	A systematic literature review and meta-analysis of RCTS and observational studies December 2019 to October 2020	Effect of corticosteroids Total **20197** patients in **44 studies:** 37 retrospective observational studies 5 RCTs **Hospitalised** (28 studies) **or ICU admitted** patients (15 studies)	31 studies conducted in China, 11 in Europe, 5 in North America, 2 in South America and 1 multi-continent	**Corticosteroids** **Primary outcome:** Short-term mortality (including 28-day, 30-day) **Secondary outcomes:** Need of mechanical ventilation, Length of hospital stay, Secondary infection	**Outcomes:** Confirmation of a beneficial effect of corticosteroids **on short-term mortality** and a reduction in need for mechanical ventilation **Overall risk estimate (OR): 0.72** (95%CI 0.57–0.87), suggesting a beneficial effect on mortality in patients hospitalized with moderate or severe respiratory failure Fewer patients required mechanical ventilation in the corticosteroids group **RR= 0.71** (95% CI 0.54–0.97)

AC: anticoagulation, AOR: adjusted odds ratio, ARDS: acute respiratory distress syndrome, CI: confidence Interval, COVID-19: coronavirus disease-2019
EUA: emergency use authorization, DA: Food and Drug Administration, HCQ: hydroxychloroquine, HR: hazard ratio, IDSA: Infectious Diseases Society of America, NIH: National Institutes of Health, NIV: non-invasive ventilation, MV: mechanical ventilation, OR: odds ratio, RCT: randomised controlled trial, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, VTE: venous thromboembolism.

moderately ill, but not severely ill, patients in preliminary research.[26] However, these studies have yet to be finalised before general consideration for use in this group. Weak therapeutic evidence exists for favipiravir, interferons alfa-2b, beta-1b and beta-1a; convalescent plasma and monoclonal antibodies, this needs further research.[41,45-47] Bamlanimivab deserves special mention with emerging data of promising efficacy. Bamlanivimab and the combination of casirivimab and imdevimab are currently recommended for mild to moderate COVID-19 at high risk or progressing to severe disease and/or hospitalisation.[17]

Dexamethasone and other corticosteroids comprised the only drug group demonstrating reductions in mortality among hospitalised patients requiring MV or high-flow oxygen. Dexamethasone was also effective in decreasing the number of people requiring oxygen.[56-58] Accordingly, the NIH Treatment Guidelines Panel recommends the use of corticosteroids for patients in need of oxygen supplementation.[22]

Remdesivir exhibited high evidence of efficacy for the therapy of COVID-19.[48-52] Even though the NIH Panel does not recommend for or against the use of remdesivir in hospitalised patients not requiring oxygen, remdesivir remains the only drug approved by the FDA for use among hospitalised patients.[22] The use of remdesivir for mild to moderate COVID-19 cases is a subject of medical research currently and remains a challenge for the medical community with the disadvantage of its route of administration. Favipiravir was found to be effective for the treatment of mild to moderate COVID-19 cases in observational studies and one controlled trial covered in this study.

Remdesivir and favipiravir have been currently included in multiple COVID-19 treatment guidelines globally.[8] Japan, Russia, Saudi Arabia, Thailand, Kenya and four states from India have recommended the use of favipiravir oral therapy in mild to moderate COVID-19 in their treatment guidelines.[53,54] Around 27 favipiravir studies including RCTs are ongoing in China, Japan, Italy, the USA, the UK, Canada, Egypt, Thailand, France and Iran.[60] The results of these studies will highlight the efficacy of this antiviral with more evidence, which is convenient for use on an outpatient basis.

Antiviral medications other than remdesivir were not seen to have sufficient evidence for COVID-19 therapy. The Solidarity trial in 30 countries, sponsored by the WHO, assessed hydroxychloroquine, interferon, lopinavir/ritonavir, and remdesivir in hospitalised patients. None of these drugs, nor tocilizumab, showed an effect on mortality.[23,39,63]

No evidence for the use of chloroquine and hydroxychloroquine has been identified among the current research available. Conversely, weak evidence has been announced by some studies against the use of these agents.[31]

CONCLUSION

The data based on sound research on all aspects of COVID-19 is mounting rapidly. The findings of the latest research on COVID-19 therapy point to the necessity of considering the results of ongoing larger trials and providing instant knowledge to health professionals. Progress in this area is vital since it may be influential in preventing later consequences, sequellae and deaths from COVID-19 among the growing patient population.

