

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Appendices

Contents

Appendix 1. The Continuous Active Learning (CAL [®]) tool	1
Appendix 2. EMBASE search strategy	2
Appendix 3. List of drugs from Health Canada and Public Health Agency of Canada	8
Appendix 4. List of included primary studies	10
Appendix 5. List of included knowledge syntheses	56
Appendix 6. Additional details for the Results section	74
Figure A1. Word cloud of description of study participants	74
Table A1. Country of primary study conduct	75
Table A2. Treatment evaluated in primary studies	77
Table A3. Treatment type of single treatment	86
Table A4. Treatment type of combination treatment	87
Table A5. Country of knowledge synthesis conduct	89
Table A6. Treatment evaluated in knowledge syntheses	90

Appendix 1. The Continuous Active Learning (CAL[®]) tool

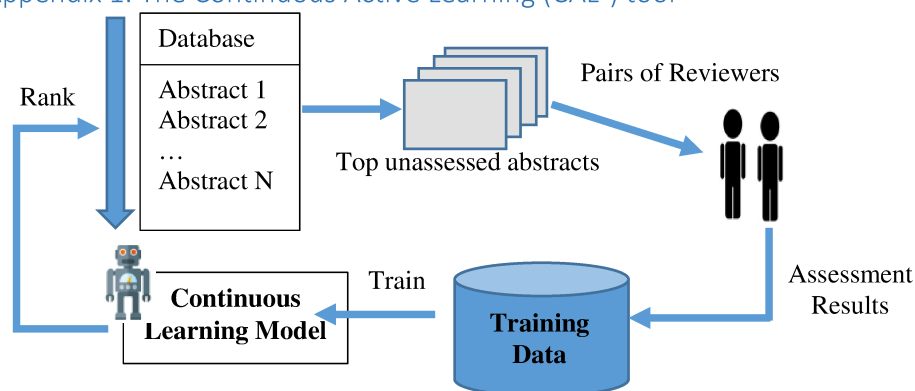


Figure. The algorithm of the CAL[®] tool

The above figure illustrates the algorithm in the CAL[®] tool. Text of the review question is used to start training the machine-learning model in the Continuous Active Learning (CAL) method. The CAL model predicts and quantifies the relevance of abstracts from a database. The abstracts are ranked in order of highest to lowest relevance. The top ranked abstracts are presented to a pair of human reviewers for relevance screening. The screening results are used to update the CAL model for better prediction, generating another batch of top ranked abstracts for screening in the next iteration of the feedback loop. The goal is to identify all relevant abstracts with minimum screening effort.

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

We selected the CAL[®] tool because it won multiple international competitions in high-recall information retrieval – the process of retrieving all relevant documents with minimal human effort (Table below)

Table. Summary of evidence on the use of the CAL[®] tool for knowledge synthesis conduct

International Competition	High-recall tasks	Key findings
Conference and Labs of the Evaluation Forum 2018 (1)	30 systematic reviews of diagnostic test studies	<i>Task 1:</i> Without any manual effort to construct literature search strategies, the CAL [®] tool was the most accurate with 97% recall (sensitivity). <i>Task 2:</i> For screening literature search results, CAL [®] was the most accurate with 99% recall.
Conference and Labs of the Evaluation Forum 2017 (2)	50 systematic reviews of diagnostic test studies	The CAL [®] tool was a top performer among the 14 tested with 97% to 100% recall at pre-defined stopping threshold.
Text Retrieval Conference Total Recall Tracks 2015/16 (3, 4)	8 legal, clinical, news, email collections	The CAL [®] tool attained an overall effectiveness not surpassed by any submitted method, manual or automatic.

For archives that could be retrieved in their entirety (e.g., MEDLINE, pre-print servers), the CAL[®] tool applied broad relevant search terms using the following Posix command:

```
egrep -i 'coronav|corona vir|wuhan|hubei|huanan|[^a-z]ncov|cov2|cov.2|novel.cov|covid|sars-cov'
```

References

1. Evangelos Kanoulas, Dan Li, Leif Azzopardi, et al. CLEF 2018 Technologically Assisted Reviews in Empirical Medicine Overview. 2018.
2. Kanoulas E, Li D, Azzopardi L, et al. CLEF 2017 technologically assisted reviews in empirical medicine overview. CEUR Workshop Proceedings, 2017.
3. Roegiest A, Cormack G, Grossman M, et al. TREC 2015 Total Recall track overview TREC. 2015.
4. Cormack GV, MR G. Multi-faceted recall of Continuous Active Learning for Technology-Assisted Review. SIGIR 2015, 2015.

Appendix 2. EMBASE search strategy

Database:

Embase Classic+Embase <1947 to 2021 July 08>

#	Query
1	exp coronaviridae/ or exp Coronaviridae infection/ or exp Coronavirus infection/
2	((wuhan or hubei or huanan) and (severe acute respiratory or pneumonia* or virus*) and outbreak*).mp.
3	(coronavir* or "corona virus*" or "coronavirus pneumonia" or betacoronavir* or COVID or COVID-19).mp.
4	("nCoV" or "cov 2" or cov2 or 2019ncov or 2019-nCoV or "2019 ncov" or "2019-ncov" or "2019 novel cov" or "2019 ncov disease*" or "2019 novel coronavirus*").mp.
5	"wuhan virus*".mp.

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

6	or/1-5
7	exp Interferons/ or interleukin-2/ or exp Immunoglobulin/ or anakinra/ or Sarilumab/ or Siltuximab/ or tumor necrosis factor/ or granulocyte macrophage colony stimulating factor/ or beta 1a interferon/ or interferon beta serine/
8	(interferon* or "Interferon-alpha" or "Interferon-beta" or "avonex" or "interferon beta-1a" or "Betaseron" or "Extavia" or "betaferon" or "beneseron" or "beta 1-b interferon" or "recombinant interferon beta-1b" or "Rebif" or "Interferon-gamma" or immunoglobulin* or "immuno globulin*" or "immune-globulin*" or anakinra or kineret or Sarilumab or kevsara or regn88 or sar153191 or Siltuximab or sylvant or cnto328 or "cnto 328" or "tumor necrosis factor*" or "tumor necrosis serum*" or cachectin or cachetin or "anti-TNF-alpha" or "TNF alfa" or "TNF alpha" or anti-granulocyte macrophage or anti-GM-CSF or "GM CSF" or gmcsf or Flebogamma or Gamunex or "Globulin-N" or "Globulin N" or Intraglobin Gammagard or Gamimune or Gamimmune or Privigen or Sandoglobulin or Venoglobulin or "Venoglobulin-I" or "Venoglobulin I" or Venimmune or Iveegam or Alphaglobin or Endobulin or "Gamimune N" or "Gamimmune N" or Gammonativ or beriglobin or biggam or carimune or cuvitrु or gammagen or gammplex or gamunex or hizentra or kiovig or norga or panzyga or sandoglobulin* or subcuvia or venogamma or vigan or interleukin-2 or interleukin).tw.
9	umifenovir/ or riamilovir/ or favipiravir/ or sofosbuvir/ or Arbidol/ or Galidesivir/
10	(Favipiravir or Triazavirin or Umifenovir or riamilovir or sofosbuvir or sofosbuvir or sovaldi or psi7851 or psi7976 or psi7977 or "EIDD-2801" or "EIDD 2801" or arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
11	Darunavir/ or Lopinavir/ or Ritonavir/ or danoprevir/ or remdesivir/
12	(ASC09 or Azvudine or Danoprevir or Darunavir or Lopinavir or ritonavir or Remdesivir or "gs 5734" or "gs5734" or prezista or "tmc 114" or tmc114 or "uic 94017" or uic94017 or abt378 or norvir).tw.
13	baloxavir marboxil/ or baloxavir marboxil.tw.
14	exp antimalarial agent/ or exp quinoline derivative/
15	(Amodiaquine or Basoquin or Camoquin or Flavoquine or Chloroquine or Resochin or Dawaquin or Lariago or Aarlen or Hydroxychloroquine or Hydroxy-chloroquine or chloroquinol or hydrochloroquine or hydrocloroquine or oxychloroquine or quensyl or "sn 8137" or ercoquin or Plaquenil or Hydroquin or Axemal or Dolquine or Quensyl or Quinoric or Imiquimiod or Aldara or Vyloma or Zyclara or Primaquine or Jasoprim or Malirid or Neo-Quipenyl or Pimaquin or Pmq or Primachina or Primacin or Primaquina or Primaquine or Primaquine or Remaquin or Tafenoquine or Krinfatel or Kozenis or Arakoda or Krintafel or Pamaquine or Plasmochin or Plasmoquine or Plsamaguine or Neo-Quipenyl or Primachin or Dihydroartemisinin or Mefloquine or lariam or laricam or mefliam or mephaquin* or tropicur or Nitazoxanide or Alinia or colufase or daxon or heliton or "salicylamide acetate" or nodik or "ph 5776" or ph5776 or ambilhar or "ba 32644" or ba32644 or "ciba 32644 ba" or "ciba 32644ba" or ciba32644ba or niradazol* or nitrothiamidazol* or nitrothiazole or "nsc 136947" or nsc136947 or yarocen or Nitrothiazole or Amokin or amokine or anoclor or aralan or aralen or arechin or arechine or

