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REVIEW ARTICLE

Utilization of Therapeutic Interventions for Coronavirus Disease-2019 (COVID-19) Hospitalized Patients and Emerging Treatment Possibilities from Clinical Trials: A Systematic Review and Meta-Analysis

Preeti Malik*, Azka Zergham*, Lakshmi Saravanan, Neel Patel, Yasmeen Kerakhan, Shamima Somi, Sanchitha Nagaraj Honganur, Aelia Akbar, Pragya Jaiswal, Aran Deol, Benedict Francis, Deep Mehta, Richa Jaiswal, Janice Gabrilove, and Urvish Patel

***Equally contributing first authors**

Author Affiliations:
Preeti Malik, MD, MPH, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Azka Zergham, MBBS, Department of Internal Medicine, Larkin Community Hospital, FL, USA.
Lakshmi Saravanan, MD(c), Department of Internal Medicine, American University of Antigua, Jabberwock Rd, Osbourn, Antigua & Barbuda.
Neel Patel, MBBS, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Yasameen Kerakhan, MBBS, Department of Internal Medicine, Abrazo Central Campus, Phoenix, AZ, USA.
Shamima Somi, MD, Department of Internal Medicine, Grand Rehabilitation and Nursing Home, Great Neck, NY, USA.
Nagaraj Sanchitha Honganur, MBBS, Department of Internal Medicine and Cardiology, University of Illinois, Chicago, USA.
Aelia Akbar, MD, MPH, Department of Internal Medicine, Loyola University, Chicago, IL, USA.
Pragya Jaiswal, MD, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA.
Aran Deol, MD, Department of Internal Medicine, Swedish Covenant Hospital, Chicago, IL, USA.
Benedict Francis, MD, Department of Internal Medicine, Jackson Park Hospital, Chicago, IL, USA.
Deep Mehta, MD, MSCR, Department of Clinical Research, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Richa Jaiswal, MD, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA.
Janice L. Gabrilove, MD, FACP, Department of Internal Medicine and Oncological Sciences, Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, NY, USA,
Urvish Patel, MD, MPH, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Corresponding author:
Preeti Malik, MD, MPH
Department of Public Health, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl, New York, NY 10029, USA.
Email: pmalik.ma@gmail.com
ORCID: 0000-0002-9427-0225

ABSTRACT

Background and Objective: Few small observational studies have described various therapeutic interventions utilized in coronavirus disease 2019 (COVID-19) patients based on single/multi-center experiences across the globe. Understanding the utilization of available and possible treatments to curb the COVID-19 pandemic is paramount. We aimed to identify the prevalence and disease-associated utilization of specific therapeutic reagents in hospitalized COVID-19 patients as a function of severity status.

Methods: In systematic review and meta-analysis, extracted data on treatments utilized and severity of COVID-19 hospitalized patients from observational studies using PRISMA guidelines from December 1, 2019 to August 20, 2020. The pooled prevalence and odds of treatment utilization were obtained, and created forest plots using random-effects models.

Results: 29 studies with 8570 COVID-19-positive patients were included. Higher odds of the utilization of steroids (pooled OR:4.47; 95%CI:3.18–6.28; p<0.00001), antibiotics (3.1;1.81–5.30; p<0.0001), and IV Immunoglobulin (IVIG) (3.76;2.11–6.72; p<0.00001) was observed in patients with severe disease. No association of remdesivir (initially administered via clinical trials and subsequently FDA-approved during this study period), lopinavir/ritonavir, or hydroxychloroquine (HCQ) treatment with the severity of disease was observed.

Conclusion: Higher utilization of steroids, lopinavir/ritonavir, antibiotics, hydroxychloroquine (HCQ), and IV Immunoglobulin (IVIG) was observed in severe COVID-19 patients. Due to limited studies on remdesivir, its accurate utilization could not be delineated. Currently, no Level A evidence favoring single-drug treatment for COVID-19 exists, and trials are needed of combination therapy to evaluate efficacy on the survival outcome.

Keywords: COVID-19, 2019-nCoV, Corticosteroids, Lopinavir/ Ritonavir, Hydroxychloroquine, Immunoglobulins, Remdesivir, and SARS-CoV-2, mortality, invasive mechanical ventilation

INTRODUCTION

The 21st century has experienced the emergence of three epidemics: severe acute respiratory syndrome coronavirus (SARS-CoV) (2003), Middle East respiratory syndrome coronavirus (MERS-CoV) (2012), and in late 2019 severe acute respiratory syndrome coronavirus (SARS-CoV-2). These viruses belong to the coronaviridae family with a positive single-stranded RNA genome [1]. After emerging in China, the Coronavirus disease 2019 (COVID-19) has spread throughout the world. It was declared a global pandemic by World Health Organization (WHO) on 11 March, 2020. As of December 29, 2020, a total of 81.9 million COVID-19 cases were reported, with 1.7 million deaths [2].

The continuing spread of COVID-19 remains a public health emergency of international concern. Although measures to fight this global pandemic are underway, there is no drug with proven efficacy to cure the disease. Many antiviral reagents, which were previously developed as treatments for outbreaks of similar viral infections such as Severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), an Acquired immunodeficiency syndrome (AIDS), and malaria, are being used to treat COVID-19 [1]. Several studies report usage of individual drugs in COVID-19 affected patients. The incident use of corticosteroids ranges from 18.4 to 86.8%, antivirals not limited to remdesivir/lopinavir-ritonavir ranges from 35-99%, antibiotics from 58-100%, IVIG from 13.1 to 38.5% [3-7]. Hydroxychloroquine was reportedly used in 73.6-85.6% of patients in some studies [4, 8, 9]. However, for all potentially fatal viral infections, including COVID-19, single therapies do not demonstrate efficacy alone in trials, and we can expect that drugs used in combination would offer the only hope of demonstrating efficacy for the outcome of mortality.

We attempted to describe and delineate current therapeutic approaches employed and the clinical context in which they are utilized to treat COVID-19, including antivirals, anti-inflammatory medications, antimalarial drugs, and antibiotics. The current literature, in particular, does not provide an in-depth systematic report on the utilization of all therapeutic interventions, both clinically available and those under investigation, employed in COVID-19 hospitalized patients. In the absence of established prescribed guidelines, such a resource could serve as a reference and framework for the healthcare community at large. For clinically available reagents, we conducted a meta-analysis to evaluate their utilization in the treatment of COVID-19 and the severity of the disease in which they were utilized. For reagents under active investigation, we conducted a comprehensive review of clinical trials underway to evaluate the safety and efficacy of novel treatment interventions for COVID-19.

METHODS

Primary Aim

The aim was to evaluate the severity-based prevalence and odds of specific therapeutic reagent utilization in hospitalized COVID-19 patients. COVID-19 was confirmed in individual studies by reverse transcription PCR, antibody testing, and symptoms.

We defined the severity of the disease as invasive mechanical ventilation (IMV) utilization, oxygen saturation<90%, intensive care unit (ICU) admission, and in-hospital mortality.

Search strategy and selection criteria

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10] and MOOSE checklist [11] from December 1, 2019 to August 20, 2020. The search engine used were PubMed, Web of Science, Scopus, and medRxiv for observational studies that described the treatment and severity of COVID-19 patients following keyword/MESH terms: (COVID-19) OR coronavirus OR SARS-CoV-2 OR 2019-nCoV. We included studies which have reported on both treatment and severity of COVID-19 hospitalized patients. Studies only reporting treatment utilization for individual patients employing descriptive statistics were specifically not included. Case reports, case series, and non-English literature were excluded. Figure 1 describes the literature search and study selection process.

Figure 1: Flow diagram of literature search and study selection process of COVID-19 disease severity and treatment Utilization.

