



A systematic review of real-world clinical practice data in COVID-19: Non-interventional studies

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Introduction

- As defined by the FDA (Food and Drug Administration), RWD (Real-World Data) is data related to a patient's health and/or health care delivery, usually collected from various sources as part of real-world clinical practice research.

Aim

- To describe the feasible and the most sought-after designs of non-interventional real-world clinical practice trials that provide evidence for the efficacy and safety of drug administration in the therapy of novel coronavirus infection.

Materials and methods

- A search strategy for the terms "covid-19" AND "real-life", "covid-19" AND "real-data", "covid-19" AND "real-world" was developed to extract articles published between December 1, 2020, and March 12, 2021, in the literature review databases: MEDLINE/PubMed, the Cochrane Database of Systematic Reviews, and the clinicaltrials.gov database.

Results

- The search yielded 137 non-repetitive articles, of which 32 were included in the review. All randomized clinical trials (pragmatic and simplified large ones), studies of the effectiveness of laboratory diagnostic methods, medical triage, social distancing and other sanitary and epidemiological measures to contain the epidemic were excluded from the review.

Fig. 1. PRISMA Literature search flow chat

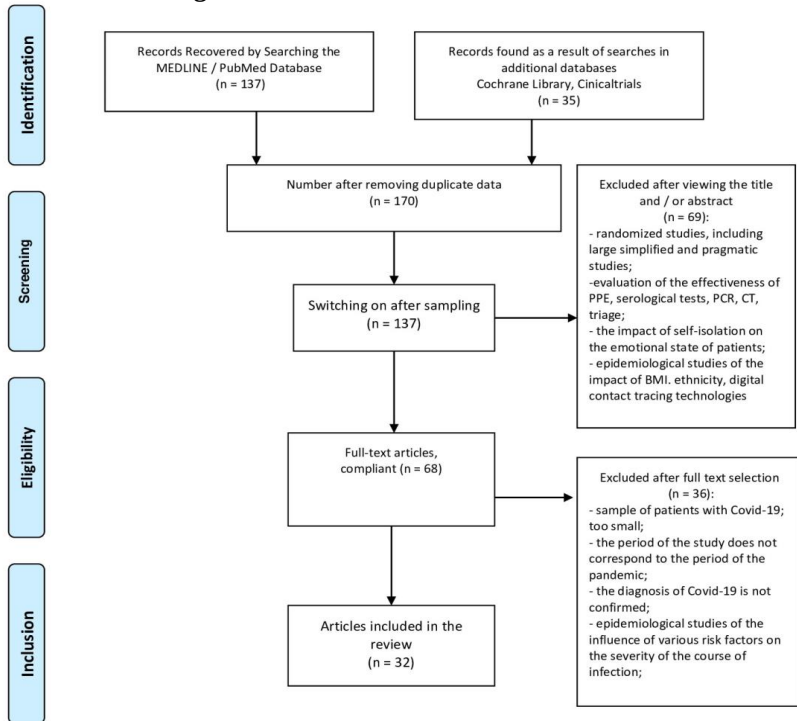
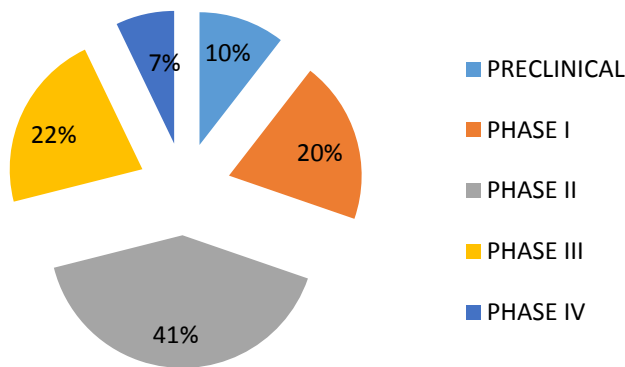