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	arequine or arthrochin or arthrochine or arthroquine or artrichin or artrichine or artriquine or avloclor or bemaphata or bemaphate or bemasulph or bipiquin or cadiquin or chemochin or chemochine or chingamine or chingaminum or chloraquine or chlorochin or chlorochine or chlorofoz or chloroquin or chloroquin* or cidanchin or "clo-kit junior" or clorichina or clorichine or cloriquine or clorochina or delagil or delagyl or dichinalex or diclokin or diquinalex or diroquine or emquin or genocin or gontochin or gontochine or gontoquine or heliopar or imagon or iroquine or klorokin or klorokine or klorokinofosfat or lagaquin or malaquin or malarex or malarivon or malaviron or maliaquine or maquine or mesylith or mexaquin or mirquin or nivachine or nivaquin* or roquine or quinachl or quingamine or repal or resochen* or resochein or resoचना or resochine or resoचिनon resoquina or resoquine or reumachlor or roquine or rp3377 or sanoquin or sanoquine or silbesan or siragan or sirajan or sn7618 or solprina or solprine or tresochin or tresochine or tresoquine or trochin or trochine or troquine).tw.
16	suramin/
17	(Carriomycin or Suramin).tw.
18	exp steroid/ or exp meprednisone/ or exp corticosteroid/ or fingolimod/ or leflunomide/ or thalidomide/
19	(steroid* or methylprednisone or meprednisone or Prednisolone or Fluprednisolone or Corticosteroid* or Fingolimod or Leflunomid* or Thalidomid*).tw.
20	ruxolitinib/
21	(Jakotinib or Ruxolitinib).tw.
22	exp monoclonal antibody/
23	(Ruxolitinib or Tocilizumab or Adalimumab or Camrelizumab or Eculizumab or Mepolizumab or "PD-1 mAb" or Tocilizumab or Adamumab or tozumab or meplazumab or monoclonal antibod*).tw.
24	("SARS-Cov-2 specific neutralizing antibod*" or "SARS-Cov specific neutralizing antibod*" or "MERS-Cov specific neutralizing antibod*" or "Anti C5a monoclonal antibod*").tw.
25	acetylcysteine/ or exp angiotensin receptor antagonist/ or exp angiotensin derivative/ or exp dipeptidyl carboxypeptidase inhibitor/ or citrate potassium/ or glycyrrhizic acid/ or dipyridamole/ or hydrogen peroxide/ or polyinosinic polycytidylic acid/ or thymosin/ or ascorbic acid/
26	(Acetylcysteine or Angiotensin or Angiotensin or "ACE inhibitor*" or ACE-2 or "Angiotensin II receptor blocker*" or ARBs or "potassium citrate" or Bromhexine or "Diammonium glycyrrhizinate" or Glycyrrhizic or Dipyridamole or Ebastine or "Hydrogen peroxide" or Pirfenidone or Polyinosinic-polycytidylic or "Polyinosinic-polycytidylic" or "Poly I-C" or "rhG-CSF" or Thymosin* or Tranilast or "Vitamin C" or "Ascorbic Acid*").tw.
27	("inhal*" adj2 gas*).tw.
28	Cyclosporine/

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

29	(Cyclosporin or cequa or "cgc 1072" or "cgc1072" or ciclomulsion or cyclasol or de076 or deximune or implanta or imusporin or neuro-stat or neurostat or opsisorin or "otx 101" or padciclo or papilock or "sp 14019" or verkazia).tw.
30	Fenretinide/
31	(fenretinide or "mcn r 1967" or "4 hydroxyphenylretinamide" or Ifendopril).tw.
32	Dalteparin/ or enoxaparin/ or tinzaparin/ or fondaparinux/ or edoxaban/ or rivaroxaban/ or apixaban/ or betrixaban/ or heparin/ or danaparoid/ or warfarin/ or dabigatran.hw.
33	(dalteparin or fragmin* or "low liquemin" or enoxaparin or clexan or clexane or inhixa or lexane or lovenox or neoparin or neoparin-nx or thorinane or tinzaparin or innohep or logiparin or fondaparinux or quixidar or dabigatran or edoxaban or lixiana or roteas or savaysa or rivaroxaban or xarelto or "bay 59 7939" or apixaban or eliques or eliquis or warfarin or adoisine or carfin or coumadan or coumadin* or marevan or panwarfarin or panwarfin or sofarin or warnerin or betrixaban or bevyxxa or dexxience or heparin or Disebrin or hepalean or lipo-hepin or menaven or multiparin or nevparin or panheparin or panheprin or praecivenin or thrombareduct or thromboliquine or vetren or danaparoid or lomoparan or orgaran).tw.
34	(Azilsartan or candesartan or eprosartan or Irbesartan or telmisartan or valsartan or losartan or olmesartan).hw. or cobicistat/ or losartan/
35	(Azilsartan or Edarbi or "tak 536" or tak536 or candesartan or amcandin or amlodipine or amlopres or camlostar or candam or candeamio or candezek or caramlo or framsyl or unisia or zenicamo or Atacand or eprosartan or epratenz or futuran or naviten or navixen or regulaten or "skf 108566" or "skf108566" or tevesten or tevetan or teveten or tevetenz or Irbesartan or irbertan or Avapro or telmisartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvea or saberverl or Micardis or valsartan or Diovan* or Prexxartan or saval or losartan or Cozaar or entrizen or lavestra or lorista or Olmesartan or Benicar or sarten or entresto or sacubitril or valsartan or byvalson or nebivolol or Aviptadil or Losartan or cozaar or cobicistat or tybost or actelsar or kinzal mono or kinzalmono or micardis or predxal or pritor or pritoral or semintra or telma-20 or tolura or angiosan or cordinate or dalzad ordiovan or diovine or kalpress or miten or nisis or prexxartan or provas or rixil or saval or tareg or tazea or troval or valpression or vals or valsocard or valtan or valtsu or alteis or belsar or benetor or benevas or benicar or cs866 or ixia or laresin or mencord or mesar or olartan or olmeblo or olmec or olmes or Olmesartan or olmetec or olupresor olsar or omesar or openvas or plaunac or rnh6270 or santini or sarten or tensar or tensiol or vivactra or votum or byvalson or cozaar).tw.
36	(benazepril or Captopril or Cilazapril or Enalapril or Fosinopril or Lisinopril or Perindopril Quinapril or Ramipril or Trandolapril).hw.
37	(Benazepril or Lotensin or Captopril or Benace or boncordin or briem or brien or "cgs 148241" or "cgs 14824a" or "cgs148241" or "cgs14824a" or cibace or cibacen* or fortekor or lotensin or tenkuoren or zinadril or ace-bloc or acenorm or acepress or acepril or aceprilex or aceril or aceten or adocor or alopresin or altran or apuzin or asisten or capace or capocard or caposan or capoten* capotril or capril or captace or captensin or capti or captoflux or captohexal or captolane or captomax or capton or captopren or captoprilan or captoril or captral or cardiopril or cardipril or