Study selection and Data Collection

Articles were initially screened by titles and abstracts to assess for relevance, and those articles with information on the treatment and severity of COVID-19 patients were retrieved. Studies reporting disease severity were selected for quantitative analysis. Preeti Malik (PM) and Deep Mehta (DM) screened all identified studies independently, and eligibility was decided bases on full-texts assessments to decide eligibility. Any disagreement was resolved through consensus with a third author, Urvish Patel (UP).

From the included studies, we extracted steroids, antibiotics, lopinavir-ritonavir, remdesivir, Hydroxychloroquine (HCQ), intravenous immunoglobulin (IVIG) and disease severity. Details on disease severity like, IMV vs no-IMV use, oxygen saturation <90% vs >90%, ICU vs. non-ICU admission, in-hospital mortality vs discharged alive and severe vs non-severe disease were collected in excel sheet by two authors (PM and DM) in consensus with a third author (UP). Table 1 describes individual study characteristics including the following details: first author's last name, publication month and year, country of origin, sample size, study design, disease severity and treatments.

Figure 1: Flow diagram of literature search and study selection process of COVID-19 disease severity and treatment utilization.

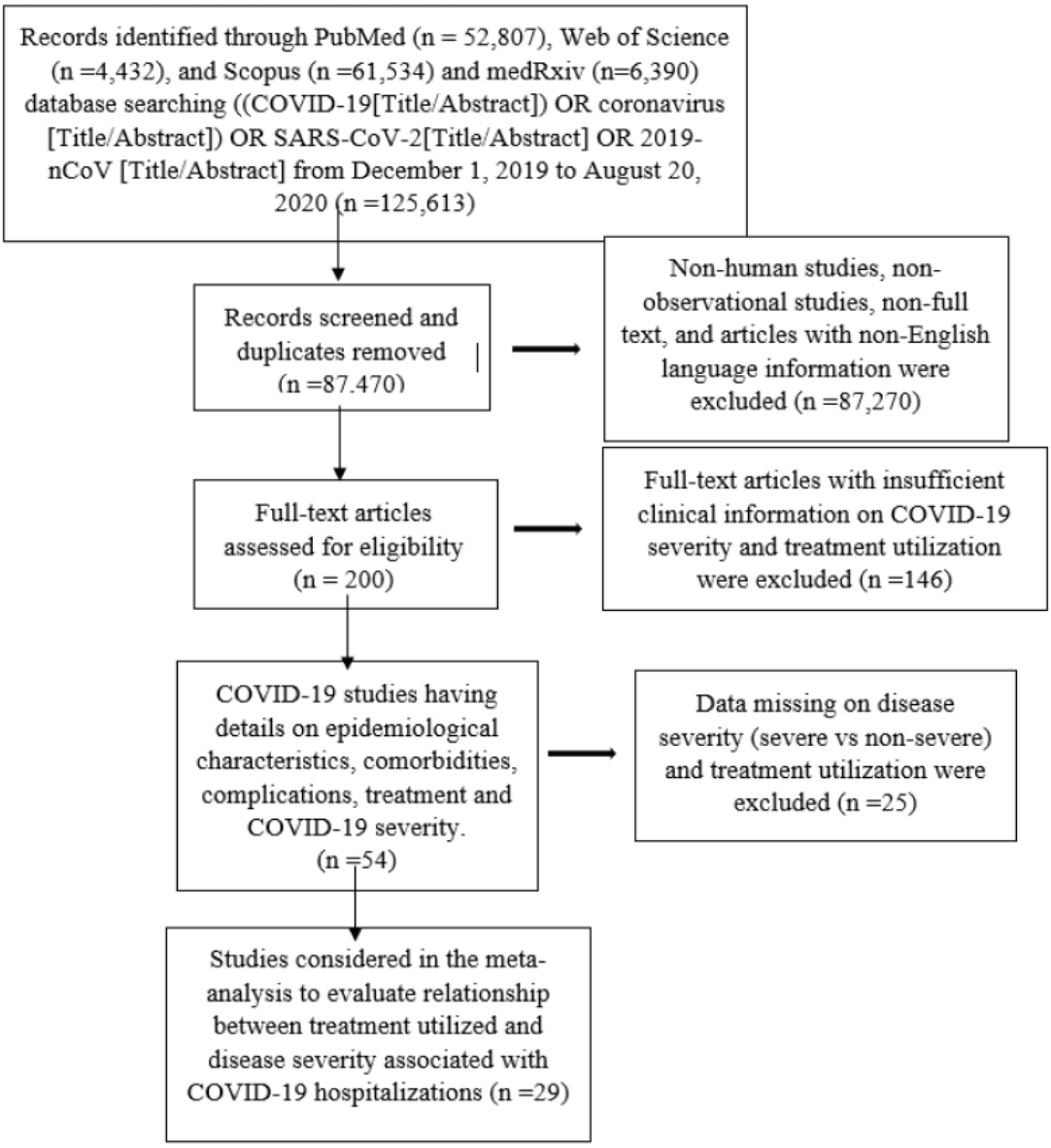

Table 1: Study characteristics, outcomes and Therapeutic Interventions used in individual study.

Study	Country	Sample size (N)	Mean/Median age (years)	Males n (%)	Study design	Outcomes	Drugs
Huang et al., Jan 2020 [32]	China	41	49	30 (73.2)	Prospective single-center	ICU vs. Non-ICU	Steroids Antibiotics
Guan et al., Feb 2020 [33]	China	1099	47	637 (58)	Retrospective multi-center	Severe vs. Non-severe*	Steroids Antibiotics IVIG

Wang et al., Feb 2020 [34]	China	138	56	75 (54.3)	Retrospective single-center	ICU vs. Non-ICU	Steroids
Yang et al., Feb 2020 [35]	China	52	59.7	35 (67.3)	Retrospective single-center	Survivor vs. Non-survivor	Steroids Antibiotics IVIG
Mo et al., Mar 2020 [36]	China	155	54	86 (55.5)	Retrospective single-center	General vs. Refractory##	Steroids IVIG
Ruan et al., Mar 2020 [37]	China	150	67 (died) 50(discharged)	102 (68)	Retrospective multi-center	Died vs. Discharged	Steroids Antibiotics
Wang et al., Mar 2020 [38]	China	69	42	32 (46.4)	Retrospective single-center	SpO2<90 vs. SpO2>=90	Steroids Antibiotics
Wu et al., Mar 2020 [39]	China	201	51	128 (63.7)	Retrospective single center	Without ARDS vs. With ARDS	Steroids Antibiotics
Zhou et al., Mar 2020 [40]	China	191	56	119 (62.3)	Retrospective multi-center cohort	Survivor vs. Non-survivor	Steroids Lopinavir-ritonavir Antibiotics IVIG
Chen et al., Mar 2020 [41]	China	21	56	17 (80.9)	Retrospective single-center	Severe vs. Moderate**	Steroids Antibiotics IVIG
Colaneri et al., Apr 2020 [42]	Italy	44	67.5	28 (63.6)	Retrospective single-center	Severe vs. Mild***	Antibiotics
Zhao et al, Apr 2020 [43]	China	91	46	49 (53.8)	Retrospective single-center	Severe vs. Mild¶	Steroids Lopinavir-ritonavir Antibiotics IVIG
Goyal et al., Apr 2020 [9]	USA	393	62.2	238 (60.6)	Retrospective multi-center	IMV vs. No IMV	Steroids Lopinavir-ritonavir HCQ Remdesivir
Wan et al., Apr 2020 [44]	China	135	47	72 (53.3)	Retrospective single-center	Severe vs. Mild**	Steroids Antibiotics
Zheng et al., May 2020 [45]	China	34	66	23 (67.6)	Retrospective single-center	IMV vs. No IMV ¶¶	Steroids Antibiotics IVIG
Hong et al., May 2020 [4]	South Korea	98	55.4	38 (38.8)	Retrospective single-center	ICU vs. Non-ICU	Steroids Lopinavir-ritonavir HCQ
Huang et. al., May 2020 [7]	China	202	44	116 (57.4)	Retrospective multi-center	Severe vs. Non-severe**	Steroids Lopinavir-ritonavir

