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European Journal of Physical and Rehabilitation Medicine
EDIZIONI MINERVA MEDICA

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European Journal of Physical and Rehabilitation Medicine 2021 Feb 18
DOI: 10.23736/S1973-9087.21.06870-2

Article type: Systematic reviews and meta-analyses

Supplementary material available online at http://www.minervamedica.it
Article first published online: February 18, 2021
Manuscript accepted: February 17, 2021
Manuscript received: February 8, 2021

Rehabilitation and COVID-19: a rapid living systematic review by Cochrane Rehabilitation Field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020

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Abstract

Background. COVID-19 infection significantly increased mortality risk and the burden of disability in most survivors, regardless of symptom severity at onset. The rehabilitation needs of people infected are receiving growing attention, as evidenced by the increasing number of publications, including those addressing the chronic consequences of infection.

Objectives. This rapid living systematic review reports the evidence published in November and December 2020 and summarises the entire body of literature on rehabilitation in COVID-19 patients published in 2020.

Methods. This update was performed using the methodology reported by the second edition conducted by Cochrane Rehabilitation REH-COVER Action. We searched PubMed, Embase, CINAHL, Scopus, Web of Science, and PEDro databases. Papers related to COVID-19 and rehabilitation were retrieved and summarised descriptively.

Results. The search retrieved 4441 studies. After the removal of duplicates and the screening for title and abstract, we retained 105 studies. Of these, we included 54 in the qualitative synthesis of this update. According to OCEBM 2011 Levels of Evidence Table, most studies (64.8%) fall within the category of Level 4 evidence. Up to 40.7% of papers included COVID-19 patients in the post-acute phase. In 2020, our rapid living systematic review included 230 studies; most of these (73.9%) were Level 4 studies, 25.7% were Level 3, and only one study was Level 2. The evidence level improved over time. While most studies (44.8%) included patients with acute COVID-19, we observed a gradual increase in the number of reports about chronic symptoms and the long-term consequences of the infection.

Conclusions. The update of the rapid living systematic review by Cochrane Rehabilitation Field demonstrates an increase in the level of evidence of studies addressing the rehabilitation needs associated with COVID-19 infection. Although most studies are still case reports/series, there is a trend towards conducting prospective investigations of the early natural history of the disease (first months post- onset). High-quality-level studies on the efficacy of rehabilitation, and long-term monitoring of the disease and its sequelae are yet to emerge.

Keywords: COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2; Coronavirus; Rehabilitation; Physical and Rehabilitation Medicine.

Introduction

In 2020, Cochrane Rehabilitation launched the REHabilitation COVID-19 Evidence-based Response (REH-COVER) action, which includes a series of rapid living systematic review of the literature. [1-8] The purpose of REH-COVER is to identify and communicate the most recent findings on COronaVIrus Disease 2019 (COVID-19) and rehabilitation (https://www.cochrane.org/news/cochrane-rehabilitation-reh-cover-rehabilitation-covid-19-evidence-based-response-action). This update of the rapid living systematic review (5th edition) reports on papers published between November and December 2020. Moreover, we provide a summary of the literature published on the topic of rehabilitation of COVID-19 patients through the entirety of 2020.

Methods

This update was performed according to the methodology reported by the second edition of the rapid living systematic review[4]. We added all eligible papers retrieved from the database search performed on January 2nd, 2021 which covered publication dates between November 1st and December 31st, 2020. We reported all results from the consolidated online table of papers included in all editions of the rapid living systematic review available on the Cochrane Rehabilitation REH-COVER action website (https://tr.im/rr_dyn).