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	catona or catoplin or catopril or cesplon or cryopril or debax or dexacap or dextro captopril or ecapres or ecaten or epicordin or epsitron or farcopril or farmoten or hiperil or hypopress or hypotensor or insucar or iopril or isopresol or katopil or ketanine or keyerpril or lapril or locap or lopirin or lopril or medepres or midrat or minitent or nolectin or "oltens ge" or petacilon or praten or primace or rilcapton or ropril or smarten or tenofax or tensicap tensiomen or tensiomin or tensobon or tensoprel or tensoril or tenzib or topace or toprilem or typril-ace or vasosta or zapto or orkaptil or Cilazapril or dynorm or inhibace or inibace or initiss or inocar).tw.
38	(justor or vasace or Enalapril or Vasotec or bpnorm or dynacil or eliten or fosenopril or fosinil or fosinonorm or fosinopril or fosinorm or fosipres or fositen or fositens or fovas or fozitec or monopril or newace or sapril or sq28555 or staril or vasopril or acerbon or alapril or alfaken or carace or cipril or coric or dapril or fibsol or inopril or linopril or linvas or lipril or lisi abz orlisibeta or lisigamma or lisihexal or lisinopril dihydrate or lisipril or lisodur or lisopress or lisopril orlisoril or lispril or listril or lysinopril or "mk 0521" or "mk 521" or "mk 522" or "mk0521or mk521" or "mk522" or noperten or novatec or presiten or prinil or prinivil or qbrelis or sinopril or tensopril or tensyn or vivatec or zestomax or zestril or Monopri or Lisinopril or Prinivil or Zestril or Perindopril or Coversyl or Quinapril or Accupril or accuprin or accupro or accupron or acequin or acutel or acuprel or acupril or asig or "ci906" or conan or ectren or korec or quinalapril or quinateen or quinazi or quinhexal or quinipril or Ramipril or acovil or altace or carasel or cardace or corpril or delix or "hoe 498" or hypren or hytren or lostapres or ramace or ramilich or triatec or tritace or unipril or vesdil or vivace or Altace or Trandolapril or Mavik or gopten or Odace or odric or udrik).tw.
39	Colistin/ or (Teicoplanin or Ivermectin or azithromycin).hw.
40	(Colistin or belcomycin or colimycin* or belcomycin or Colicort or colimycin or colistine or colomycin or coly mycin or colymicin or multimycin or polymyxin or Teicoplanin or planium or tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichoplanin or teichoplanine or teicomid or teicopix or teiplamil or Planium or Tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichomycin or teichoplanin* or teicomid or teicopix or teiplamil or Ivermectin or Avermectin or cardomec or diapec or efecti or epimekor or eqvalan or eqvalenor or ivermectina or ivermectol or ivexterm or ivomec or mectizan or "mk 933" or "mk933" or oramec or quanox or revectina or seguro or sklice or soolantra or stromectol or azithromycin or aruzilina or atizor or azadose or azasite or azatril or azenil or azibiot or azimin or azithral or azithromycin or azitrocin or azitromax azitromicin* or aziwok or azomyne or aztrin or azydrop or azyter or azithromycin or bazyt or "cp 62933" or "cp 62993" or "cp62933" or "cp62993" or erythromycin or Forcin or Inedol or infectoazit or "isv 401" or "isv401" or kromicin or macrozit or mezatrin or octavax or ordipha or ribotrex or sumamed or tobyl or tromix or trozocina or ultreon or vinzam or xithrone or "xz 450" or "xz450" or Zaret or Zarom or zetamax or zeto or zibramax or zifin or zimericina or zistic or zithromax or zithrox or zitinn or zitrim or zitrobifan or zitrocin or zitromax or zmax).tw.
41	Tamoxifen.hw. or dasatinib/ or Epirubicin/ or Gemcitabine/ or Homoharringtonin/ or Imatinib/ or toremifene/ or Valrubicin/
42	(dasatinib or Ellence or Epirubicin* or epid or epifil or epiham or epilem or epirubicine or farmorrubicina or farmorubicin or pharmorubicin or Gemcitabine or difluorodeoxycytidine or Gemcite or gemtro or gemzar or infugem or "ly188011" or Homoharringtonine or harringtonine

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	or omacetaxine or ceftalonin or omapro or synribo or Imatinib or "cgp 57148" or "cgp57148b" or gleevac or gleevec or glivec or glivic or ruvise or Tamoxifen or ebefen or kessar or tamoplac or tamoxasta or tamoxifene or toremifene or estrimex or fareston or fc1157a or Valrubicin or valstar or valtaxin).tw.
43	Disulfiram/ or Emetine/ or Clomipramine/ or Loperamide/ or Caspofungin/ or Terconazole/ or Colchicine/ or Promethazine/ or Azelastine/ or Aprepitant/ or Chlorpromazine/ or Icatibant/ or Bepotastine/ or prostacyclin/ or Vapreotide/ or Conivaptan/ or Nitric oxide/ or (Perphenazine or Metformin).hw.
44	(Disulfiram or antabus or Antabuse or esperal or disulfizam or Emetine or Emetin or Clomipramine or Anafranil or anafranilin or anafranyl or clomicalm or hydiphen or Loperamide or immodium or Caspofungin or Cancidas or Terconazole or fungistat or terazol or "r 42470or Colchicine" or colchysat or mitigare or "nsc 757" or Promethazine or allerfen or antiallersin or atosil or fenergan or hiberna or Phenergan or Pipolphen or Prothazine or Romergan or Sayomol or Azelastine or Astelin or "a5610 or afluon" or alerdual or alergodil or allergodrop or allergospray or allespray or allestin or astepto or azedil or azelamed or azelavision or azeper or azeptin or carelastin or corifina or "e 0659" or "e0659" or lasticom or lastin or lastinaz or loxin or oculastin or optivar or pollival or proallergodil or radethacin or radethazin or rhinolast or rinelaz or tebarat or visuzel or vividrin or vivispray or Aprepitant or cinvanti or emend or aprepitant or "1754030" or "mk 0869" or "ono7436").tw.
45	(Perphenazine or decentan or etaperazine or ethaperazine or "sch 3940" or thilatazin or tranquisan or trifalon or trilafan or trilafon or trilifan or triliphan or Chlorpromazine or hiberna or contomin or largactil or megaphen or neurazine or plegomazin or promacid or promapar or propaphenin or solidon or sonazine or tarocitil or "thor prom" or thorazine or vegetamin or zuledin or Icatibant or firazyr or Metformin or diabetosan or diabex or dianben or diformin or fluamine or flumamine or fortamet or glifage or gliguanid or glucoformin or gluconil or glucophage or glucophage-mite or glucostop or glukophage or glumetza or haurymellin or meguan or merckformin or metforal or metformax or metiguanide or riomet or risidon or siofor or Bepotastine or bepreve or talion or Epoprostenol or prostacyclin or caripul or cycloprostin or epoprostenol or flolan or Vapreotide or doctised or octastatin or Conivaptan or vaprisol or "Nitric oxide" or inomax or noxivent).tw.
46	(convalescence/ and plasma transfusion/) or (Convalesc* adj2 plasma).tw.
47	Natural killer cell/ or exp mesenchymal stem cell/
48	("Recombinant human ACE-2" or "APN0" or "Natural killer cell" or "natural killer cells" or "NK cell" or "NK cells" or mesenchymal).tw.
49	Arbidol/ or Galidesivir/
50	(arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
51	n methyl dextro aspartic acid receptor blocking agent/
52	("n methyl dextro aspartic acid receptor" or "n methyl d aspartate a" or " NMDA antagonist*" or " NMDA inhibitor*" or " NMDA block*" or " NMDA receptor*").tw.

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

53	or/7-52
54	6 and 53
55	exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.
56	55 not human/
57	54 not 56
58	limit 57 to dd=20210131-20210518
59	limit 58 to yr="2021"

Search run on July 9, 2021 using the Ovid platform, Embase database. Search was limited by date range, from January 31, 2021 to May 18, 2021, and run in database to update an existing search from May 01, 2020 to January 31, 2021.