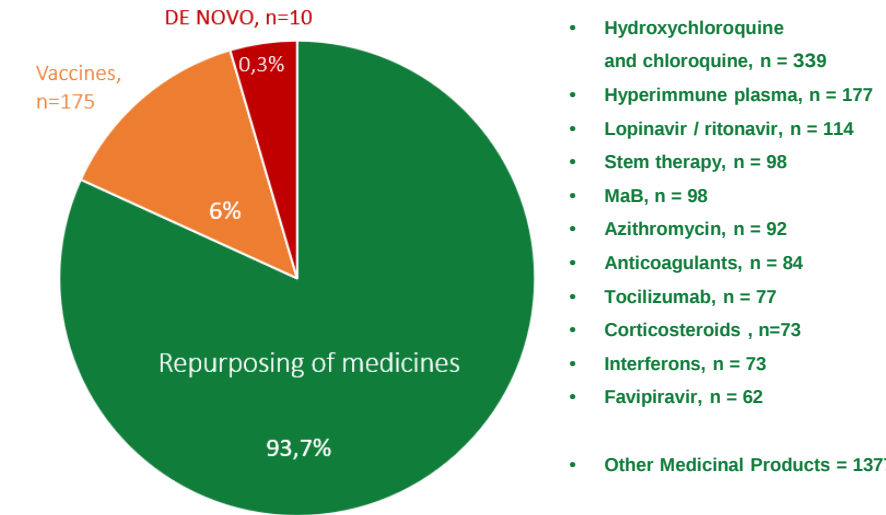
Fig. 2. Clinical trials for COVID-19 [1]