							Antibiotics IVIG
Cao et al., Jun 2020 [46]	China	80	53	38 (47.5)	Retrospective single-center	Severe vs. Non-severe**	Steroids
Deng et al., Jun 2020 [47]	China	65	32.5(Severe+Critical), 35 (Moderate)	36 (55.4)	Retrospective cohort study	(Severe+Critical) vs. Moderate**	Steroids Antibiotics IVIG
Mikami et al., Jun 2020 [8]	USA	2820	62(survivor), 76(Non-survivor)	1611 (41.2)	Retrospective multi-center cohort	Survivor vs. Non-survivor	Steroids Lopinavir-ritonavir HCQ Remdesivir
Shahriarirad et al., Jun 2020 [48]	Iran	113	53.75	71 (62.8)	Retrospective multi-center	Severe vs non-severe*	Steroids Antibiotics
Wang et al., Jun 2020 [5]	China	275	49	128 (46.5)	Retrospective single-center	Severe vs non-severe**	Steroids
Zhang et al., Jun 2020 [49]	China	221	55	108 (48.9)	Retrospective single-center	Severe vs non-severe**	Steroids
Gregoriano et al., Jun 2020 [50]	Switzerland	99	67	62 (62.6)	Retrospective cohort study	Severe vs non-severe**	Lopinavir-ritonavir Antibiotics HCQ
Li et al., Jul 2020 [51]	China	548	60	279 (50.9)	Retrospective single-center	Severe vs non-severe**	Steroids Lopinavir-ritonavir IVIG
Xu et al., Jul 2020 [52]	China	239	62.5	143 (59.8)	Retrospective multi-center	Survivor vs. Non-survivor	Steroids Lopinavir-ritonavir Antibiotics IVIG
Zhang et al., Jul 2020 [53]	China	788	55(Severe),70(Critical), 37.5(Mild)	407 (51.6)	Retrospective multi-center	(Severe+Critical) vs. Mild	Lopinavir-ritonavir IVIG
Ferguson et al., Aug 2020 [54]	USA	72	60.4	38 (52.8)	Retrospective multi-center	ICU vs. Non-ICU	Steroids Lopinavir-ritonavir Antibiotics HCQ Remdesivir
Yang et al., Aug 2020 [55]	China	136	56	66 (48.5)	Retrospective multi-center	(Severe+Critical) vs. Mild	Steroids Lopinavir-ritonavir

							Antibiotics IVIG
Total	8570						

* Using the American Thoracic Society guidelines for community-acquired pneumonia;
**World Health Organization and the National Health Commission of China interim guidelines defined disease severity and improvement as follows: Mild cases: The mild clinical symptoms and no pneumonia in imaging. Moderate cases: symptoms like fever and respiratory tract symptoms, etc., and pneumonia can be seen in imaging. Severe cases: Meeting any of the following — respiratory distress, respiratory rate ≥ 30 breaths/min; SpO2 ≤ 93% at rest; and PaO2/FIO2 ≤ 300. Patients with >50% lesion progression within 24 to 48 hours. Critical/extremely severe cases: if they have one of the following: respiratory failure requiring mechanical ventilation, shock, and other organ failure requiring ICU treatment.
***Patients were included in the mild disease group if they did not need high-flow oxygen support and in the severe disease group if they were provided with high-flow oxygen support;
#Severe disease was defined as a composite outcome of acute respiratory distress syndrome (ARDS), intensive care unit care, or death. ARDS was diagnosed according to the Berlin definition.9 SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction assay of nose and/or throat swab samples.
##General COVID-19 was defined according to following criteria:(i) obvious alleviation of respiratory symptoms (e.g., cough, chest distress and breath shortness) after treatment; (ii) maintenance of normal body temperature for ≥3 days without the use of corticosteroid or antipyretics; (iii) improvement in radiological abnormalities on chest CT or X-ray after treatment; (iv) a hospital stays of ≤10 days. Otherwise, it was classified as refractoryCOVID-19
¶ Not mentioned;
¶¶ Non-invasive mechanical ventilation (NIV) included nasal oxygen therapy, mask oxygen inhalation, and high-flow nasal cannula (HFNC).
IVIG- intravenous immunoglobulin; ARDS- Acute respiratory distress syndrome.
IMV- Invasive mechanical ventilation
HCQ: Hydroxychloroquine

Statistical Analysis

We have used Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for the meta-analysis. The pooled prevalence of available reagents was calculated. The Mantel-Haenszel formula was used for obtaining odds ratios (ORs) and its 95% confidence intervals (95%CI) for the treatment utilization based on the severity of COVID-19 patients in each study, irrespective of heterogeneity. The I^2 statistic was used to assess statistical heterogeneity, and a value >50% was considered significant heterogeneity. A 2-tailed *p*-value of < 0.05 was considered statistically significant. Publication bias was assessed visually using funnel plots. We used The Newcastle-Ottawa Scale (NOS) to assess the quality and bias in the included studies, which rates selection, comparability, and outcome [12] (**Table 3**). Most studies were assessed to be of moderate quality. Sensitivity analysis was performed to assess the effect of publication bias and heterogeneity by excluding outlying studies on the funnel plot.

Secondary Aim

To conduct a comprehensive review of clinical trials underway in different phases being evaluated for their efficacy and safety in the treatment of COVID-19 patients.

We searched for COVID-19 therapeutic trials using the clinical trials.gov repository. We identified and categorized the trials into completed, actively recruiting, active- but not recruiting (closed to enrollment), terminated, and suspended categories. The information on the trial identification number, country, phase, drug details, outcomes measured, and current status of the trial as of October 15, 2020 have been collected and tabulated.

Table 2 describes the trial identification number, country, phase, drug details, outcomes measured, and current status of trial as of October 15, 2020 of all the completed trials.

Table 2: Drugs in pipelines (Completed clinical trials) involving direct care of COVID-19 hospitalizations.

ClinicalTrials.gov Identifier	Country	Phase	Drug name	Outcome measured
NCT04321421	Italy	N/A	Hyperimmune plasma	Death| time to extubation| length of intensive care unit stay| time to CPAP weaning| viral load| immune response
NCT04542694	Russia	Phase 3	Favipiravir| Drug: Standard of care	Time to clinical improvement| Rate of clinical status improvement
NCT04343768	Iran	Phase 2	HCQ| Lopinavir/Ritonavir| Interferon Beta-1A| Interferon Beta-1B	Time to clinical improvement|Mortality|SpO2 Improvement| Incidence of new mechanical ventilation use| Duration of hospitalization
NCT04280705	USA	Phase 3	Placebo| Remdesivir	Time to Recovery
NCT04381884	Argentina	Phase 2	Ivermectin plus standard care |standard care.	Reduction in SARS-CoV-2 viral load
NCT04315298	USA	Phase 2| Phase 3	Sarilumab vs. Placebo	Percent change in C-reactive protein (CRP) levels in patients with serum IL-6 level greater than the upper limit of normal
NCT04380519	Russia	Phase 2 | Phase 3	Biological: RPH-104 80 mg| Drug: Olokizumab 64 mg| Drug: Placebo	Changes of patients' clinical status on a 6 points ordinal scale over time
NCT04569188	Italy	Phase 2	Biological: Convalescent plasma	Death| Viral load
NCT04304053	Spain	Phase 3	HCQ | Standard Public Health measures	Clinical and virological outcome in exposed contacts.
NCT04392414	Russia	Phase 2	COVID-19 convalescent plasma |Standard plasma	The proportion of patients with the normal body temperature (37.2C) at the day 1, 2, 3, 4, 5, 6, 7 after the start of therapy.
NCT04331795	USA	Phase 2	Tocilizumab	Clinical response| Overall survival| Survival to hospital discharge| Progression of COVID-19 pneumonitis
NCT04292899	USA	Phase 3	Remdesivir| Standard of Care	The OR for Improvement on a 7-point Ordinal Scale: Day 14.
NCT04292730	USA	Phase 3	Remdesivir| Standard of Care	The OR for Improvement on a 7-point Ordinal Scale: Day 11.
NCT04244591	China	Phase 2| Phase 3	methylprednisolone therapy| Standard care	Lower Murray lung injury score| The difference of PaO2/FiO2 between two groups| Lower Sequential Organ Failure Assessment (SOFA) score
NCT04320615	USA	Phase 3	Tocilizumab (TCZ)| Placebo	Time to clinical improvement assessed Using a 7-Category Ordinal Scale.
NCT04363736	USA	Phase 2	Tocilizumab	Serum Concentration of interleukin-6 (IL-6), Ferritin and CRP Following Administration of 4 &8 mg/kg IV TCZ.