Appendix 3. List of drugs from Health Canada and Public Health Agency of Canada

Categories	Drug names/descriptions
ACE Inhibitors	<ul style="list-style-type: none"> Benazepril (Lotensin), Captopril (Capoten), Cilazapril (Inhibace), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril), Perindopril (Coversyl), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)
Angiotensin II Receptor Blocker (ARB)	<ul style="list-style-type: none"> Azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), telmisartan (Micardis), valsartan (Diovan, Prexxartan), losartan (Cozaar), olmesartan (Benicar), entresto (sacubitril/valsartan), byvalson (nebivolol/valsartan),
Antibiotics/antiparasitic	<ul style="list-style-type: none"> Suramin, Carriomycin, Suramin sodium, Colistin, Teicoplanin, Ivermectin, azithromycin
Antibodies	<ul style="list-style-type: none"> SARS-Cov-2 specific neutralizing antibodies Bevicizumab, Ruxolitinib, Tocilizumab, Adalimumab, Camrelizumab, Eculizumab, Mepolizumab, "PD-1 mAb", Tocilizumab, tozumab, abciximab (Reopro), adalimumab (Humira/Amjevita), alefacept (Amevive), alemtuzumab (Campath), basiliximab (Simulect), belimumab (Benlysta), bezlotoxumab (Zinplava), canakinumab (Ilaris), certolizumab (Cimzia), cetuximab (Erbix), daclizumab (Zenapax/Zinbryta), denosumab (Prolia/Xgeva), efalizumab (Raptiva), golimumab (Simponi), inflectra (Remicade), ipilimumab (Yervoy), ixekizumab (Taltz), natalizumab (Tysabri), nivolumab (Opdivo), olaratumab (Lartruvo), omalizumab (Xolair), palivizumab (Synagis), panitumumab (Vectibix), pembrolizumab (Keytruda), rituximab (Rituxan), tocilizumab

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	(Actemra/ RoActemra), trastuzumab (Herceptin), secukinumab (Cosentyx), ustekinumab (Stelara), Meplazumab
Anticancer/chemotherapy	<ul style="list-style-type: none"> • Dasatinib, Epirubicin, Gemcitabine hydrochloride, Homoharringtonine, Imatinib mesylate, Tamoxifen, Toremifene, Valrubicin
Anticoagulants	<ul style="list-style-type: none"> • dalteparin, enoxaparin, tinzaparin, fondaparinux heparin, dabigatran, edoxaban, rivaroxaban, apixaban, warfarin, betrixaban, heparin, danaparoid
Antimalarials	<ul style="list-style-type: none"> • Amodiaquine, Basoquin, Camoquin, Flavoquine, Chloroquine, Resochin, Dawaquin, Lariago, Aarlen, Hydroxychloroquine, Hydroxy-chloroquine, Plaquenil, Hydroquin, Axemal, Dolquine, Quensyl, Quinoric, Imiquimod, Aldara, Vyloma,, Zyclara, Primaquine, Jasoprim, Malirid, Neo-Quipenyl, Pimaquin, Pmq, Primachina, Primacin, Primaquina, Primaquine, Primaquine, Remaquin, Tafenoquine, Krinfatel, Kozenis, Arakoda, Krintafel, Pamaquine, Plasmochin, Plasmoquine, Plsamaguine, Neo-Quipenyl, Primachin, Dihydroartemisinin, mefloquine, Nitazoxanide, Nitrothiazole
Antiviral – Direct acting	<ul style="list-style-type: none"> • Protease inhibitors: boceprevir, telaprevir, lopinavir, ritonavir, lopinavir/ritonavir (Kaletra), darunavir/cobicistat (Prezcobix), indinavir (Crixivan), saquinavir (Invirase) • Integrase inhibitors: raltegravir, elvitegravir, dolutegravir • Entry (fusion) inhibitors: maraviroc (celsentri) • Nucleoside reverse transcriptase inhibitors: abacavir, ziagen, emtricitabine, emtriva, lamivudine, epivir, tenofovir (Viread), zidovudine, azidothymidine, retrovir • Nonnucleoside reverse transcriptase inhibitors : , doravirine, pifeltro, efavirenz, sustiva, etravirine, intelence, nevirapine, viramune, rilpivirine, edurant • Acyclic nucleoside phosphonate analogues: cidofovir diphosphates • Acyclic guanosine analogues: acyclovir • Pyrophosphate analogues: foscarnet, fomivirsen • Oligonucleotides • Nucleotide analog inhibitor: sofosbuvir • Nucleoside inhibitor: ribavirin (Ibavyr) • Matrix 2 protein inhibitors: amantadine • RNA polymerase inhibitors: Rimantadine • Neuraminidase inhibitors: oseltamivir (Tamiflu), peramivir (Rapivab), zanamivir (Relenza) • Antiretrovirals: ASC09, Azvudine, Danoprevir, Darunavir, Lopinavir, ritonavir, Remdesivir
Antiviral – Other	<ul style="list-style-type: none"> • Baloxavir, marboxil, EIDD-2801
Antivirals – Broad spectrum	<ul style="list-style-type: none"> • Favipiravir, Triazavirin, Umifenovir (arbidol hydrochloride), Galidesivir

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Immune support/modulating	<ul style="list-style-type: none"> • Convalescent plasma • Recombinant human ACE-2: APN01 • Natural killer (NK) cells • Mesenchymal stem cells • Interferons: Interferon-alpha, Interferon-beta, Interferon-gamma, interferon β – 1b (Betaseron/Extavia), interferon beta – 1a (Rebif) • Intravenous Immunoglobulin: Flebogamma DIF; Gamunex; Globulin-N; Globulin N; Intraglobin; Intraglobin F, Gammagard; Gamimune; Gamimmune, Privigen; Sandoglobulin; Venoglobulin; Venoglobulin-I; Venoglobulin I; Venimmune; Iveegam; Alphaglobin; Endobulin; Gamimune N; Gamimmune N; Gammonativ
Interleukin Inhibitors	<ul style="list-style-type: none"> • Interleukin (IL)-1 Inhibitor: Anakinra • Interleukin (IL)-6 Inhibitors: Sarilumab (Kevzara); Siltuximab • Anti-Tumor necrosis factor-alpha (anti-TNF-alpha) • Anti-Granulocyte-macrophage colony-stimulating factor (anti-GM-CSF)
Kinase Inhibitors	<ul style="list-style-type: none"> • Baricitinib, Acalabrutinib (Calquence), Fedratinib, Ruxolitinib, Jakotinib, Ruxolitinib, Sunitinib, Erlotinib
Nonspecific anti-inflammatory and immunosuppressive drugs	<ul style="list-style-type: none"> • Fingolimod Hydrochloride, Leflunomide, Thalidomide, Methylprednisone, Prednisolone, Fluprednisolone, Corticosteroids, Cyclosporin A, Glycyrrhizic Acid/Glycyrrhizic
Other	<ul style="list-style-type: none"> • Disulfiram (acetaldehyde dehydrogenase inhibitor), Emetine (alkaloid emetic), Clomipramine (antidepressant), Loperamide (antidiarrheal), Caspofungin (antifungal), Terconazole (antifungal), Colchicine (anti-gout agent), Promethazine hydrochloride (antihistamine), Azelastine (antihistamine), Aprepitant (anti-nausea/antiemetic), Perphenazine (antipsychotic), Chlorpromazine hydrochloride (antipsychotic), Icatibant (Bradykinin B2 Receptor Antagonists), Metformin (diabetes), Bepotastine (histamine 1 antagonist), Epoprostenol (prostaglandin), Vapreotide (somatostatin), Conivaptan (vasopressin inhibitor), Nitric oxide (vasodilator), Acetylcysteine (prodrug), Potassium citrate (alkalinizer), Dipyridamole (vasodilator), Hydrogen peroxide, Cobicistat (Tybost), Bromhexine (mucolytic), Ebastine (H1 receptor agonist), Pirfenidone (antifibrotic), Polyinosinic-polycytidylic (Poly I-C), rhG-CSF, Thymosin, Tranilast, Ascorbic Acid, Aviptadil (neuropeptide), Ifendopril (NMDA inhibitor), fenretinide (synthetic retinoid), famotidine (H2 receptor antagonist)

Appendix 4. List of included primary studies

1. Abaleke E, Abbas M, Abbasi S, Abbott A, Abdelaziz A, Abdelbadiee S, et al. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet*. 2021;397(10274):605-12.
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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Appendix 5. List of included knowledge syntheses.