The findings demonstrated in this review may be of assistance for medical practitioners in order to highlight the therapeutics with the best current evidence to assist in their decisions on treatment approaches for COVID-19.

MAIN POINTS

- While there is currently no globally approved treatment for COVID-19, multiple agents are under trial for the treatment COVID-19; yet a discrepancy exists between high income and other countries of the world regarding the drugs preferred.
- This study presents an overview of the mostly evidence-based global research on this issue, with randomised controlled trials, systematic reviews and meta-analyses comprising 15 out of the total 25 studies included.
- The results show sufficient evidence for the efficacy of remdesivir and corticosteroids based on international research, with reduced mortality demonstrated only for corticosteroids.
- Favipiravir, anticoagulation, interferons and monoclonal antibodies were agents with promising but weaker evidence of therapeutic efficacy and so need further investigations.
- The inclusion of favipiravir studies may be a reminder to global researchers to review the evidence about this agent as well, since it has been prescribed widely in a number of countries worldwide.

ETHICS

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.A., Ş.Ç., Design: Ö.A., Ş.Ç., Data Collection and/or Processing: Ö.A., Ş.Ç., Analysis and/or Interpretation: Ö.A., Ş.Ç., Literature Search: Ö.A., Ş.Ç., Writing: Ö.A., Critical Review: Ş.Ç.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study had received no financial support.

REFERENCES

1. World Health Organisation. Emergencies preparedness, response. Pneumonia of unknown cause – China. Available from: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/ (Accessed on May, 5 2020).
2. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infect Prev Pract. 2020; 2(3): 100061.
3. World Health Organisation. Available from: www.who.int.
4. CDC COVID-19 Response Team. Characteristics of Health Care Personnel with

COVID-19 - United States, February 12-April 9, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(15): 477-81.

5. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health. 2020; 13(5): 667-73.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan,China. JAMA. 2020; 323(11): 1061-9. Erratum in: JAMA. 2021; 325(11): 1113.
7. Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. JAMA Netw Open. 2020; 3(6): e2012270.
8. Kim PS, Read SW, Fauci AS. Therapy for early COVID-19: A critical need. JAMA. 2020; 324(21): 2149-50.
9. Tahiri Joutei Hassani R, Bennis A.. Hdroxychloroquine as antiviral prophylaxis for exposed caregivers to COVID-19: An urgent appraisal is needed. J Infect Public Health. 2020; 13(6): 865-7.
10. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, et al. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res. 2020; 151(5): 459-67.
11. Gupta N, Agrawal S, Ish P. Chloroquine in COVID-19: the evidence. Monaldi Arch Chest Dis. 2020; 90(1).
12. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in COVID-19. BMJ. 2020; 369: m1432.
13. McEniery CM, Fisk M, Miles K, Kaloyirou F, Hubsch A, Smith J, et al. ChemoPROphyLaxIs with hydroxychloroquine For covId-19 infeCtious disease (PROLIFIC) to prevent COVID-19 infection in frontline healthcare workers: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1):604. Erratum in: Trials. 2020; 21(1): 641.
14. World Health Organisation. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. (2020). Retrieved from: https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19 (Accessed on 20 Aug 2020).
15. Berardicurti O, Ruscitti P, Ursini F, D'Andrea S, Ciaffi J, Meliconi R, et al. Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis. Clin Exp Rheumatol. 2020; 38(6): 1247-54.
16. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob. 2020; 19(1): 23.
17. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. What's New. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/whats-new/ Last Updated: February 11, 2021. (Accessed on 18 Feb 2021).
18. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020; 250: 117583.
19. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID- 19). Asian Pac J Allergy Immunol. 2020; 38(1): 10-8.
20. García IG, Rodriguez-Rubio M, Mariblanca AR, de Soto LM, García LD, Villatoro JM, et al. A randomised multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts (MeCOVID Trial): A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1): 466.
21. The COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated: November 3, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/
22. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Last updated: November 3, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/ (Accessed on 1 December 2020).
23. Parr JB. Time to reassess Tocilizumab's role in COVID-19 pneumonia. JAMA Intern Med. 2021; 181(1): 12-5.
24. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6(1): 245.
25. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020; 76(1): 122-4.
26. ATTACC, ACTIV-4a & REMAP-CAP Multiplatform RCT. Results of interim analysis. Release date: Jan 28 2021. Retrieved from: https://nhlbi-connects.org/documents/mpRCT%20Interim%20Presentation.pdf (Accessed on Feb 26, 2021).
27. 27. NIH COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last Updated: February 11, 2021. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/ Accessed 26 Feb 2021. (Accessed on 26 Feb 2021).
28. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020; 382(25): 2411-8.
29. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369: m1849.
30. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: A living systematic review. Ann Intern Med. 2020; 173(4): 287-96.
31. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Update Alert 2: Hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19. Ann Intern Med. 2020; 173(7): W128-9.
32. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in hospitalised patients with COVID-19. N Engl J Med. 2020; 383(21): 2030-40.
33. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al.