Results

Evidence synthesis

We identified 4441 studies from the databases. After duplicates removal and title and abstract screening, we evaluated 105 studies and included 54 in the qualitative synthesis (Figure 1). Supplementary Digital Material 1: Supplementary Table I (available on the Cochrane Rehabilitation website: https://tr.im/rr_dyn) provides a detailed overview of the new evidence. The studies published in this update were conducted in the following World Health Organization Regions: 31 in Europe (8 Italy[9–16], 5 United Kingdom[17–21], 3 Spain[22–24], 2 France[25,26], 1 Austria[27], 1 Denmark[28], 1 Germany[29], 1 Ireland[30], 1 Israel[31], 1 Netherlands[32], 1 Romania[33], 2 Russia[34,35], 1 Switzerland[36], 1 Turkey[37], 1 Netherlands and Belgium[38], and 1 United Kingdom and Italy[39]), 13 in the Americas (11 United States of America[40–50], 1 in Canada[51], 1 Mexico[52]), 5 in Eastern Mediterranean (3 Iran[53–55], 1 Qatar[56], 1 Tunisia[57]), 3 in Western Pacific (China[58–60]), and 2 in South-East Asia (India[61,62]).

Evidence level of included studies

Due to the heterogeneity of published studies, a meta-analysis was not appropriate; thus, the results are described qualitatively. Based on the Oxford Centre for Evidence-Based (OCEBM) 2011 Levels of Evidence,[63] most studies (n=35, 64.8%) were Level 4 (13 case reports[20,22–26,42–44,48,50,54,62], 12 case series[9–12,14,33,34,46,47,49,55,56], and 10 historical cohort studies[17,31,36,37,40,41,51,57–59]), whereas the remainder 19 (35.2%) were Level 3 (8 cohort studies[15,19,21,27,28,32,39,60,64], 8 cross-sectional studies[13,16,18,29,30,38,45,53], 2 non-randomized controlled studies – RCTs [35,61], and 1 case-control study[52]) (Table I).

Most studies (n=39, 72.2%) investigated the natural history/determining factors of the disease (14 cohort studies[15, 17, 19,21,27,28, 31,32,39, 40,51,58,59,60] 2 cross-sectional[18,45], 1 case control study[52], 11 case reports[20,22,23,25,26,42–44,48,54,62], and 11 case series[9–12,14,33,34,46,47,49,55]). Seven papers (13%) reported

epidemiological data on disease prevalence (6 cross-sectional studies [13,16,29,30,38,53] and 1 historical cohort study[57]), and four (7.4%) described the clinical presentation of COVID-19 infection (2 case report[24,50], 1 case series[56], and 1 historical cohort study[37]). Finally, four studies investigated health service organization (2 historical cohort studies[36,41]) and intervention efficacy (2 non-RCTs[35,61]).

Clinical characteristics

Most studies (n=24, 44.4%) included COVID-19 patients in the post-acute phase[11–14,16,19,23,25,30,32,34,37,39–42,44,45,52,54,55,58,59,61], 18 in the acute phase[15,17,20–22,24,26,35,36,46–48,50,51,56,57,60,62], and 10 in the chronic phase[9,10,18,27–29,31,33,38,53], one manuscript described the late-onset consequences of COVID-19[43] , and one study reported the impact of COVID-19 on people with disability due to multiple sclerosis[49]. Seventeen studies reported on the delivery of rehabilitation care in the following settings: 8 in post-acute rehabilitation (5 specialized[12–14,16,61] and 3 general services[25,26,41]), 6 in acute care[17,20,22,35,46,60], 2 in outpatient[34,62], and one at home[40]. According to the ICF-based classification of the limitations of functioning of rehabilitation interest (LFRI), most papers (n=22; 40.7%) described the impact of COVID-19 infection on nervous system structure and related functions[11,13,15,16,19–21,23,24,26,29,33,42,43,47,49,50,55–57,59,61], sixteen (29.6%) on respiratory structures and related functions[9,10,22,27,30,32,34–36,40,48,51,54,58,60,62], ten on generic body structures and functions[14,18,25,28,31,37,38,46,52,53], three on activity limitation and participation restriction[12,39,45], one on digestive function[17], one on cardiovascular functions[44], and the remainder on health services, systems, and policies[41]. The following section summarizes the main evidence.