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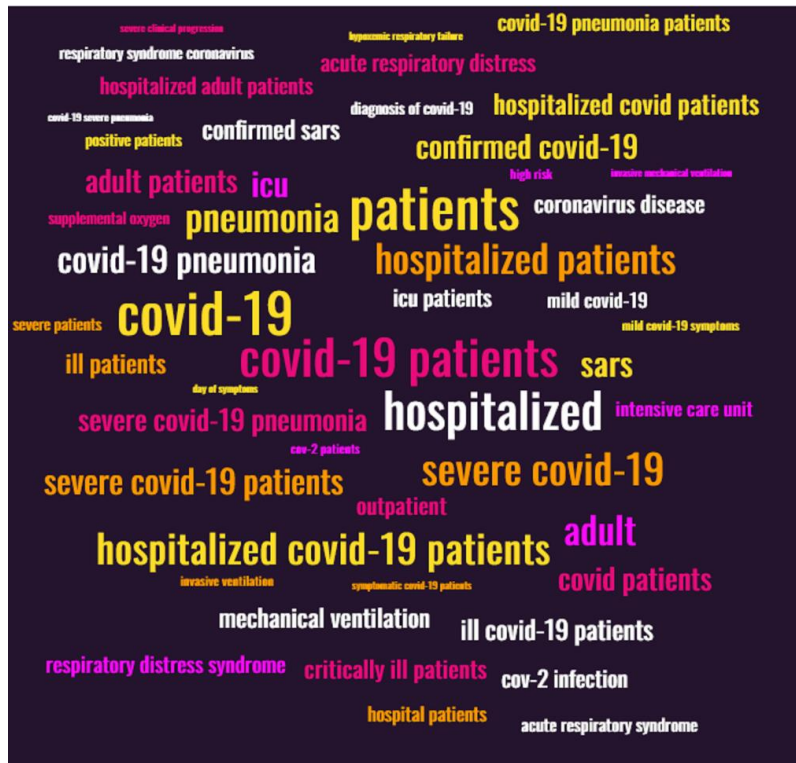
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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Appendix 6. Additional details for the Results section

Figure A1. Word cloud of description of study participants



Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A1. Country of primary study conduct

Country	Total	RCT	Non-RCT
Total	616	188	428
USA	161 (26)	37 (20)	124 (29)
China	107 (17)	27 (14)	80 (19)
Italy	47 (8)	2 (1)	45 (11)
Spain	41 (7)	3 (2)	38 (9)
France	39 (6)	5 (3)	34 (8)
India	23 (4)	15 (8)	8 (2)
Iran	21 (3)	15 (8)	6 (1)
United Kingdom	21 (3)	19 (10)	2 (0)
Brazil	17 (3)	13 (7)	4 (1)
Turkey	12 (2)	1 (1)	11 (3)
Mexico	11 (2)	6 (3)	5 (1)
Argentina	10 (2)	7 (4)	3 (1)
The Netherlands	8 (1)	2 (1)	6 (1)
Greece	6 (1)	2 (1)	4 (1)
Pakistan	6 (1)	4 (2)	2 (0)
Russia	6 (1)	1 (1)	5 (1)
Belgium	5 (1)	1 (1)	4 (1)
Egypt	5 (1)	4 (2)	1 (0)
Saudi Arabia	5 (1)	0 (0)	5 (1)
Bangladesh	4 (1)	2 (1)	2 (0)
Singapore	4 (1)	0 (0)	4 (1)
South Korea	4 (1)	0 (0)	4 (1)
Bahrain	3 (0)	2 (1)	1 (0)
Canada	3 (0)	3 (2)	0 (0)
Denmark	3 (0)	2 (1)	1 (0)
Germany	3 (0)	1 (1)	2 (0)
Iraq	3 (0)	2 (1)	1 (0)
Oman	3 (0)	1 (1)	2 (0)
Poland	3 (0)	0 (0)	3 (1)
United Arab Emirates	3 (0)	0 (0)	3 (1)
Austria	2 (0)	0 (0)	2 (0)
Chile	2 (0)	2 (1)	0 (0)
Cuba	2 (0)	1 (1)	1 (0)
Ireland	2 (0)	0 (0)	2 (0)
Israel	2 (0)	0 (0)	2 (0)
Qatar	2 (0)	1 (1)	1 (0)
Sweden	2 (0)	0 (0)	2 (0)
Australia	1 (0)	1 (1)	0 (0)
Columbia	1 (0)	1 (1)	0 (0)
Hong Kong	1 (0)	0 (0)	1 (0)
Indonesia	1 (0)	1 (1)	0 (0)
Kuwait	1 (0)	0 (0)	1 (0)
Nigeria	1 (0)	1 (1)	0 (0)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Country	Total	RCT	Non-RCT
Total	616	188	428
Norway	1 (0)	1 (1)	0 (0)
Peru	1 (0)	0 (0)	1 (0)
Philippines	1 (0)	0 (0)	1 (0)
Romania	1 (0)	0 (0)	1 (0)
Suriname	1 (0)	0 (0)	1 (0)
Switzerland	1 (0)	0 (0)	1 (0)
Taiwan	1 (0)	1 (1)	0 (0)
Thailand	1 (0)	0 (0)	1 (0)
WHO - 30 countries	1 (0)	1 (1)	0 (0)

Notes: Values are numbers of primary studies and related percentages.

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A2. Treatment evaluated in primary studies