NCT04354870	USA	Phase 2	Hydroxychloroquine	Frequency of seroconversion to SARS-CoV-2|Incidence of COVID-19 symptoms in the 4 weeks preceding seroconversion
NCT04356534	Bahrain	N/A	Convalescent plasma| standard of care	Requirement for invasive ventilation| Change in viral clearance.
NCT04349241	Egypt	Phase 3	favipiravir| Standard of care therapy	Viral clearance| Clinical improvement| Radiological Improvement
NCT04358068	USA	Phase 2	HCQ|AZT| Placebo for HCQ| Placebo for AZT	Proportion of participants who died from any cause, or were hospitalized, or had an urgent visit to emergency room or clinic
NCT04389944	Switzerland	N/A	convalescent plasma	SAE and Virologic clearance
NCT04530422	Egypt	Phase 3	Sofosbuvir plus Ledipasvir	Therapeutic success (cured)|28 days in hospital mortality| Percentage of clinical failure of treatments.
NCT04358081	USA	Phase 3	HCQ| HCQ+AZT| Placebo	Percentage of participants who achieve clinical response| Percentage of Participants with Viral Clearance
NCT04408456	India	Phase 3	HCQ| Standard therapy	Incidence confirmed or probable case of COVID-19|.
NCT04523831	Bangladesh	Phase 3	Ivermectin and Doxycycline	Early and Late clinical improvement of the patients.
NCT04273321	China	N/A	Methylprednisolone	Incidence of treatment failure in 14 days|.
NCT04446104	Singapore	Phase 3	HCQ| Ivermectin| Zinc| Povidone-Iodine| Vitamin C	Incidence of laboratory-confirmed COVID-19 |Rate of hospitalization for COVID-19 and non-COVID-19.
NCT04551781	Egypt	N/A	20 Mg Prednisone| control	Resolution of CT chest infiltrates as evaluated by radiologist on a score of no infiltrates, <5%, 5-25%and >25 % infiltrates
NCT04345276	China	Phase 4	Danoprevir+Ritonavir	Adverse outcomes| Time to recovery| Rate of no fever, no cough, no dyspnea, no requiring supplemental oxygen | Rate of undetectable new coronavirus pathogen nucleic acid.
NCT04291729	China	Phase 4	Ganovo+ritonavir/-Interferon nebulization	Adverse outcomes| Time to recovery| Rate of no fever, no cough, no dyspnea, no requiring supplemental oxygen| Rate of undetectable new coronavirus pathogen nucleic acid.
NCT04383535	Argentina	N/A	Other: Convalescent SARS COVID-19 plasma| Placebo	Clinical status during follow-up at 7th, 14th and 30th day| time until hospital discharge (days), ICU discharge (days)| time to death.
NCT04554979	Egypt	N/A	Hydroxychloroquine	COVID-19 disease spectrum and duration| GIT manifestations among COVID-19 patients
NCT04261517	China	Phase 3	Hydroxychloroquine	The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3, day 5, and day 7.

NCT04346446	India	Phase 2	Convalescent Plasma| Supportive Care| Random Donor Plasma	Proportion of patients remaining free of mechanical ventilation in both groups| mortality in both groups| Improvement in Pa02/Fi02 ratio in both groups.
NCT04375098	Chile	Phase 2	Convalescent plasma	Percentage Mechanical Ventilation, hospitalization longer than 14 days or death during hospitalization.
NCT04491994	Pakistan	Phase 3	Hydroxychloroquine	Number of Participants with Progression| Viral Clearance
NCT04358614	Italy	Phase 2|Phase 3	Baricitinib	To evaluate the impact of baricitinib in terms of serious or non-serious adverse events incidence rate.
NCT04343092	Iraq	Phase 1	Ivermectin (IVM)	Number of cured patients and Mean time to cure of the COVID-19 patients
NCT04349410	USA	Phase 2|Phase 3	AZT|HCQ|Remdesivir|Tocilizumab|Methylprednisolone|Interferon-Alpha 2B|Losartan| Convalescent Serum	Improvement in FMTVDM Measurement with nuclear imaging| Ventilator status| Survival status
NCT04422561	Egypt	Phase 2|Phase 3	Ivermectin	Development of Symptoms (Fever, Cough, Sore Throat, Myalgia, Diarrhea, Shortness of Breath) |Development of COVID
NCT04374071	USA	N/A	Methylprednisolone	Transfer to ICU| Need for Mechanical Ventilation| Mortality| Development and Severity of ARDS| Length of hospital stay.
NCT04475588	India	Phase 2	Itolizumab IV infusion| Best supportive care.	One-month mortality rate between the two arms.
NCT04343261	USA	Phase 2	Convalescent Plasma	Mortality| Viral Load| Serum Antibody Titers
NCT04492501	Pakistan	N/A	Therapeutic Plasma exchange| | Convalescent Plasma| Tocilizumab| Remdesivir | Mesenchymal stem cell therapy	Survival| duration of hospitalization | Time to resolution of cytokine release storm |Time of viral clearance | Complications
NCT04434144	Bangladesh	N/A	Ivermectin + Doxycycline | HCQ+ Azithromycin	Number of participants with "treatment success" determined by a negative RT PCR for COVID19. |Number of participants with "adverse effects" determined by the existence of the pharmacological side effects of drug given.
NCT04332991	USA	Phase 3	Hydroxychloroquine| Placebo	COVID Ordinal Outcomes Scale on Day 15|all-cause mortality assessed on day 15 and 29.
NCT04350281	Hong Kong	Phase 2	Interferon Beta-1B| Hydroxychloroquine	Time to negative NPS viral load, NEWS 0|Length of Hospitalization| Adverse events| Mortality| Inflammatory markers changes
NCT04384380	Taiwan	N/A	Hydroxychloroquine Sulfate 200 MG [Plaquenil]	Time to negatively RT-PCR| Virologic assessment| Number of participants with treatment-related adverse events as assessed by CTCAE v4.0