Epidemiology - Impairment in respiratory structures and related functions

One non-randomised controlled trial proposed a feasible rehabilitation program for acute patients in the intensive care unit (ICU)[35]. Three prospective and three historical cohort studies reported data on the natural history of patients in acute care (for a total 122 cases)[51,60], post-acute (1675 cases in total)[32,40,58], and chronic phase (145 cases)[27]. The authors reported that many post-COVID-19 patients had persistent symptoms at discharge from the ICU [60] or even at 6 [32] or 14 weeks[27] and that the risk of rehospitalisation was higher for males and patients with comorbiditiessuch as heart failure, or diabetes with complications[40]. These results highlight the need for rehabilitation care to be provided after hospital discharge[60] with extended follow-up using CT imaging and pulmonary function testing to assess the sequelae of COVID-19 fully[58]. A cross-sectional study[30] of 128 post-acute COVID-19 patients reports a high prevalence of persisting fatigue (even after physical recovery), regardless of initial disease severity. Two case series[9,10] describe lung fibrosis as a chronic consequence of COVID-19 infection. Finally, seven case report or case series described the possible evolution of patients who underwent respiratory physical therapy in the acute[22,48,62] and post-acute phase[34,54].

Epidemiology - Impairment in nervous system structures and related functions

Zhang X et al.[21] conducted a prospective cohort study of 1746 COVID-19 patients and 415,596 healthy controls which suggest that physical activity may have a protective effect on COVID-19 outcomes.

Two cohort studies reported a high percentage of neurological manifestations in acute patients, with the resulting need for longer ICU/total hospital stay[15], and a high percentage of persistent clinical and radiological abnormalities at 8-12 weeks post-admission[19]. Three cross-sectional studies reported neurological impairment in post-acute[13,16] and chronic patients[29]: cognitive fatigue,

apathy, and executive dysfunction in patients with neurological complications[16], muscle strength and performance impairment in hospitalised patients recovering from COVID-19[13], and sustained mild cognitive deficits in young patients who recovered from uncomplicated COVID-19[29].

Seven descriptive studies focused on nervous system involvement in COVID-19 patients, either as the presenting symptom or as a complication during the acute phase (e.g. stroke[47,50,56], Guillain-Barré syndrome[20], encephalitis[26], bilateral facial nerve palsy[24], or isolated symptoms such as headache, smell impairment, taste impairment, myalgia, sleep disturbance, visual loss, focal weakness, disorientation, behaviour disorders[57]). Six descriptive studies reported nervous system involvement in the post-acute phase, including stroke [23,42,55] or anxiety leading to limitations in activities of daily living[59]. Two descriptive studies reported chronic consequences of COVID-19 infection (polyneuropathy and myopathy[33]) or even late-onset complications (cerebral venous thrombosis and intracerebral hematoma) 19 days after complete recovery[43].

Kataria et al.[49] presented positive outcomes in three patients with multiple sclerosis who experienced COVID-19.

Finally, Brugliera et al.[11] described compressive nerve injuries, assessed by electromyography and electroneurography (EMG-ENG), occurring as prone positioning-related complications in seven ICU patients.

Epidemiology - Any activity limitation and participation restriction

Two studies reported that low functional status and pre-admission frailty were associated with the need for an increased level of care at discharge and with institutionalization[39,45].

One descriptive study[12] reported the feasibility of a subacute rehabilitation program for mechanically ventilated COVID-19 patients.

Epidemiology - Impairment of any other body structure and function

Five analytical studies (1115 cases) reported that dyspnoea, fatigue, weakness, loss of smell and taste, nausea and pain are the most frequently persisting symptoms after COVID-19 [18,28,38,52,53]. These results are supported by two historical cohort studies of 2674 COVID-19 patients in different disease phases[31,37]. Results reveal that it can take months for symptom to resolve, with consequent impact on the quality of life, even among non-hospitalised people who experienced mild disease in the acute phase[38]. Accordingly, follow-up evaluations are needed, and rehabilitation might be helpful even in a later phase. The remaining three descriptive papers illustrated the importance of a patient-tailored rehabilitation approach in acute[46] and post-acute phase[14,25].