	Total	RCT	Non-RCT
Total	630	190	440
Tocilizumab	87 (14%)	12 (6%)	75 (17%)
Hydroxychloroquine	78 (12%)	22 (12%)	56 (13%)
Convalescent Plasma	55 (9%)	15 (8%)	40 (9%)
Steroid	37 (6%)	1 (1%)	36 (8%)
Lopinavir/Ritonavir	29 (5%)	5 (3%)	24 (5%)
Methylprednisolone	26 (4%)	3 (2%)	23 (5%)
Remdesivir	25 (4%)	16 (8%)	9 (2%)
Enoxaparin	18 (3%)	1 (1%)	17 (4%)
Hydroxychloroquine/Azithromycin	18 (3%)	2 (1%)	16 (4%)
Anakinra	16 (3%)	2 (1%)	14 (3%)
Dexamethasone	16 (3%)	4 (2%)	12 (3%)
Anticoagulant-Therapeutic	15 (2%)	2 (1%)	13 (3%)
Azithromycin	15 (2%)	6 (3%)	9 (2%)
Anticoagulant-Prophylactic	11 (2%)	0 (0%)	11 (3%)
Ivermectin	11 (2%)	9 (5%)	2 (0%)
Heparin	9 (1%)	0 (0%)	9 (2%)
Favipiravir	8 (1%)	6 (3%)	2 (0%)
Sarilumab	8 (1%)	7 (4%)	1 (0%)
Colchicine	7 (1%)	4 (2%)	3 (1%)
Glucocorticoids	7 (1%)	0 (0%)	7 (2%)
Bamlanivimab	6 (1%)	4 (2%)	2 (0%)
Chloroquine	6 (1%)	2 (1%)	4 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Mesenchymal Stem Cells	6 (1%)	4 (2%)	2 (0%)
Steroid	6 (1%)	0 (0%)	6 (1%)
Thymosin-Alpha1	6 (1%)	1 (1%)	5 (1%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antiviral	5 (1%)	0 (0%)	5 (1%)
Arbidol	5 (1%)	2 (1%)	3 (1%)
Aspirin	5 (1%)	0 (0%)	5 (1%)
Interferon	5 (1%)	3 (2%)	2 (0%)
Prednisone	5 (1%)	1 (1%)	4 (1%)
Statins	5 (1%)	0 (0%)	5 (1%)
Antibiotic	4 (1%)	0 (0%)	4 (1%)
Anticoagulant	4 (1%)	0 (0%)	4 (1%)
Hydrocortisone	4 (1%)	2 (1%)	2 (0%)
Lopinavir/Ritonavir/Hydroxychloroquine	4 (1%)	0 (0%)	4 (1%)
Ribavirin	4 (1%)	0 (0%)	4 (1%)
Therapeutic Plasma Exchange	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (2%)	1 (0%)
Acei Arb	3 (0%)	0 (0%)	3 (1%)
Baricitinib	3 (0%)	1 (1%)	2 (0%)
Casirivimab/Imdevimab	3 (0%)	2 (1%)	1 (0%)
Famotidine	3 (0%)	0 (0%)	3 (1%)
Interferon-Alpha-2b	3 (0%)	0 (0%)	3 (1%)
Interferon Alpha-2b	3 (0%)	1 (1%)	2 (0%)
Lenzilumab	3 (0%)	2 (1%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha	3 (0%)	0 (0%)	3 (1%)
Neutralizing Antibody	3 (0%)	1 (1%)	2 (0%)
Zinc Iv	3 (0%)	3 (2%)	0 (0%)
Acei Arb Statin	2 (0%)	0 (0%)	2 (0%)
Avifavir	2 (0%)	2 (1%)	0 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Canakinumab	2 (0%)	0 (0%)	2 (0%)
Ceftriaxone	2 (0%)	0 (0%)	2 (0%)
Chlorpromazine	2 (0%)	0 (0%)	2 (0%)
Corticosteroids/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Darunavir/Cobicistat	2 (0%)	1 (1%)	1 (0%)
Fondaparinux	2 (0%)	0 (0%)	2 (0%)
Functional Inhibition Of Acid Sphingomyelinase	2 (0%)	0 (0%)	2 (0%)
Haloperidol	2 (0%)	0 (0%)	2 (0%)
Heparin-Prophylaxis	2 (0%)	0 (0%)	2 (0%)
Inhaled Budesonide	2 (0%)	2 (1%)	0 (0%)
Interferon Beta-1b	2 (0%)	0 (0%)	2 (0%)
Interferon Kappa/Trefoil Factor 2	2 (0%)	2 (1%)	0 (0%)
Interferon Lambda-1a	2 (0%)	2 (1%)	0 (0%)
Interlukin-6 Inhibitors	2 (0%)	0 (0%)	2 (0%)
Itolizumab	2 (0%)	2 (1%)	0 (0%)
Ivermectin/Doxycycline	2 (0%)	2 (1%)	0 (0%)
Leflunomide	2 (0%)	0 (0%)	2 (0%)
Lopinavir	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Azithromycine	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Doxycycline	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Ribavirin/Interferon Beta-1b	2 (0%)	1 (1%)	1 (0%)
Mavrilimumab	2 (0%)	1 (1%)	1 (0%)
Methylprednisolone/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Neuromuscular Blocking Agents	2 (0%)	0 (0%)	2 (0%)
Nitazoxanide	2 (0%)	2 (1%)	0 (0%)
Oseltamivir	2 (0%)	0 (0%)	2 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Prednisolone	2 (0%)	0 (0%)	2 (0%)
Ribavirin/Interferon-Alpha	2 (0%)	0 (0%)	2 (0%)
Statin	2 (0%)	0 (0%)	2 (0%)
Stem Cell Nebulization	2 (0%)	0 (0%)	2 (0%)
Steroid-Pulse	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Methylprednisolone	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Steroid	2 (0%)	0 (0%)	2 (0%)
Umifenovir	2 (0%)	0 (0%)	2 (0%)
Vitamin C/Zinc	2 (0%)	2 (1%)	0 (0%)
Acyclovir	1 (0%)	0 (0%)	1 (0%)
Amantadine	1 (0%)	0 (0%)	1 (0%)
Amoxicillin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Intravenous Immunoglobulin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Methylprednisolone	1 (0%)	0 (0%)	1 (0%)
Antiviral/Antiviral/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Apixaban-Prophylaxis	1 (0%)	0 (0%)	1 (0%)
Apixaban-Therapeutic	1 (0%)	0 (0%)	1 (0%)
Aprepitant	1 (0%)	1 (1%)	0 (0%)
Arbidol/Hydroxychloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Artemisinin-Piperaquine	1 (0%)	0 (0%)	1 (0%)
Auxora	1 (0%)	1 (1%)	0 (0%)
Azithromycin/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Prednisolone/Naproxen/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Azvudine	1 (0%)	1 (1%)	0 (0%)
Bacillus Calmette–Guérin Vaccine	1 (0%)	1 (1%)	0 (0%)
Baloxavir Marboxil	1 (0%)	1 (1%)	0 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Bamlanivimab/Etesevimab	1 (0%)	1 (1%)	0 (0%)
Baricitinib/Remdesivir	1 (0%)	1 (1%)	0 (0%)
Berinerit	1 (0%)	0 (0%)	1 (0%)
Betamethasone	1 (0%)	1 (1%)	0 (0%)
Bevacizumab	1 (0%)	0 (0%)	1 (0%)
Bromhexine/Hydrochloride	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Hydrochloride/Antiviral	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Spirolactone	1 (0%)	0 (0%)	1 (0%)
Camostat Mesilate	1 (0%)	1 (1%)	0 (0%)
Cerc-002	1 (0%)	1 (1%)	0 (0%)
Choloroquine	1 (0%)	1 (1%)	0 (0%)
Cigb-325	1 (0%)	1 (1%)	0 (0%)
Clarithromycin	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Tocilizumab	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Lopinavir/Ritonavir/Interferon Alpha	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Ns-Immunosuppresant	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Anakinra	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Cotrimoxazole	1 (0%)	0 (0%)	1 (0%)
Cyclooxygenase-2	1 (0%)	0 (0%)	1 (0%)
Cyclosporine A	1 (0%)	0 (0%)	1 (0%)
Dexamethasone/Tofacitinib	1 (0%)	0 (0%)	1 (0%)
Diphenhydramine/Ammonium Chloride	1 (0%)	1 (1%)	0 (0%)
Doxycycline	1 (0%)	1 (1%)	0 (0%)
Dutasteride	1 (0%)	1 (1%)	0 (0%)
Eculizumab	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Epoprostenol - Aerosolized	1 (0%)	0 (0%)	1 (0%)
Equine Polyclonal Antibodies	1 (0%)	1 (1%)	0 (0%)
Favipiravir/Chloroquine Hydroxychloroquine/Lopinavir/ Ritonavir Or Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Chloroquine Hydroxychloroquine/Lopinavir/ Ritonavir Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Interferon Beta-1b	1 (0%)	1 (1%)	0 (0%)
Firazyr	1 (0%)	0 (0%)	1 (0%)
Flash Frozen Plasma	1 (0%)	1 (1%)	0 (0%)
Fluticasone Spray/Triamcinolone	1 (0%)	0 (0%)	1 (0%)
Fluvoxamine	1 (0%)	1 (1%)	0 (0%)
Glucocorticoids/Interferon	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine Or Chloroquine	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Hydroxychloroquine/Favipiravir	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxyzine	1 (0%)	0 (0%)	1 (0%)
Inhaled Adenosine	1 (0%)	0 (0%)	1 (0%)
Inhaled Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Inhaled Nitric Oxide	1 (0%)	1 (1%)	0 (0%)
Interferon-B 1a/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Arbidol	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Itraconazole	1 (0%)	1 (1%)	0 (0%)
Ivermectin/Azithromycin	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Leflunomide/Interferon Alpha 2a	1 (0%)	1 (1%)	0 (0%)
Levamisole	1 (0%)	1 (1%)	0 (0%)
Levofloxacin	1 (0%)	0 (0%)	1 (0%)
Linezolid	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir Or Hydroxychloroquine+Prednisone	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Chloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha/Abidor Ribavirin Cholroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon Beta-2b	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon/Interferon	1 (0%)	0 (0%)	1 (0%)
Losartan	1 (0%)	1 (1%)	0 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)
Meropenem	1 (0%)	0 (0%)	1 (0%)
Mesenchymal Stromal Cells	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Dexamethasone	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Ivig	1 (0%)	1 (1%)	0 (0%)
Multi-Mechanism Approach	1 (0%)	0 (0%)	1 (0%)
Nebulised Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Olokizumab	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Opaganib	1 (0%)	0 (0%)	1 (0%)
Otilimab	1 (0%)	1 (1%)	0 (0%)
Pentoxifylline	1 (0%)	1 (1%)	0 (0%)
Pipamperone And Citalopram	1 (0%)	1 (1%)	0 (0%)
Piperacillin	1 (0%)	0 (0%)	1 (0%)
Polymerized-Collagen	1 (0%)	1 (1%)	0 (0%)
Poractant Alfa	1 (0%)	0 (0%)	1 (0%)
Progesterone	1 (0%)	1 (1%)	0 (0%)
Prophylactic Anticoagulant	1 (0%)	0 (0%)	1 (0%)
Proxalutamide	1 (0%)	1 (1%)	0 (0%)
Pyridostigmine	1 (0%)	1 (1%)	0 (0%)
Recombinant Interleukin-2	1 (0%)	0 (0%)	1 (0%)
Remdesivir/Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Ribavarin/Lopinavir/Ritonavir/Interferon-Alpha	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Arbidol/Hydroxichloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Hydroxichloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Rimantadine	1 (0%)	0 (0%)	1 (0%)
Ruxolitinib	1 (0%)	0 (0%)	1 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Daclatasvir/Hydroxychloroquine	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Ledipasvir	1 (0%)	1 (1%)	0 (0%)
Soludexide	1 (0%)	1 (1%)	0 (0%)
Sulodexide	1 (0%)	1 (1%)	0 (0%)
Telmisartan	1 (0%)	1 (1%)	0 (0%)
Theophylline/Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Tocilizumab/Convalescent Plasma	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	630	190	440
Tocilizumab/Favipiravir	1 (0%)	1 (1%)	0 (0%)
Toxilizumab/Steroids/Anakinra/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Triazavirin	1 (0%)	1 (1%)	0 (0%)
Vermeectin/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Vilobelimab	1 (0%)	1 (1%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (0%)	0 (0%)	1 (0%)
Vitamins/Dietary Supplements	1 (0%)	0 (0%)	1 (0%)
Zanamivir	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A3. Treatment type of single treatment