NCT04376814	Iran	N/A	Favipiravir|: HCQ| Lopinavir / Ritonavir	Mortality, Length of hospitalization| Laboratory Treatment Response (Blood cell count and CRP).
NCT04332380	Colombia	Phase 2	Plasma	Change in Viral Load, Immunoglobulin M COVID-19 antibodies Titers, and Immunoglobulin G COVID-19 antibodies Titers.
NCT04407208	Indonesia	Phase 1	Convalescent plasma	Plaque reduction neutralization test (PNRT)|D-dimer| C-Reactive Protein (CRP)|International Normalized Ratio (INR)|Oxygenation Index.
NCT04342650	Brazil	Phase 2	Chloroquine Diphosphate| Placebo	Proportion of patients with onset of SARS, 7days after randomization| Incidence of cardiac lesions and Cardiac dysfunctions
NCT04275414	China	Phase 2	Bevacizumab Injection	Partial arterial oxygen pressure (PaO2) to fraction of inspiration O2 (FiO2) ratio| at 24 hours and 7days.
NCT04485169	Pakistan	N/A	Therapeutic Plasma Exchange	Survival| Duration of Hospitalization| Timing of PCR negativity| Time to CRS resolution| Complications
NCT04323592	Italy	N/A	Methylprednisolone| standard care	Composite Primary End-point: Admission to ICU, Need for MV, or All-cause Death by Day 28|In-hospital Death Within 28 Days |Admission to ICU|Endotracheal Intubation.
NCT04445506	USA	N/A	Dexamethasone	Effect on transfers to ICU and escalation of care needing mechanical ventilation| effect on length of stay| Change in CRP levels
NCT04327388	Argentina	Phase 3	Sarilumab SAR153191|Placebo	Time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale| Percent of patients alive at Day 29|Proportion of patients with one-point improvement at days 4, 7, 15, 21, 29.
NCT04441424	Iraq	N/A	Convalescent plasma| HCQ+AZT	Death versus survival of treated patients| The length of stay in hospitals
NCT04321278	Brazil	Phase 3	HCQ+AZT| Drug: HCQ	Evaluation of the clinical status| All-cause mortality| Number of days free from mechanical ventilation| Duration of mechanical ventilation and hospitalization|
NCT04519385	Egypt	N/A	Tocilizumab| Dexamethasone	Participants with Overall Survival at 14 days|Fio2/Pao2
NCT04389320	Egypt	N/A	Hydroxychloroquine	Immunoglobulin measurement
NCT04323527	Brazil	Phase 2	Chloroquine diphosphate	50% Mortality rate reduction by day 28|Absolute mortality on days 7 and 14.
NCT04392219	UK	Phase 1	Drug: EIDD-2801|Drug: Placebo	Safety and Tolerability of Single and multiple Ascending Dose (SAD) of EIDD-2801 (Part 1 and 3). Pharmacokinetics (PK) of EIDD-2801 when given as Single Doses (Part 2)
NCT04442958	Turkey	N/A	Convalescent Immune Plasma	Plasma ferritin level, Lymphocyte count, D-Dimer level, CRP level, Plasma procalcitonin and Plasma fibrinogen level.

NCT04276688	Hong Kong	Phase 2	Lopinavir/ritonavir| Ribavirin | Interferon Beta-1B	Time to negative NPS, negative saliva and clinical improvement| Hospitalization| Mortality| Immune reaction,
NCT04308668	USA| Canada	Phase 3	Hydroxychloroquine | Placebo	Incidence of COVID19 disease and Overall change in disease severity among those who are asymptomatic at baseline.
NCT04444986	Turkey	Phase 1	FAVIR|AVIGAN	AUC0-tlast Cmax |AUC0-inf of favipiravir.
NCT04406194	Turkey	Phase 1	FAVICOVIR| AVIGAN	AUC0-tlast Cmax |AUC0-inf of favipiravir
NCT04400682	Turkey	Phase 1	FAVIRA| AVIGAN	AUC0-tlast Cmax |AUC0-inf of favipiravir
NCT04407000	Turkey	Phase 1	Favipiravir (LOQULAR)| Favipiravir (Avigan)	Primary PK End Points AUC0-tlast and Cmax.

N/A- not applicable; HCQ- hydroxychloroquine; AZT- Azithromycin; RDV- Remdesivir; SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2; RT-qPCR- real-time quantitative polymerase chain reaction; ECMO- extracorporeal membrane oxygenation; ICU- intensive care unit; NEWS-National Early Warning Score; SOFA- Sequential Organ Failure Assessment; convP- convalescent plasma; BCG- Bacille Calmette-Guarin

Table 3: Risk of bias of included studies (NOS) Study.

	Newcastle–Ottawa Scale			**Overall risk of bias**
	Selection	**Comparability**	**Exposure**	
Huang et al., Jan 2020	**	*	**	High
Guan et al., Feb 2020	***	*	*	Low
Wang et al., Feb 2020	***	*	**	Moderate
Yang et al., Feb 2020	**	*	**	High
Chen et al., Mar 2020	***	*	**	Moderate
Mo et al., Mar 2020	**	*	*	High
Ruan et al., Mar 2020	***	*	**	Moderate
Wang et al., Mar 2020	***	*	*	Low
Wu et al., Mar 2020	**	*	**	High
Zhao et al, Mar 2020	***	*	**	Moderate
Colaneri et al., Apr 2020	**	*	*	High
Zhao et al., Apr 2020	****	*	*	Low
Goyal et al., Apr 2020	***	*	*	Low
Wan et al., Apr 2020	***	*	**	Moderate
Zheng et al., Apr 2020	***	*	**	Moderate
Hong et al., May 2020	***	*	*	Low
Huang et. al., May 2020	**	*	**	High
Cao et al., May 2020	**	*	*	High
Deng et al., Jun 2020	**	*	*	High
Mikami et al., Jun 2020	****	*	*	Low
Shahriarirad et al., Jun 2020	***	*	**	Moderate
Wang et al., Jun 2020	**	*	*	High
Zhang et al., Jun 2020	***	*	*	Low

Gregoriano et al., Jun 2020	**	*	*	High
Li et al., Jul 2020	***	*	**	Moderate
Xu et al., Jul 2020	***	*	*	Low

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Chen et al., Mar 2020	***	*	**	Moderate
Mo et al., Mar 2020	**	*	*	High
Ruan et al., Mar 2020	***	*	**	Moderate
Wang et al., Mar 2020	***	*	*	Low
Wu et al., Mar 2020	**	*	**	High
Zhao et al, Mar 2020	***	*	**	Moderate
Colaneri et al., Apr 2020	**	*	*	High
Zhao et al., Apr 2020	****	*	*	Low
Goyal et al., Apr 2020	***	*	*	Low
Wan et al., Apr 2020	***	*	**	Moderate
Zheng et al., Apr 2020	***	*	**	Moderate
Hong et al., May 2020	***	*	*	Low
Huang et. al., May 2020	**	*	**	High
Cao et al., May 2020	**	*	*	High
Deng et al., Jun 2020	**	*	*	High
Mikami et al., Jun 2020	****	*	*	Low
Shahriarirad et al., Jun 2020	***	*	**	Moderate
Wang et al., Jun 2020	**	*	*	High
Zhang et al., Jun 2020	***	*	*	Low
Gregoriano et al., Jun 2020	**	*	*	High
Li et al., Jul 2020	***	*	**	Moderate
Xu et al., Jul 2020	***	*	*	Low