Epidemiology – other papers

Two descriptive studies collected data on cardiovascular[44] and digestive function[17], respectively. Kanjwal et al.[44] reported a case of postural orthostatic tachycardia syndrome in an otherwise healthy female after a month from a mild form of COVID-19. Dawson et al.[17] described the dysphagia and functional swallow outcomes during recovery from COVID-19 in a large historical cohort. Finally, Levin et al.[41] presented the challenges and opportunities involved in adapting to a pandemic surge and the operational considerations in moving patients through the continuum of acute and post-acute care.

Micro-level – Interventions

One non-RCT suggested that structured exercise protocols be effective in the acute phase for the early rehabilitation of patients with respiratory failure[35]. Another non-RCT reported the efficacy of a 3-stage exercise protocol, delivered from the ICU stay, through the post-acute phase and up to discharge at home, to improve physical functional performance[61].

Meso level – Services

Two historical cohort studies described the challenges and opportunities involved in adapting to this pandemic and presented protocols developed to support COVID-19 throughout the continuum of acute and post-acute care[36,41].

Synthesis of the scientific literature of 2020

Based on the OCEBM 2011 Levels of Evidence[63] table, most studies included in the two living systematic reviews in 2020 were Level 4 evidence (n=170, 73.9%), 59 papers (25.7%) were Level 3 evidence, and only one was Level 2 evidence (see Table II for further details).

Evidence on rehabilitation needs in COVID-19 patients improved over the months, with Level 3 studies raising from 0% (April 2020) to 18% (May 2020) and 35.2% (present update). Unfortunately, no further Level 2 studies were identified, after the one included in the April update.[2] Cumulative month-by-month distribution of papers by evidence level is represented in Figure 2.

Most studies focused on the epidemiology of COVID-19-related rehabilitation needs, primarily reporting on the natural history/determining factors of the disease (n=114, 49.6%), clinical presentation of COVID-19 infection (n=59, 25.7%), and symptom/impairment prevalence (n=27,

11.7%). Twenty studies (8.7%) analysed data on health service organisations, while ten (4.3%) investigated intervention efficacy. We found no evidence on rehabilitation needs at the system level (macro-level).

Most studies (n=103, 44.8%) included COVID-19 patients in the acute phase, decreasing from 60% in April 2020[2] to 20% in the current update; 78 papers concerned the post-acute phase (33.9%), increasing from 40% in April 2020[2] to 44.4% now. Eleven studies included COVID-19 patients in the chronic phase (4.8%), with a percentage growing from 0% in April 2020[2] to 18.5% now. Two manuscripts described the late-onset consequences of COVID-19 (0.9%), first appearing in the October update[8]. Finally, fifteen studies (6.5%) reported the impact of COVID-19 infection on people with pre-existing disability, included in July 2020[5] and this update. In 9% of the studies, the COVID-19 phase was not applicable.

Discussion

This rapid living systematic review by Cochrane Rehabilitation REH-COVER Action presents the evidence available in the last two months of 2020, shedding light on the trends and content of the scientific research addressing rehabilitation needs and COVID-19 from the start of the pandemic to December 31st, 2020.

The following key points are emphasised:

1) *Level of evidence*

Over the course of 2020, we observed a shift in the level of evidence from the prevalence of expert opinions (when original reports were still missing) to the growing availability of primary studies, which reached the total number of 230 by the end of the year. The proportion of case reports and case series (almost all papers published in the first four

months of 2020), has progressively decreased with an increase of historical cohorts and analytical studies collecting data from large samples. Concurrently, the proportion of OCEBM 2011[63] Level 3 studies increased to 35.2% in the current update compared to the October 2020 update (22.7%)[8], with a decreasing number of OCEBM 2011[63] Level 4 studies (64.8% vs 77.2%). The main limitation is still reflected by the substantial lack of evidence from high-level analytical studies and clinical trials.