Tab. 1. Brief description of RWD studies

No.	Name	Study type	Period	Intervention	Location	Number of patients	Author, publication date, source
1	Hydroxychloroquine and tocilizumab therapy in COVID-19 patients- An observational study	multicenter retrospective non-interventional cohort uncontrolled study	from March 1 to May 5, 2020	hydroxychloroquine, hydroxychloroquine + azithromycin, azithromycin, tocilizumab	USA	2512	Andrew Ip et al., Aug 2020
2	High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study	single-center retrospective non-interventional controlled cohort study	there is no data	methylprednisolone ≥ 250 mg / day	Italy	573	Enric Monreal et al. Oct 2020
3	Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England	multicenter retrospective non-interventional cohort study	from February 16 to August 31, 2020	hypoglycemic drugs	United Kingdom	13479	Kamlesh Khunti et al., March 2021
4	Predictors of clinical deterioration in patients with suspected COVID-19 managed in a 'virtual hospital' setting: a cohort study	single-center prospective non-interventional cohort study	from March 17 to May 17, 2020	standard treatment	United Kingdom	900	Nick A Francis et al., March 2021
5	Add-On Chinese Medicine for Coronavirus Disease 2019 (ACCORD): A Retrospective Cohort Study of Hospital Registries	multicenter retrospective non-interventional cohort study	from January 15 to March 13, 2020	traditional chinese medicine	China	1788	Zixin Shu et al., March 2021
6	Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System	single-center retrospective post-marketing uncontrolled safety study	from January 17 to February 19, 2020	standard treatment	China	217	Ji Sun et al., April 2020
7	Analysis of the prophylactic effect of thymosin drugs on COVID-19 for 435 medical staff: A hospital-based retrospective study	questionnaire survey of medical personnel about the state of health	from January 25 to March 25, 2020	post-exposure prophylaxis with thymosin drugs	China	435	Xiulan Liu et al., September 2020
8	Hydroxychloroquine in Hospitalized Patients with COVID-19: Real-World Experience Assessing Mortality.	multicenter retrospective controlled uncontrolled cohort study	from January 20 to May 14, 2020	hydroxychloroquine, hydroxychloroquine + azithromycin, azithromycin,	USA	25958	Frank H Annie et al., November 2020.
9	Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Death in Patients Hospitalised with COVID-19: A Retrospective Italian Cohort Study of 43,000 Patients	multicenter non-interventional retrospective uncontrolled cohort study	from February 21 to April 21, 2020	ACE inhibitors as monotherapy or in combination with ARBs and CCBs; α2-adrenergic receptor agonists, β-blockers and diuretics	Italy	42926	Gianluca Trifiro' et al., August 2020
10	Psychiatric Disorders and Hydroxychloroquine for Coronavirus Disease 2019 (COVID-19): A VigilBase Study	multicenter retrospective cohort post-marketing safety study	from January 1 to June 16, 2020	hydroxychloroquine	European Union	1754	Philippe Garcia et al., October 2020
11	Beneficial effect of corticosteroids in preventing mortality in patients receiving tocilizumab to treat severe COVID-19 illness	single-center non-interventional retrospective uncontrolled study	from March 17 to April 14, 2020	tocilizumab, tocilizumab + GCS	Spain	1092	Manuel Rubio-Rivas et al., December 2020
12	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	multicenter retrospective uncontrolled cohort study	from December 2019 to January 2020	lopinavir / ritonavir, antibiotics, systemic corticosteroids, intravenous immunoglobulins	China	191	Fei Zhou et al., March 2020
13	Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study	multicenter retrospective non-interventional cohort study	from March 1 to April 22, 2020	tocilizumab	USA	630	Noa Biran et al., Aug 2020.
14	Clinical Features and Outcomes of Patients With Human Immunodeficiency Virus With COVID-19	multicenter retrospective non-interventional study	from February 21 to April 16, 2020	antiretroviral therapy for HIV, standard therapy for COVID-19	Italy	47	Cristina Gervasoni et al., November 2020
15	Fondaparinux Use in Patients With COVID-19: A Preliminary Multicenter Real-World Experience	multicenter non-interventional retrospective study	from February 15 to March 15, 2020	fondaparinux, enoxaparin	Italy	100	Vincenzo Russo et al., October 2020
16	Plasma Concentrations and Safety of Lopinavir / Ritonavir in COVID-19 Patients	single-center retrospective non-interventional study	from March 18, 2020 to April 1, 2020, n	lopinavir / ritonavir	USA	31	Chouchana, Laurent et al., February 2021.
17	Tocilizumab for severe COVID-19 pneumonia: Case series of 5 Australian patients	single-center retrospective open-label uncontrolled case series study	from March 30 to April 11, 2020	tocilizumab	Australia	5	Timothy A West et al., Aug 2020
18	Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy	multicenter health questionnaire	from January to May 2020	anticancer therapy for multiple myeloma	European Union and UK	75	Gordon Cook et al., July 2020
19	Tetracyclines in COVID-19 patients quarantined at home: Literature evidence supporting real-world data from a multicenter observational study targeting inflammatory and infectious dermatoses	multicenter prospective non-interventional study	from March 9 to May 3, 2020	tetracycline	Italy	38	Laura Cristina Gironi et al, December 2020
20	Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19	multicenter retrospective subanalysis of patient register	March 23 to April 2, 2020	oral anticoagulants	Ecuador, Germany, Italy and Spain	1002	José Miguel Rivera-Caravaca et al, October 2020
21	Clinical course and treatment efficacy of COVID-19 near Hubei Province, China: Amulticentre, retrospective study.	multicenter retrospective pharmacoepidemiological study	from January 20 to February 8, 2020.	standard therapy	China	149	Qing - Lei Zeng et al., June 2020
22	Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study	multicenter non-interventional controlled cohort study	from March 1 to July 31, 2020	enoxaparin, fondaparinux, dalteparin, direct oral anticoagulants (apixaban, rivaroxaban, dabigatran)	USA	4297	Christopher T Rentsch et al., February 2021
23	COVID-19 infections and outcomes in a live registry of heart failure patients across an integrated health care system	multicenter retrospective non-interventional study	April 16, 2020	standard treatment	Italy	206	César Caraballo et al, September 2020
24	Remdesivir-based therapy improved the recovery of patients with COVID-19 in the multicenter, real-world SARSTer study	multicenter retrospective controlled non-interventional study	from March 1 to August 31, 2020	remdesivir	Poland	333	Robert Flisiak et al., December 2020.
25	Does Angiotensin II receptor blockers increase the risk of SARS-CoV-2 infection? A real-life experience	multicenter retrospective study	from April 9 to November 10, 2020	ARB	Italy	306	A. De Vito et al., 2021
26	Experience with olokizumab in patients with COVID-19	multicenter retrospective non-interventional study	from 31.05.2020 to 31.08.2020	arlegia (olokizumab)	Russian Federation	610	Antonov Vladimir Nikolaevich et al., 2020
27	Hydroxychloroquine plus azithromycin and early hospital admission are beneficial in COVID-19 patients: Turkish experience with real-life data.	single-center retrospective non-interventional cross-sectional study	from March 13 to April 20, 2020	azithromycin + hydroxychloroquine	Turkey	83	Elif Tanriverdi et al., February 2021
28	Clinical Characteristics and Outcomes of Patients Hospitalized for COVID-19 in Africa: Early Insights from the Democratic Republic of the Congo	multicenter retrospective non-interventional controlled cohort study	from March 20 to July 31, 2020	hydroxychloroquine / chloroquine + azithromycin + enoxaparin, lopinavir + ritonavir, hydroxychloroquine / chloroquine + third-generation cephalosporin + enoxaparin and assisted ventilation, remdesivir + third-generation cephalosporin + enoxaparin + vitamin C, and assisted ventilation.+ lopinavir + ritonavir + third-generation cephalosporin + enoxaparin + dexamethasone and assisted ventilation	Democratic Republic of the Congo	766	Jean B Nachea et al., Oct 2020.
29	Itolizumab Treatment for Cytokine Release Syndrome in Moderate to Severe Acute Respiratory Distress Syndrome Due to COVID-19: Clinical Outcomes, A Retrospective Study	retrospective non-interventional controlled trial	there is no data	tocilizumab	India	25	Vishal Gore et al., February 2021
30	Hydroxychloroquine versus lopinavir / ritonavir in severe COVID-19 patients: Results from a real-life patient cohort	single-center prospective controlled non-interventional study	from March 1 to April 26, 2020	hydroxychloroquine, lopinavir + ritonavir	Austria	156	Mario Karolyi et al., Aug 2020
31	Real-life use of remdesivir in hospitalized patients with COVID-19	single-center retrospective non-interventional study	from June 1 to September 30, 2020	remdesivir	Spain	123	C Garcia-Vidal et al., March 2021
32	COVID-19 in ocrelizumab-treated people with multiple sclerosis	retrospective non-interventional uncontrolled study	from January 1 to July 13, 2020	ocrelizumab	USA	357	Richard Hughes et al., December 2020