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020; 3(4): e208857.

34. Frellick M. NIH Panel counters FDA: No solid data on plasma for COVID-19. Retrieved from: https://www.medscape.com/viewarticle/935058#vp_3 September 02, 2020. (Accessed on 10 Oct 2020).

35. Brown BL, McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus Apher Sci. 2020; 59(3): 102790.

36. Psaltopoulou T, Sergentanis TN, Pappa V, Politou M, Terpos E, Tsiodras S, et al. The emerging role of convalescent plasma in the treatment of COVID-19. HemaSphere. 2020; 4(3): e409.

37. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020; 92(10): 1890-901.

38. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et.al. Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323(16): 1582-9.

39. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. IDSA. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (Accessed on Nov 27, 2020).

40. U.S. Food and Drug Administration. Letter of FDA Emergency Use Authorization to Eli Lilly and Company dated November 10, 2020. In: Phillips C, Eli Lilly and Company, 2020. Available at: https://www.fda.gov/media/143602/download (Accessed on 2 December 2020).

41. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med. 2021; 384(3): 229-37.

42. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association between early treatment with tocilizumab and mortality among critically Ill patients with COVID-19. JAMA Intern Med. 2021; 181(1): 41-51.

43. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Intern Med. 2021; 181(1): 24-31.

44. Interferons (Alfa, Beta). Last Updated: August 27, 2020. Retrieved from: https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/interferons/#:~:text=Interferons%20are%20a%20family%20of,and%20in%20vivo%20antiviral%20properties. (Accessed on Nov 18, 2020).

45. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020; 395(10238): 1695-704.

46. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, et al. Interferon-α2b treatment for COVID-19. Front Immunol. 2020; 11: 1061. Erratum in: Front Immunol. 2020; 11: 615275.

47. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients. Available from: https://www.synairgen.com/wp-content/uploads/2020/07/200720-Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.pd. (Accessed on November 20, 2020).

48. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of COVID-19 - Preliminary Report. Reply. N Engl J Med. 2020; 383(10): 994.

49. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of COVID-19 - Final Report. N Engl J Med. 2020; 383(19): 1813-26.

50. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10236): 1569-78. Erratum in: Lancet. 2020; 395(10238): 1694.

51. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med. 2020; 382(24): 2327-36.

52. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in patients with severe COVID-19. N Engl J Med. 2020; 383(19): 1827-37.

53. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: An Open-label control study. Engineering (Beijing). 2020; 6(10): 1192-8.

54. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021; 102: 501-8.

55. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. [Preprint] medRxiv. 2020.

56. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and hope during the pandemic. JAMA. 2020; 324(13): 1292-5.

57. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: A meta-analysis. JAMA. 2020; 324(13): 1330-41.

58. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020; 24(1): 696.

59. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020; 382(19): 1787-99.

60. Stiles S. COVID-19: Are there far-reaching cardiac complications? Available from: https://www.medscape.org/viewarticle/938664?nlid=138212_2681&src=wnl_cmemp_201120_mscpedu_fmed&uac=66188AY&impID=2688515&faf=1 (Accessed on Nov 20, 2020).

61. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265-73.

62. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. 2020; 5(11): 1281-5.

63. Mc Namara D. IDSA Updates COVID Guidelines for Antibodies, Antivirals, Other Drugs. Nov 23, 2020. Retrieved from: https://www.medscape.com/viewarticle/941479?nlid=138431_2049&src=WNL_mdplsnews_201_mscpedit_imed&uac=66188AY&spon=18&impID=2702740&faf=1 (Accessed on Nov 28, 2020).