2) *Geographical area of interest*

Most papers (n=31) included in this update were conducted in Europe, consistent with previous rapid living systematic reviews. Overall, in 2020, 116 (50.4%) papers described COVID-19 patients from the European Region, 66 (28.7%) from Americas, 31 (13.5%) from Western Pacific, 11 (4.8%) from Eastern Mediterranean Regions, 6 (2.6%) from the South-East Asia Region. This trend was consistent throughout 2020. The highest number of papers on COVID-19 and rehabilitation in 2020 was produced in the USA (n=54; 23.4%) and Italy (n=50; 21.7%), i.e. two Countries most affected by the pandemic. The interpretation of epidemiological data should consider that more than 80% papers come from high-income countries; the outcomes described may not represent rehabilitation needs in COVID-19 patients in other geographical areas.

3) *Research question*

Most (72.2%) studies included in the present update investigated the natural history/determining factors of COVID-19, and 13% reported epidemiological data on disease prevalence. Looking at the retrieved literature, half (114 of 230 papers) collected epidemiological data, primarily about the natural history/determining factors of the disease, whereas 25.7% papers described the clinical presentation of COVID-19.

4) *COVID-19 phases*

Most studies (44.4%) included COVID-19 patients in the post-acute phase. However, consistent with a pattern evident in the October 2020 update[8], a growing number of studies described the chronic consequences of COVID-19 with one study reporting on late-onset complications. Overall, in 2020, the research progressively shifted from the description of COVID-19 related disability in the acute phase (accounting for 44.8% of total papers published in 2020), to the complications occurring in the post-acute (33.9%) and chronic phases (4.8%). Moreover, studies started to describe possible risk factors for unfavourable outcome. Finally, two studies (0.9%) reported late-onset consequences of COVID-19, thus shedding light on the severe consequences of COVID-19 infection on long-lasting activity limitations and participation restrictions.

5) *Characterisation of LFRI*

About 71% of papers included in the present update described the impact of COVID-19 infection on nervous system structure and related functions (40.7%) or respiratory structures and related functions (29.6%). These findings are in line with the picture emerging from the descriptive and analytical studies published in 2020 and included in all the rapid living systematic reviews. In particular, a high risk has been shown in physically recovered COVID-19 patients of developing neurological complications (e.g. stroke, Guillain Barré, polyneuropathy, myopathy, dysphagia, aphasia, encephalitis, critical illness neuro-myopathy, palsy of the third and the seventh cranial nerves etc.), respiratory complications (e.g. persistent dyspnoea or lung fibrosis), and not specific symptoms (e.g. fatigue, pain, cognitive impairment, paraesthesia, loss of smell and taste, and nausea). In this regard, this update included papers describing persisting symptoms up to 14 weeks after COVID-19 infection[32,27] and reporting a risk of rehospitalisation higher for males and patients with comorbidities[40]. Overall, the evidence about the chronic sequelae or late-onset

complications of COVID-19 is still sparse, demonstrating the need for studies on chronic evolution.

6) *Prognosis of COVID-19 outcomes*

The current update included a prospective study,[21] that associated history of intense physical activity to more favourable COVID-19 outcomes in a broad cohort of 1746 participants. Overall, scientific literature available in 2020, pointed out several poor prognostic factors for COVID-19 patients, including male sex, pre-existing vascular risk factor, previous cortical strokes, low body mass index, prolonged immobilisation, long length of stay in intensive care unit and COVID-19 clinical severity.