- Fig. 3. The most studied groups of drugs for COVID-19 according to the international register of clinical trials COVID-19 (Global Coronavirus COVID-19 Clinical Trial Tracker)
- n = 2823. > 600,000 patients. 01.04.2021 [2]



Conclusion

All studies examining the effects of hydroxychloroquine and chloroquine have shown no effect on intrahospital mortality as a primary endpoint. The results of the studies confirmed the positive effect of glucocorticosteroids on the reduction of in-hospital mortality rates. An analysis of the registry of patients with type 2 diabetes by Kamlesh Khunti et al. (2021) showed that in the context of the COVID-19 pandemic, there is no clear indication for changing the prescription of hypoglycemic drugs. Traditional Chinese herbal medicines as monotherapy or as a component of polytherapy have received mixed reviews from experts around the world. When studying the effect of RAAS blockers on all-cause mortality risks and risks of Covid-19 infection, the conclusions were contradictory. Studies of real clinical practice confirm the existence of a link between the fact of prescription of biological drugs and a decrease in mortality among patients with a severe course of coronavirus infection. According to a study by Vishal Gore et al. (2021), a single dose of itolizumab accelerated recovery in adult patients with COVID-19 by controlling immune hyperactivation. Multiple sclerosis patients taking ocrelizumab have predominantly mild to moderate Covid-19 severity, with most patients not requiring hospitalization. All lopinavir/ritonavir studies reflected an unsatisfactory safety profile and no effect on mortality in Covid-19. Prophylactic anticoagulant therapy is an effective method to reduce the risk of mortality from Covid-19.

Conducting high-quality non-randomized RWD studies is essential in supporting medical and public health decision-making in the COVID-19 pandemic. The main advantage of these studies is that information is collected in a real-world heterogeneous patient population, reflecting the current daily practice of care for patients with a particular nosology. These studies provide information that cannot be answered by pre-registration RCTs due to possible limitations of external validity. For example, in the case of determining the superiority of drugs close in pharmacological properties from one group, to identify rare adverse events, long-term treatment outcomes. Being the main source of evidence describing symptoms and patient characteristics that influence the identification of risk factors for morbidity and mortality, they can strengthen the external validity of registration RCTs, supplementing them with a wider range of indicators.

References

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