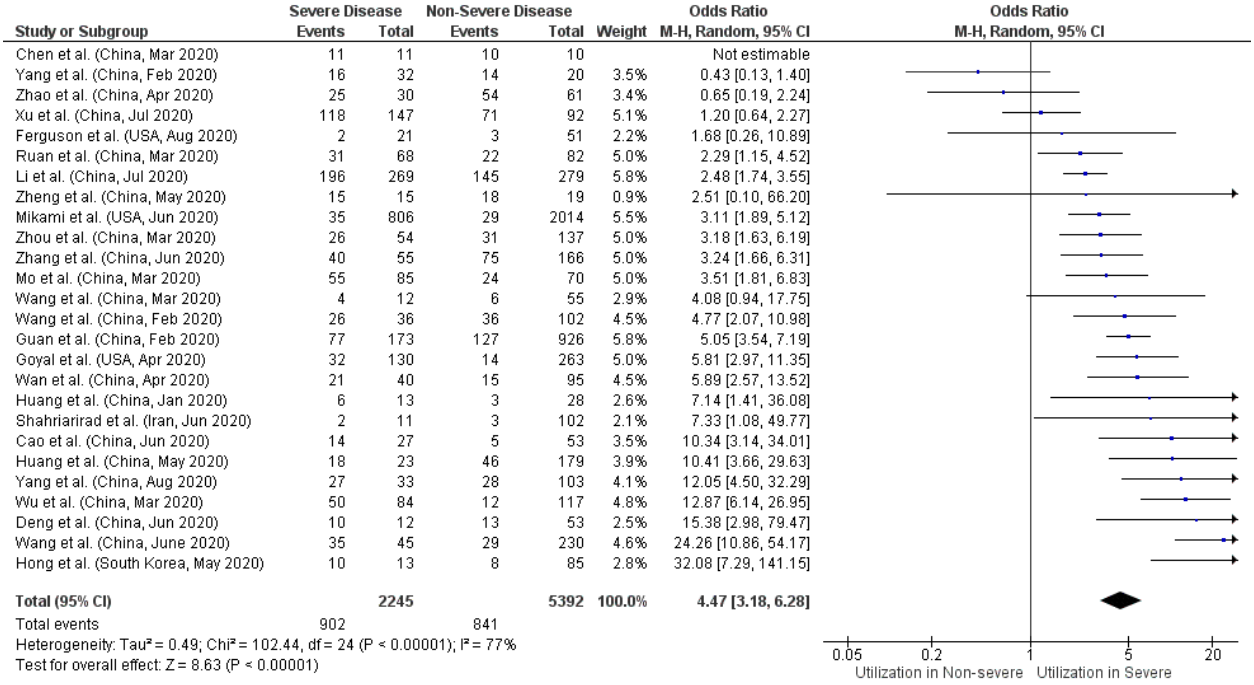
RESULTS

We found 200 articles eligible for the study, after detailed assessment and considering strict inclusion and exclusion criteria; as of August 20, 2020 we included 29 observational studies with 8570 COVID-19-positive patients **(Figure 1).** Of 29 studies, 22 are from China, 3 from USA, 1 each from Italy, Switzerland, and South Korea. These studies provided information regarding the utilization of steroids, Lopinavir-ritonavir, remdesivir, antibiotics, hydroxychloroquine, and IVIG. Of note, our specific inclusion criteria for our systematic review did not uncover any studies to enable evaluation of the severity-based prevalence of biologics or immune modulates such as anti-interleukin-6 (IL-6) approaches.

Steroids: Twenty-six studies reported data on the use of steroids and disease severity, providing a total sample size of 7637 COVID-19 patients for evaluation. The prevalence of steroid use was 40% in patients with severe disease [40% (902/2245) vs. 15.6% (841/5392)]. Meta-analysis of 26 studies showed that steroids had 4.47-fold higher odds of utilization in patients with severe disease (pooled OR:4.47; 95%CI:3.18–6.28; $p<0.00001$). 77% between-study heterogeneity was identified ($p<0.00001$) **(Figure 2).** Sensitivity analysis was conducted by eliminating the seven outlying studies

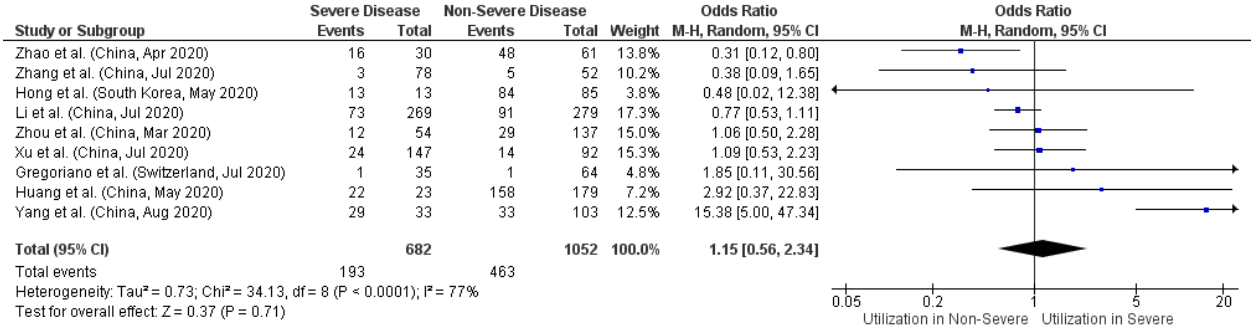
on the funnel plot in order to account for heterogeneity. Results after sensitivity analysis also showed a significant pooled OR of 3.87 (3.30-4.55; p<0.00001) with 38% heterogeneity in the data (p =0.05).

Figure 2: Forest plot of steroids utilization and outcome in COVID-19 hospitalized patients.



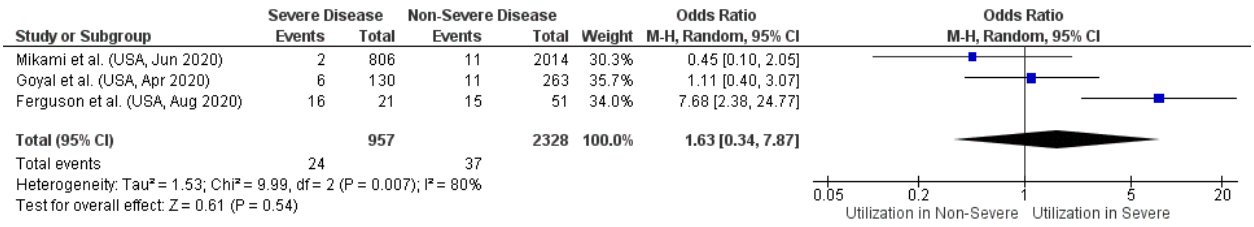
Lopinavir-ritonavir: 9 studies with a sample size of 1734 patient's association between lopinavir-ritonavir and disease severity were identified. The prevalence of lopinavir-ritonavir use was higher in patients with the non-severe disease [44% (463/1052) vs. 28.3% (193/682)]. Meta-analysis of all 9 studies showed that utilization of lopinavir-ritonavir was not significantly associated with the severity of COVID-19 patients with pooled OR of 1.15 (0.56–2.34; p=0.71), with a 77% between-study heterogeneity (p <0.0001) **(Figure 3)**. We performed a sensitivity analysis by eliminating the outlying studies on funnel plot (Yang et al.), which also showed no significant association between lopinavir-ritonavir use and disease severity with pooled OR of 0.78 (0.56-1.11; p=0.17) with 14% heterogeneity in the data (p =0.32).

Figure 3: Forest plot of lopinavir/ritonavir utilization and outcome in COVID-19 hospitalized patients.