7) *Efficacy of rehabilitation approaches*

The lack of RCTs or quasi-RCTs remains a major limitation of the currently available evidence. This shortcoming limits our understanding of the efficacy of specific rehabilitation approaches in COVID-19 patients. Only 10 out of 230 studies focused on COVID-19 outcomes at the micro-level (4.3%): they included one RCT, two non-randomised trials, five prospective cohort studies, one historical cohort study, and one case report. These papers conclude that specific rehabilitation protocols are needed to support patients recovering from COVID-19 from the early phase of hospitalisation to post-acute care. Readers should exercise caution in applying prone positioning, as it may be a risk factor for compression neuropathies unless performed by experienced health professionals.

In conclusion, this update of the rapid living systematic review on rehabilitation needs and COVID-19 supports the scientific community's high interest in the sequelae of COVID-19 in the short- and medium-term. Accumulating evidence highlights the risk of persistent health needs in COVID-19 survivors up to 4-5 months of infection. The lack of high-level analytical studies and RCTs or quasi

RCTs continues to be the main limitation. Data on the long-term consequences of COVID-19 and the efficacy of specific rehabilitation approaches in the acute and post-acute phase are needed.

Acknowledgements

None.

Conflicts of interest

All authors declare no conflict of interests, funding sources or consultant relationships with any organisations involved in this research.

Authors' contributions

Alessandro de Sire and Elisa Andrenelli equally contributed to this work as first authors.

Database searching: Stefano G. Lazzarini and Michele Patrini; Study selection and data extraction: Alessandro de Sire, Elisa Andrenelli, Francesco Negrini, Stefano G. Lazzarini, and Michele Patrini; Data analysis and interpretation: Alessandro de Sire and Elisa Andrenelli; Manuscript drafting: Alessandro de Sire and Elisa Andrenelli; Study supervision: Maria G. Ceravolo; Critical revision: Alessandro de Sire, Elisa Andrenelli, Francesco Negrini, Stefano G. Lazzarini, Michele Patrini, Maria G. Ceravolo and the International Multiprofessional Steering Committee of Cochrane Rehabilitation REH-COVER action. Study submission: Francesco Negrini. All authors read and approved the final version of the manuscript.

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Figures and Tables legend

Table I. Level of evidence of the studies included in the present rapid living systematic review.

Table II. Level of evidence of the included studies during 2020.

Figure 1. PRISMA Flow diagram.

Figure 2. Month-by-month distribution of the Levels of Evidence (according to the OCEBM 2011[63]) of the included studies during 2020.

Tables

Table I. Level of evidence of the studies included in the present rapid living systematic review.