	Total	RCT	Non-RCT
Total	711	202	509
Non-Steroidal Immunosuppressant	126 (18%)	27 (13%)	99 (19%)
Steroid	110 (15%)	15 (7%)	95 (19%)
Antiviral	97 (14%)	40 (20%)	57 (11%)
Antimalaria	87 (12%)	25 (12%)	62 (12%)
Anticoagulant	66 (5%)	5 (3%)	61 (12%)
Anticoagulant-Therapeutic	17 (2%)	2 (1%)	15 (3%)
Anticoagulant-Prophylactic	14 (2%)	0 (0%)	14 (3%)
Convalescent Plasma	56 (8%)	16 (8%)	40 (8%)
Antibiotic	29 (4%)	7 (3%)	22 (4%)
Anti- Inflammatory	20 (3%)	8 (4%)	12 (2%)
Interferon Therapy	16 (2%)	7 (3%)	9 (2%)
Antiparasitic	14 (2%)	12 (6%)	2 (0%)
Immunomodulator	14 (2%)	4 (2%)	10 (2%)
Neutralizing Antibodies	13 (2%)	7 (3%)	6 (1%)
Mesenchymal Stem Cells	9 (1%)	4 (2%)	5 (1%)
Statin	7 (1%)	0 (0%)	7 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antihistamine	4 (1%)	0 (0%)	4 (1%)
Antipsychotic	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (1%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A4. Treatment type of combination treatment

Total	Total 116	RCT 29	Non-RCT 87
Antimalaria/Antibiotic	19 (16%)	2 (7%)	17 (20%)
Steroid/NS-Immunosuppressant	10 (9%)	0 (0%)	10 (11%)
Antimalaria/Antiviral/Antiviral	8 (7%)	1 (3%)	7 (8%)
Antiviral/Antiviral	5 (4%)	3 (10%)	2 (2%)
Antiviral/Interferon	5 (4%)	0 (0%)	5 (6%)
Antimalaria/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antimalaria/Antiviral/Antibiotic	4 (3%)	4 (14%)	0 (0%)
Antiparasitic/Antibiotic	4 (3%)	3 (10%)	1 (1%)
Antiviral/Antiviral/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antiviral/Antiviral/Antiviral/Interferon	4 (3%)	0 (0%)	4 (5%)
Antiviral/NS-Immunosuppressant	4 (3%)	3 (10%)	1 (1%)
NS-Immunosuppressant/Steroid	4 (3%)	0 (0%)	4 (5%)
ACEI/ARB	3 (3%)	0 (0%)	3 (3%)
Antiviral/Antibiotic	3 (3%)	2 (7%)	1 (1%)
Antiviral/Antiviral/Interferon	3 (3%)	1 (3%)	2 (2%)
ACEI/ARB/Statin	2 (2%)	0 (0%)	2 (2%)
Antimalaria/Antiviral/NS-Immunosuppressant	2 (2%)	0 (0%)	2 (2%)
Antiviral/Anti-Inflammatory	2 (2%)	2 (7%)	0 (0%)
Steroid/Steroid	2 (2%)	0 (0%)	2 (2%)
Vitamin C/Zinc	2 (2%)	2 (7%)	0 (0%)
Anticoagulant/Ns-Immunosuppressant	1 (1%)	0 (0%)	1 (1%)
Antihistamine/Disinfectant	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Mucolytic	2 (2%)	1 (3%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Antibiotic	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Antiviral/Antiviral/Antiviral	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Interferon	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Mucolytic	1 (1%)	1 (3%)	0 (0%)
Antiviral/Antiviral/Antibiotic/Anti-Inflammatory/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Antiviral/Antimalaria/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Immunomodulator	1 (1%)	1 (3%)	0 (0%)
Antiviral/Interferon/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Steroid	1 (1%)	0 (0%)	1 (1%)
Bronchodilator/Hemorrhologic Agent	1 (1%)	0 (0%)	1 (1%)
Mucolytic/Diuretic	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressant/Convalescent Plasma	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressants/IVIG	1 (1%)	0 (0%)	1 (1%)
Steroid/Anti-Inflammatory	1 (1%)	0 (0%)	1 (1%)
Steroid/Interferon	1 (1%)	0 (0%)	1 (1%)
Steroid/IVIG	1 (1%)	1 (3%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (1%)	0 (0%)	1 (1%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total	RCT	Non-RCT
Total	116	29	87
Vitamins/Dietary Supplements	1 (1%)	0 (0%)	1 (1%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A5. Country of knowledge synthesis conduct

	Total (n = 299)	With protocol (n = 88)	Without protocol (n = 211)
United States	57 (19%)	13 (15%)	44 (21%)
China	40 (13%)	13 (15%)	27 (13%)
India	34 (11%)	12 (14%)	22 (10%)
Iran	18 (6%)	3 (3%)	15 (7%)
United Kingdom	18 (6%)	3 (3%)	15 (7%)
Saudi Arabia	13 (4%)	1 (1%)	12 (6%)
Canada	12 (4%)	5 (6%)	7 (3%)
Italy	12 (4%)	8 (9%)	4 (2%)
Indonesia	9 (3%)	2 (2%)	7 (3%)
Malaysia	7 (2%)	0 (0%)	7 (3%)
Egypt	5 (2%)	2 (2%)	3 (1%)
France	5 (2%)	3 (3%)	2 (1%)
Peru	5 (2%)	1 (1%)	4 (2%)
Taiwan	5 (2%)	1 (1%)	4 (2%)
Australia	4 (1%)	1 (1%)	3 (1%)
Brazil	4 (1%)	1 (1%)	3 (1%)
Chile	4 (1%)	4 (5%)	0 (0%)
Japan	4 (1%)	2 (2%)	2 (1%)
Nepal	4 (1%)	0 (0%)	4 (2%)
Spain	4 (1%)	1 (1%)	3 (1%)
Bangladesh	3 (1%)	0 (0%)	3 (1%)
Greece	3 (1%)	1 (1%)	2 (1%)
Korea	3 (1%)	1 (1%)	2 (1%)
Pakistan	3 (1%)	0 (0%)	3 (1%)
The Netherlands	3 (1%)	1 (1%)	2 (1%)
Denmark	2 (1%)	1 (1%)	1 (0%)
Germany	2 (1%)	2 (2%)	0 (0%)
Israel	2 (1%)	1 (1%)	1 (0%)
Lebanon	2 (1%)	0 (0%)	2 (1%)
Mexico	2 (1%)	2 (2%)	0 (0%)
Thailand	2 (1%)	2 (2%)	0 (0%)
Switzerland	1 (0%)	0 (0%)	1 (0%)
Tunisia	1 (0%)	0 (0%)	1 (0%)
Nigeria	1 (0%)	1 (1%)	0 (0%)
Portugal	1 (0%)	0 (0%)	1 (0%)
Qatar	1 (0%)	0 (0%)	1 (0%)
Romania	1 (0%)	0 (0%)	1 (0%)
Sweden	1 (0%)	0 (0%)	1 (0%)
Turkey	1 (0%)	0 (0%)	1 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