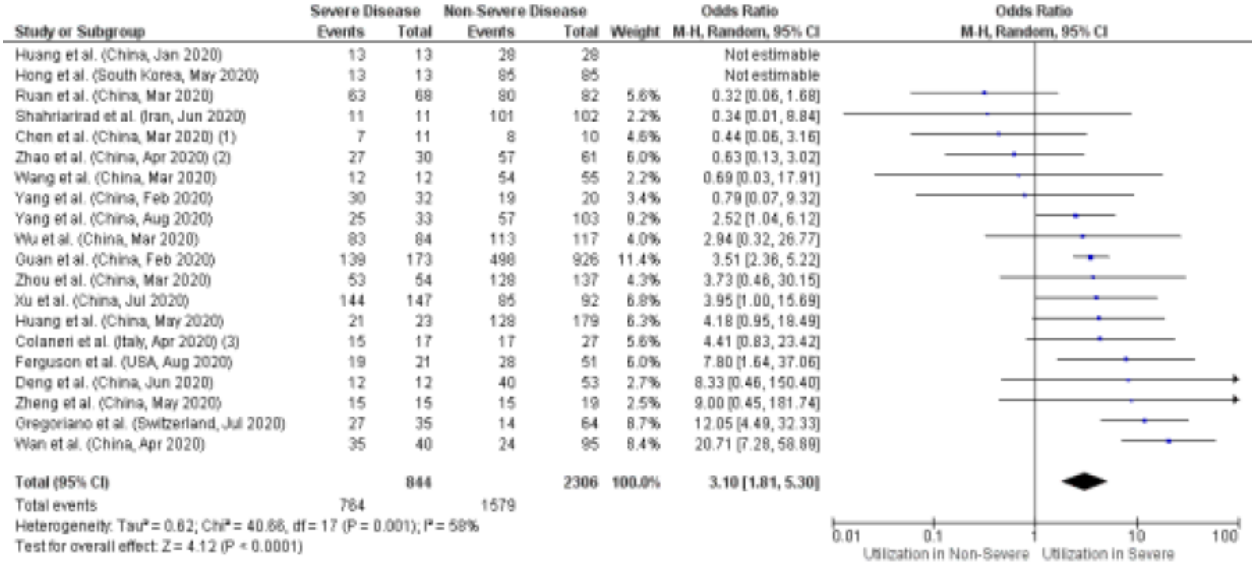
Remdesivir: 3 studies reported data on remdesivir, including 3285 patients for evaluation. The prevalence of remdesivir use was higher in patients with severe disease compared to non-severe disease [2.5% (24/957) vs. 1.6% (37/2328)]. In a meta-analysis of all three studies, we found that remdesivir use was not significantly associated with the severity of COVID-19 patients with pooled OR of 1.63 (95%CI:0.34–7.87; p=0.54), with 80% heterogeneity (p =0.007) **(Figure 4)**.

Figure 4: Forest plot of remdesivir utilization and outcome in COVID-19 hospitalized patients.



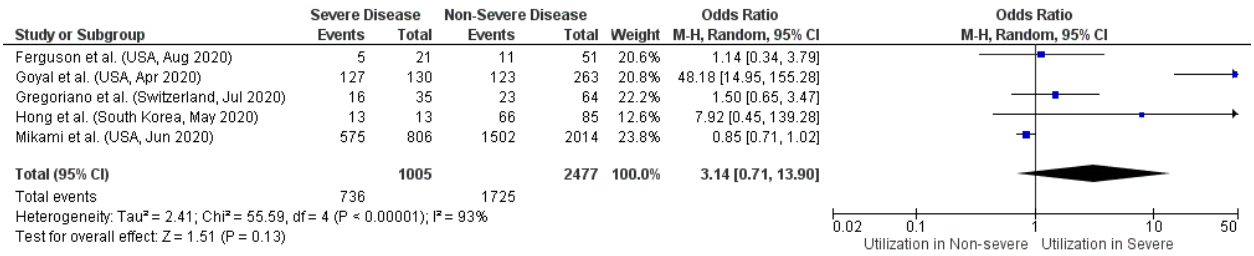
Antibiotics: A total of 20 studies reported data on antibiotics use with disease severity giving a total sample size of 3150 COVID-19 patients for evaluation. The prevalence of antibiotic use was higher in patients with severe disease [90.5% (764/844) vs. 68.5% (1579/2306)]. Meta-analysis of all 20 studies showed that antibiotics had 3.10-fold higher odds of being used in patients with severe disease compared to non-severe disease (95%CI:1.81–5.30; p<0.0001) with 58% heterogeneity identified between studies (p=0.001) **(Figure 5).** Sensitivity analysis results after eliminating two outlying studies on funnel plot (Gregoriano et al. and Wan et al.) also showed significant pooled OR of 2.36 (95%CI:1.47-3.78; p=0.0004) with 31% heterogeneity (p=0.11).

Figure 5: Forest plot of antibiotics utilization and outcome in COVID-19 hospitalized patients.



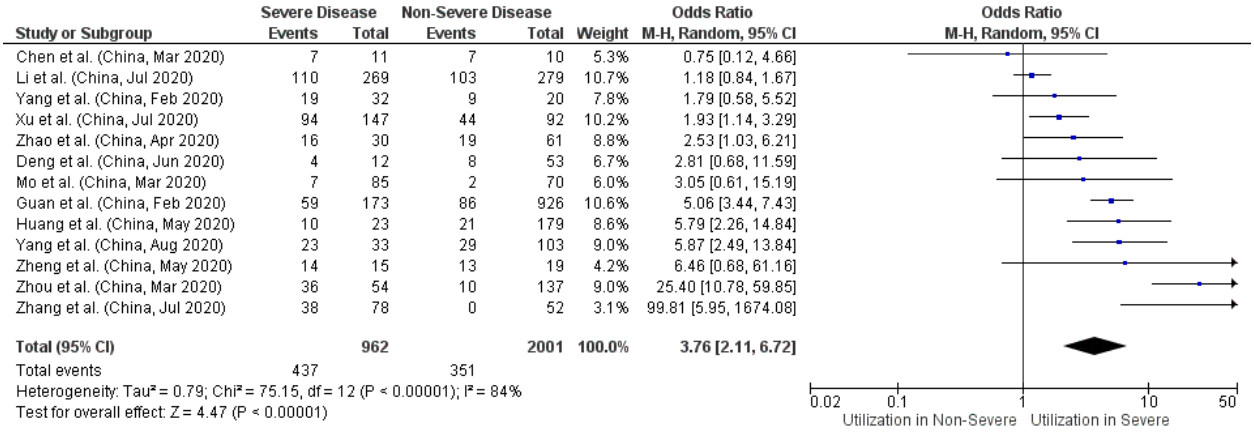
Hydroxychloroquine (HCQ): The prevalence of HCQ use was higher in patients with severe disease [73.2% (736/1005) vs. 69.6% (1725/2477)]. In our meta-analysis of 5 studies, we found that HCQ use was not significantly associated with the severity of COVID-19 patients with pooled OR of 3.14 (95%CI:0.71–13.90; p=0.13), with 93% heterogeneity between studies (p <0.00001) **(Figure 6)**. Sensitivity analysis was performed by eliminating Goyal et al. on the funnel plot. Results after sensitivity analysis also showed no significant association between HCQ use and disease severity (OR: 1.04; 95%CI:0.66-1.63; p=0.86) with 28 % heterogeneity (p =0.25).

Figure 6: Forest plot of hydroxychloroquine utilization and outcome in COVID-19 hospitalized patients.



IVIG: We found 13 studies with data on IVIG and a total sample size of 2963 patients for evaluation. The prevalence of IVIG use was higher in patients with severe disease [45.4% (437/962) vs. 17.5% (351/2001)]. Meta-analysis of all 13 studies showed that IVIG had 3.76-fold higher odds to be used in patients with severe disease compared to non-severe disease (95%CI:2.11–6.72; p<0.00001) **(Figure 7)** with 84% heterogeneity (p<0.00001). Sensitivity analysis was conducted by eliminating the three outlying studies on funnel plot (Xu et al., Li et al., and Zhou et al.). Results after sensitivity analysis also showed a significant pooled OR of 3.92 (95%CI:2.52-6.10; p<0.00001) with 38% heterogeneity in the data (p=0.10).

Figure7: Forest plot of IVIG utilization and outcome in COVID-19 hospitalized patients.



Review of Clinical trials of reagents under investigation.

As of October 15, 2020, there were 2108 interventional clinical trials on COVID-19 treatments being carried out worldwide, and 133/2108 (6.3%) have been completed. Most trials are ongoing in the USA (594), followed by France (180) and China (92). However, we are awaiting the results of these completed trials to understand the role of reagents in COVID-19 as a function of severity and their incorporation into treatment algorithms for COVID-19.