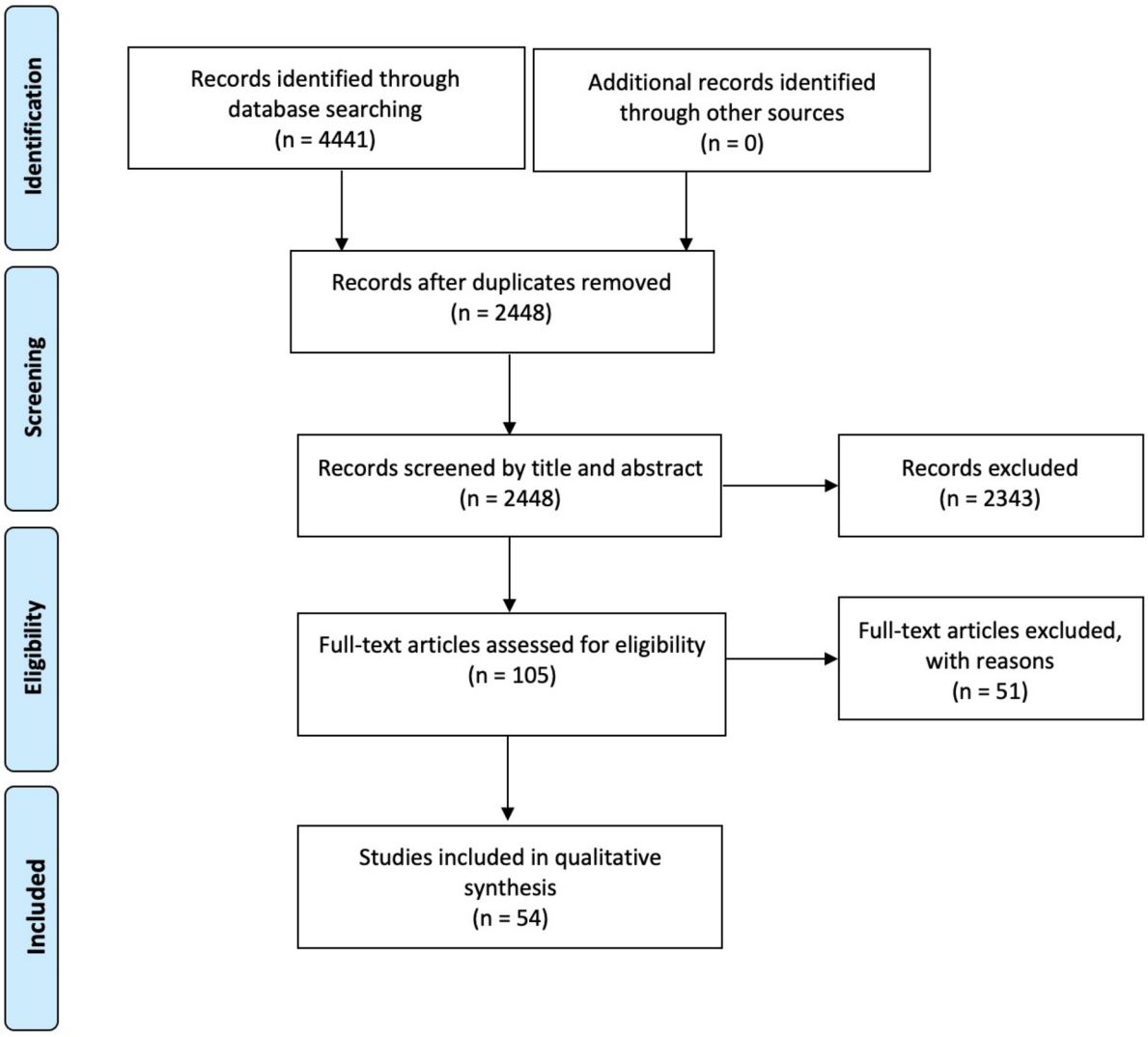
	Level 1	**Level 2**	**Level 3**	**Level 4**	**Total**
Epidemiology - Clinical presentation	0	0	0	4 (7.4%)	**4 (7.4%)**
Epidemiology – Prevalence	0	0	6 (11.1%)	1 (1.9%)	**7 (13%)**
Epidemiology - Natural history / Determining and modifying factors	0	0	11 (20.4%)	28 (51.9%)	**39 (72.2%)**