Table A6. Treatment evaluated in knowledge syntheses

	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Hydroxychloroquine	58 (11%)	15 (10%)	43 (12%)
Remdesivir	39 (8%)	11 (7%)	28 (8%)
Tocilizumab	35 (7%)	10 (7%)	25 (7%)
Corticosteroid	35 (7%)	10 (7%)	25 (7%)
Convalescent Plasma	33 (6%)	10 (7%)	23 (6%)
Lopinavir-Ritonair	24 (5%)	8 (5%)	16 (4%)
Chloroquine	19 (4%)	6 (4%)	13 (4%)
Hydroxychloroquine/Azithromycin	14 (3%)	1 (1%)	13 (4%)
Antivirals	12 (2%)	4 (3%)	8 (2%)
Anticoagulant	11 (2%)	2 (1%)	9 (2%)
Azithromycin	11 (2%)	3 (2%)	8 (2%)
Favipiravir	10 (2%)	1 (1%)	9 (2%)
Hydroxychloroquine/Chloroquine	10 (2%)	4 (3%)	6 (2%)
Colchicine	9 (2%)	2 (1%)	7 (2%)
Dexamethasone	9 (2%)	1 (1%)	8 (2%)
Arbidol	7 (1%)	1 (1%)	6 (2%)
Invermectin	7 (1%)	3 (2%)	4 (1%)
Glucocorticoid	7 (1%)	3 (2%)	4 (1%)
Acei/Arb	6 (1%)	4 (3%)	2 (1%)
Therapeutic Anticoagulant	5 (1%)	2 (1%)	3 (1%)
Prophylactic Anticoagulant	4 (1%)	3 (2%)	1 (0%)
Anakinra	4 (1%)	3 (2%)	1 (0%)
Famotidine	4 (1%)	1 (1%)	3 (1%)
Jak-Inhibitors	4 (1%)	2 (1%)	2 (1%)
Sarilumab	4 (1%)	4 (3%)	0 (0%)
Antibiotics	3 (1%)	1 (1%)	2 (1%)
Antimalaria	3 (1%)	1 (1%)	2 (1%)
Chloroquine/Hcq/Azithromycin	3 (1%)	3 (2%)	0 (0%)
Immunomodulation Treatment	3 (1%)	1 (1%)	2 (1%)
Interferon-Beta	3 (1%)	1 (1%)	2 (1%)
Intravenous Immunoglobulin	3 (1%)	1 (1%)	2 (1%)
Methylprednisolone	3 (1%)	0 (0%)	3 (1%)
Statins	3 (1%)	0 (0%)	3 (1%)
Umifenovir	3 (1%)	0 (0%)	3 (1%)
Vitamin D	3 (1%)	1 (1%)	2 (1%)
Antiplatelets	2 (0%)	1 (1%)	1 (0%)
Antivirals/Antibiotics	2 (0%)	2 (1%)	0 (0%)
Baloxavir Marboxil	2 (0%)	0 (0%)	2 (1%)
Bromhexine	2 (0%)	1 (1%)	1 (0%)
Cell-Based Therapies	2 (0%)	1 (1%)	1 (0%)
Chloroquine/Azithromycin	2 (0%)	0 (0%)	2 (1%)
Corticosteroids/Iv Immunoglobulin/ Or Siltuximab/Tocilizumab	2 (0%)	1 (1%)	1 (0%)
Hydrocortisone	2 (0%)	0 (0%)	2 (1%)
Hyperimmune Immunoglobulin	2 (0%)	1 (1%)	1 (0%)
Immunoglobulins	2 (0%)	0 (0%)	2 (1%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Interferon-Beta-1a	2 (0%)	1 (1%)	1 (0%)
Interleukin- 6 Inhibitors	2 (0%)	0 (0%)	2 (1%)
Mesenchymal Stem Cells	2 (0%)	1 (1%)	1 (0%)
Ruxolitinib	2 (0%)	0 (0%)	2 (1%)
Tocilizumab/Sarilumab	2 (0%)	0 (0%)	2 (1%)
Acalabrutinib	1 (0%)	0 (0%)	1 (0%)
All Pharmacologicals	1 (0%)	1 (1%)	0 (0%)
Anticoagulant Therapeutic	1 (0%)	1 (1%)	0 (0%)
Antiinflammatories	1 (0%)	0 (0%)	1 (0%)
Antiretroviral	1 (0%)	0 (0%)	1 (0%)
Antirheumatic	1 (0%)	1 (1%)	0 (0%)
Antitumor	1 (0%)	0 (0%)	1 (0%)
Arbidol/Lopinavir+Ritonavir	1 (0%)	0 (0%)	1 (0%)
Aspirin	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Hcq	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Zinc	1 (0%)	0 (0%)	1 (0%)
Calcifediol	1 (0%)	0 (0%)	1 (0%)
Clazakisumab	1 (0%)	1 (1%)	0 (0%)
Convalescent Plasma Or Hyperimmune Plasma	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Antivirals	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/ Tocilizumab/Anakinra/Ivig	1 (0%)	0 (0%)	1 (0%)
Cytokine Therapy	1 (0%)	0 (0%)	1 (0%)
Dpp-4 Inhibitor	1 (0%)	1 (1%)	0 (0%)
Favipiravir/ Baloxavir Marboxil	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Other Antivirals	1 (0%)	0 (0%)	1 (0%)
Galidesivir/Sofosbuvir/Ribavirin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Azithromycin/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin/Or Lopinavir/Ritonavir	1 (0%)	1 (1%)	0 (0%)
Hydroxychloroquine/Lopinavir-Ritonair	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Hyrdocortisone	1 (0%)	0 (0%)	1 (0%)
Ibrutinib	1 (0%)	0 (0%)	1 (0%)
Ifn B-1b/ Immunomodulatory/Antivirals	1 (0%)	0 (0%)	1 (0%)
Immune Modulation Drugs	1 (0%)	0 (0%)	1 (0%)
Immune Therapy/Or Antiviral Therapy/Or Both	1 (0%)	0 (0%)	1 (0%)
Immunoglobulin	1 (0%)	0 (0%)	1 (0%)
Immunomodulation/Hcq/Cq	1 (0%)	0 (0%)	1 (0%)
Prophylaxis Coagulant	1 (0%)	1 (1%)	0 (0%)
Interferon-Beta/Rbv	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b	1 (0%)	0 (0%)	1 (0%)
Interferons	1 (0%)	0 (0%)	1 (0%)
Interleukin-6 Inhibitors	1 (0%)	1 (1%)	0 (0%)
Interleukin-6/Tocilizumab	1 (0%)	1 (1%)	0 (0%)

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Intravenous Steroids	1 (0%)	0 (0%)	1 (0%)
Jak-Inhibitor/Type I Interferon	1 (0%)	0 (0%)	1 (0%)
Levilimab	1 (0%)	1 (1%)	0 (0%)
Lopinavir	1 (0%)	1 (1%)	0 (0%)
Lopinavir-Ritonair/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Remdesivir	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Ribavirin/Interferon Beta	1 (0%)	0 (0%)	1 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)
Methylprednisone	1 (0%)	0 (0%)	1 (0%)
Neutralizing Antibody	1 (0%)	0 (0%)	1 (0%)
Nsaids	1 (0%)	0 (0%)	1 (0%)
Olokizumab	1 (0%)	1 (1%)	0 (0%)
Oseltamivir/Lopinavir/Ritonavir/Arbidol/Ribavirin/Sfjdc/ Other	1 (0%)	0 (0%)	1 (0%)
Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Recombinant Human Gcsf	1 (0%)	0 (0%)	1 (0%)
Renal Replacement Therapy/ Glucocorticoids	1 (0%)	0 (0%)	1 (0%)
Repurposed Pharmacological Agents	1 (0%)	1 (1%)	0 (0%)
Ribavirin	1 (0%)	1 (1%)	0 (0%)
Rna-Dependent Rna Polymerase	1 (0%)	0 (0%)	1 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	0 (0%)	1 (0%)
Stem Cell Therapy	1 (0%)	0 (0%)	1 (0%)
Sulodexide	1 (0%)	0 (0%)	1 (0%)
Type I Interferons	1 (0%)	0 (0%)	1 (0%)
Vitamin C	1 (0%)	0 (0%)	1 (0%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.