As of the date of our review, clinical trials evaluating specific therapeutics for COVID-19 included: convalescent plasma (12%), HCQ (13%), steroids (3%), favipiravir (3%), tocilizumab (3%), and interferon (3%), remdesivir (2%), lopinavir/ritonavir (2%), azithromycin (2%), ivermectin (2%) and 55% other reagents (**Table 2).**

DISCUSSION

SARS-CoV-2 is the newly emerging virus responsible for the current global pandemic of COVID-19. At the time of our study, there was no proven effective treatment for patients with severe coronavirus disease 2019 (COVID-19). Our meta-analysis, including the literature published from December 1, 2019 to August 20, 2020, found that utilization of steroids, antibiotics, and IVIG was higher in COVID-19 patients with severe disease compared to non-severe disease. Additionally, there was no significant association with the utilization of antiviral drugs such as remdesivir, lopinavir/ritonavir, or HCQ and severity in hospitalized COVID-19 patients.

Corticosteroids have anti-inflammatory, antifibrotic, and vasoconstrictive effects. Over the past few decades, the utility of corticosteroids in critically ill patients with pneumonia, septic shock, or Acute Respiratory Distress syndrome (ARDS) was tested by clinical trials [13]. Furthermore, meta-analyses of these recent clinical trials showed that the use of corticosteroids was associated with immediate resolution of shock and mechanical ventilation = reducing mortality in both septic shock and ARDS [14]. However, many clinicians are still hesitant to

prescribe steroids for these conditions due to inconsistent findings across studies explained by limited sample size, variable dosing, and underreported or unmeasured adverse effects in these clinical trials. A prospective meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) including 1703 patients, of which 59% were from the RECOVERY trial [15]. The 28-day mortality was lower in patients randomized to corticosteroids: (OR:0.66 [95% CI, 0.53, -0.82]; $p < 0.001$), with little heterogeneity across studies [15]. Also, there was no difference in the association between corticosteroids and reduced mortality among dexamethasone and hydrocortisone, and not specific to any particular corticosteroid [15]. This meta-analysis suggests that the use of steroids is often employed among critically ill COVID-19 patients, although the exact threshold at which an individual patient should be prescribed corticosteroids remains unclear. These studies further extend our meta-analysis derived observations of higher utilization of steroids in COVID-19 patients with the severe disease by healthcare professionals.

The second-generation antiretroviral drug combination lopinavir/ritonavir inhibits viral protease, And recent research on SARS-CoV and MERS-CoV carried out in vitro and in vivo has shown its inhibitory effect on both viruses [16, 17]. Our meta-analysis showed no severity-based prevalence of utilization of lopinavir in COVID-19 hospitalized patients. This pattern of treatment utilization likely reflects the incorporation of findings from Cao et al., [18] which demonstrated that lopinavir–ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or reduce viral RNA detectability in patients with serious COVID-19. Although additional clinical trials of lopinavir/ritonavir are ongoing, the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment.

Remdesivir, a nucleoside analog prodrug that inhibits viral RNA polymerases, has shown some in vitro activity against pathogenic human coronaviruses, including SARS-CoV-2, and inhibits MERS, SARS-CoV-1, and SARS-CoV-2 replication in animal models [19]. The US Food and Drug Administration, in May 2020, granted Emergency Use Authorization to the experimental antiviral drug remdesivir (manufactured by Gilead) for severe COVID-19 hospitalized patients[20]. Soon after, the demand for remdesivir increased, and many clinical trials were launched. A double-blinded randomized clinical trial by Beigel et al. reported with an ongoing trial that Remdesivir was superior to placebo in shortening the time to recovery in COVID-19 hospitalized patients and evidence of lower respiratory tract infection [21]. In our meta-analysis, we also noted no severity-based prevalence of remdesivir utilization. In addition, only three studies reporting the use of remdesivir from the USA met our inclusion criteria; hence we cannot provide enough evidence of association of remdesivir utilization with disease severity. Many additional clinical trials are underway which will hopefully further delineate the utility and proper setting for the use of remdesivir in COVID-19 patients.

Chloroquine and hydroxychloroquine are used for the treatment of malaria with a good tolerability profile. Various studies have demonstrated chloroquine activity *in vitro* and animal models against SARS-CoV [22, 23]. Their antiviral mechanisms of action include increasing endosomal pH which is necessary for fusion between the virus and the host cell and also interfere with the ACE2 cell receptor and having immunomodulatory activity. Our meta-analysis found higher utilization of HCQ in patients with severe COVID-19. This likely reflects the initial belief, in the early stages of the pandemic, that HCQ might be of clinical benefit for patients with COVID-19 and emergency use authorization by regulatory authorities, enabling providers to prescribe this medication. Subsequent studies, starting from June 2020 and with a final analysis in November 2020, have shown that treatment with HCQ does not provide any benefits to hospitalized patients. Consequently, HCQ is no longer prescribed for COVID-19 treatment. [24].

Many studies showed the role of active immunization through the administration of interferon and passive immunotherapy by convalescent plasma or synthesized monoclonal and polyclonal antibodies in the management of COVID-19 [25]. The IVIG is a pooled human blood product that gives passive immunity and regulates immune function. IVIG has anti-inflammatory and immunomodulatory effects on different immune cells, but the specific molecular mechanisms and role of the effectiveness of IVIG treatment in COVID-19 are still unclear [26]. Studies done in China showed that high doses of intravenous immunoglobulins (IVIG) could be effective in severely and critically ill COVID-19 patients [27]. Our meta-analysis with the majority of studies from China also found higher utilization of IVIG in COVID-19 patients with severe disease. Clinical trials also showed that IVIG is well tolerated, but side effects like aseptic meningitis, renal impairment, and thrombosis have been

reported [28]. Very few clinical studies on the use of a high dose of IVIG for the management of COVID-19 have been reported, but still, we need strong evidence to delineate the use of IVIG in COVID-19 treatment [26].

Strength and Limitations

The most important limitation is the heterogeneity of the included studies, which might be due to variability among studies in regard to the definition of disease severity and outcomes. Furthermore, all the included studies were retrospective, as at the time of analysis, there were no prospective studies describing treatment and severity. Most of our studies included in the analysis are from China and may not be representative of the general population in other countries. Also, we had only three studies reporting the use of Remdesivir from the USA, which met our inclusion criteria; hence we cannot provide enough evidence of the association of remdesivir utilization with disease severity. Furthermore, we don't have enough evidence to prove that these drugs were administered in the early or late phase of the disease due to the different methodologies of the observational studies included in the meta-analysis. Also, our meta-analysis studies have only reported in-hospital treatment, and the lack of pre-hospital treatment led to a biased population with more severe and untreated diseases. Few studies have reported an 85% reduction in hospitalization and death with the use of multiple drugs in pre-hospital treatment [29-31]. Despite these limitations, a meta-analysis of 8570 confirmed COVID-19 patients suggests that the use of steroids, antibiotics, and IVIG was higher in COVID-19 patients with severe disease compared to non-severe disease. Additionally, our meta-analysis did not find any significant association of antiviral utilization, such as remdesivir, lopinavir/ritonavir, or hydroxychloroquine, with the severity of COVID-19 hospitalized patients. Our study provides a comprehensive description of the disease severity prevalence of treatments utilized in the management of hospitalized COVID-19 patients, reported in the literature through August 2020. These findings may serve to educate the broader healthcare community to comprehend better the range of treatment approaches that have been pursued in an effort to control this devastating disease.

CONCLUSION

Our meta-analysis revealed that hospitalized COVID-19 patients with severe disease were more frequently treated with steroids, antibiotics, and intravenous immunoglobulin (IVIG). However, we found no significant association between disease severity and the use of lopinavir/ritonavir, remdesivir, or hydroxychloroquine in COVID-19 hospitalization. Currently, new therapeutic strategies, including mRNA vaccines, viral vector vaccines, and protein subunit vaccines, are rapidly emerging. It has significant potential to alter the course and impact of this global pandemic and will significantly add to our therapeutic armamentarium against this disease.

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