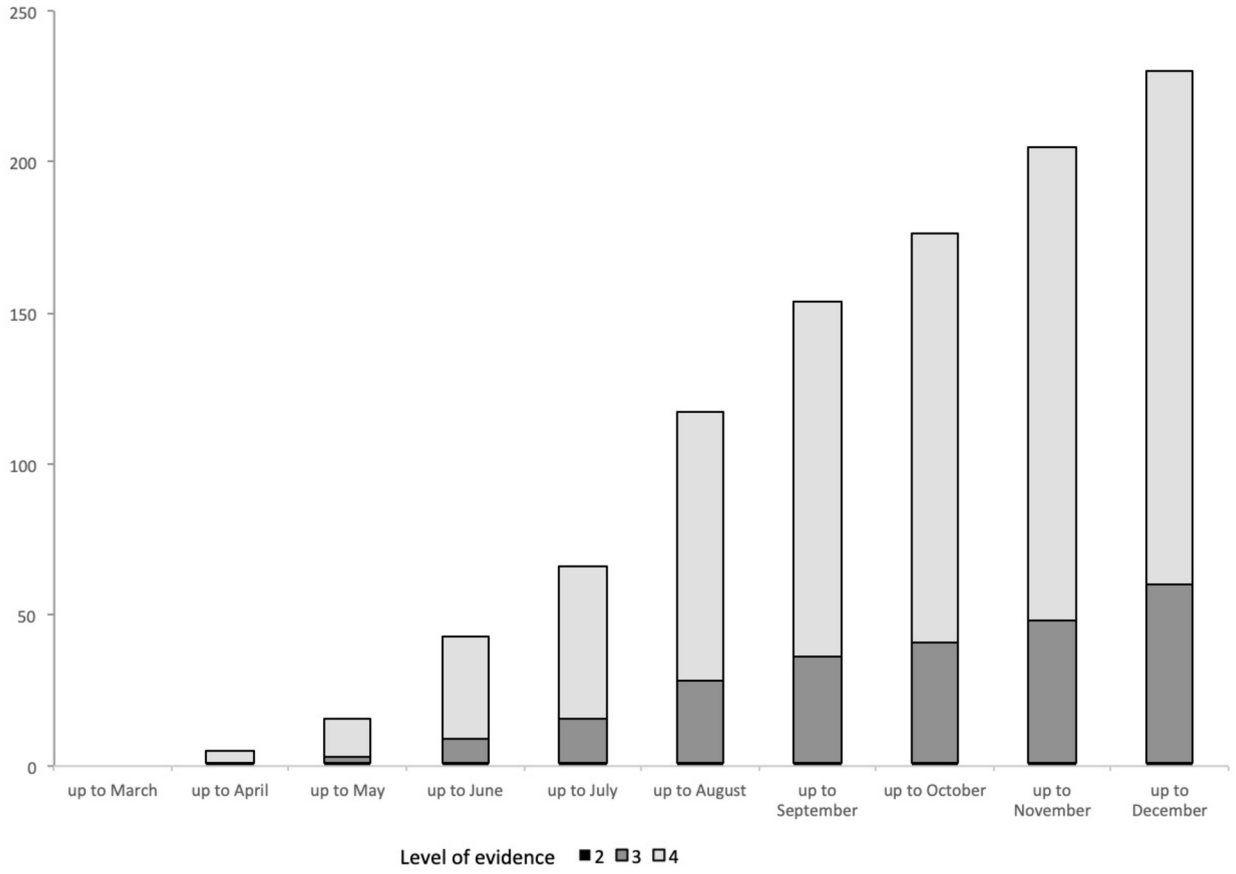
Micro – Interventions (efficacy/harms)	0	0	2 (3.7%)	0	**2 (3.7%)**
Meso Level	0	0	0	2 (3.7%)	**2 (3.7%)**
Macro Level	0	0	0	0	**0**
Total	**0**	**0**	**19 (35.2%)**	**35 (64.8%)**	**54 (100%)**

Table II. Level of evidence of the included studies during 2020.

	Level 1	**Level 2**	**Level 3**	**Level 4**	**Total**
Epidemiology - Clinical presentation	0	0	3 (1.3%)	56 (24.3%)	**59 (25.7%)**
Epidemiology – Prevalence	0	0	19 (8.3%)	8 (3.5%)	**27 (11.7%)**
Epidemiology - Natural history / Determining and modifying factors	0	0	25 (10.9%)	89 (38.7%)	**114 (49.6%)**

Micro – Interventions (efficacy/harms)	0	1 (0.4%)	7 (3.0%)	2 (0.9%)	**10 (4.3%)**
Meso Level	0	0	5 (2.2%)	15 (6.5%)	**20 (8.7%)**
Macro Level	0	0	0	0	**0**
Total	**0**	**1 (0.4%)**	**59 (25.7%)**	**170 (73.9%)**	**230 (100%)**





Supplementary Digital Material

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