Review paper

Complications after COVID-19 – review of scientific reports and meta-analysis

Powikłania po COVID-19 – przegląd doniesień naukowych i metaanaliza

Miłosz Opuchlik, Anna Maria Opuchlik, Arkadiusz Żurawski, Magdalena Zabojszcz, Małgorzata Biskup, Kamil Markowski, Zbigniew Śliwiński

Collegium Medicum, Jan Kochanowski University, Kielce, Poland

Medical Studies/Studia Medyczne 2024; 40 (2): 225–239
DOI: https://doi.org/10.5114/ms.2024.140984

Key words: respiratory diseases, cardiovascular complications, neurological complications, COVID-19, vascular thrombosis.

Słowa kluczowe: choroby układu oddechowego, powikłania sercowo-naczyniowe, powikłania neurologiczne, COVID-19, zakrzepica naczyniowa.

Abstract

Introduction: The typical complications considered in the paper include cardiovascular, neurological, respiratory, and vascular thrombosis-related complications.
Aim of the research: To analyse the complications induced by COVID-19.
Material and methods: The authors performed a thorough systematic review in databases related to COVID complications, as well as scientific articles and publications. The analysis focused on original research on post-COVID-19 complications, which was an inclusion criterion. Among the papers selected for analysis were surveys that involved patients who had undergone COVID-19 infection and related complications. Many papers were cross-sectional studies. Most studies used the PAPI questionnaire, which is the most common research method when quantitative techniques are concerned. The studies were analysed using a meta-analysis involving a PRISMA method.
Results: The studies indicated a correlation between the incidence of COVID-19 and the complications that arose from it.
Conclusions: The results obtained suggest multifaceted monitoring of post-COVID-19 complications in the longer term.

Streszczenie

Wprowadzenie: Typowe powikłania rozważane w artykule to: powikłania sercowo-naczyniowe, neurologiczne, oddechowe i naczyniowe związane z zakrzepicą.
Cel pracy: Analiza powikłań spowodowanych przez COVID-19.
Materiał i metody: Autorzy dokonali systematycznego przeglądu w bazach danych związanych z powikłaniami COVID, a także artykułów i publikacji naukowych. Analiza koncentrowała się na oryginalnych badaniach nad powikłaniami po COVID-19, które stanowiły kryterium włączenia. Wśród artykułów wybranych do analizy znalazły się ankiety z udziałem pacjentów po zakażeniu COVID-19 i związanych z tym powikłaniach. Wiele prac było badaniami przekrojowymi. W większości badań stosowano kwestionariusz PAPI, który jest najczęstszą metodą badawczą w przypadku technik ilościowych. Badania analizowano za pomocą metaanalizy z wykorzystaniem metody PRISMA.
Wyniki: Badania wykazały korelację między częstością występowania COVID-19 i wynikającymi z niego powikłaniami.
Wnioski: Uzyskane wyniki sugerują wieloaspektowe monitorowanie powikłań po COVID-19 w dłuższej perspektywie.

Introduction

The COVID-19 pandemic caused by SARS-CoV-2, which has proven to be one of the most dangerous infectious diseases, has had an impact on society in every country. SARS-CoV-2 is still under monitoring worldwide. New studies and meta-analyses regularly emerge that provide insight into the complications induced by COVID-19, the number of persons affected, and who is at risk of developing these complications. Current data indicate that approximately 14% of patients had a severe course of the disease, and in 5% it was critical. Meanwhile, it has been found to date that 37% of those infected develop what is known as long COVID, which is defined as a condition in which at least one ailment related to COVID-19 infection develops within 3 months of infection. Disturbing symptoms can occur while the disease is still present or after recovery. A study in China found that 49% of respondents experienced negative consequences

of COVID-19; in contrast, data from Bergen, Norway, reported 52% of individuals [1]. A review conducted in May 2021 by scientists from Stanford University shed a different light on the complications of COVID-19 when they found that symptoms of the disease persisted in up to 70% of patients in the first months after recovery [2]. Complications of COVID-19 do not only affect hospitalised patients. Those who have had a mild course of the disease are also exposed to its negative effects. The risk group includes mainly elderly patients and those with comorbidities (e.g. bronchial asthma, chronic obstructive pulmonary disease), patients undergoing immunosuppressive treatment, and those who developed severe symptoms in the first week of the disease. In the spring of 2020, during the first wave of the COVID-19 pandemic, doctors expected mainly respiratory ailments. It soon became apparent that complications of the new disease affected not only the lungs, but also the cardiovascular system (myocarditis, heart rhythm disturbances, e.g. accelerated heartbeat, irregular heartbeat, inflammatory changes in the blood vessels, hypertension, acute coronary syndrome). A particularly serious hazard after COVID-19 is thromboembolic complications. These are characterised by the formation of clots in the deep venous system, which can result in stroke, myocardial infarction, or pulmonary embolism. Neurological complications also occur after COVID-19. These include memory and concentration problems. Researchers recognise that following coronavirus there is an increased risk of Alzheimer's disease or other neurological conditions. Other nervous system consequences of COVID-19 include recurrent headaches, dizziness, impaired consciousness, sleep disorders, depression, encephalitis, and symptoms of post-traumatic stress disorder. It is highlighted that complications after COVID-19 are common. Some people observe mild symptoms that resolve spontaneously after some time. However, serious health effects that require immediate treatment do occur. SARS-CoV-2 infection does not end in the acute phase but becomes chronic or gives long-term complications. This demonstrates that it is a multi-system and multi-organ disease. Studies of patients have provided insight into the many mechanisms of complications. It has been found that receptors called ACE2 and TMPRSS2, which are used by SARS-CoV-2 for cell entry, are widespread also in human cells. PCR testing revealed the presence of viral RNA in various tissues, which implies that SARS-CoV-2 may infect cells outside the respiratory system, although direct evidence of such infection is still limited. A possible cause of complications may be an infection-related uncontrolled immune response. At the beginning of the pandemic, thrombus-induced obstruction of large vessels in the lungs and limbs was observed in intensive care unit patients in China, France, or Italy. According to some studies, the problem may have affected almost half of all critically ill patients. Later studies showed in many COVID-19 patients the presence of clots also in the small arteries and capillaries of the lungs, as well as in the vessels of other organs such as the heart, kidneys, brain, and liver. In severely ill patients, high levels of D-dimers, which are protein fragments that signal the presence of clots, were detected. Post-COVID complications can affect anyone who has contracted COVID-19.

Aim of the research

The aim of this study is to analyse complications after COVID-19. The authors of the article set out to examine the following issues: to what extent did the disease caused by the SARS-CoV-2 virus affect the health of a given person, what complications occurred after COVID-19, and which complications were the most common? The authors wanted to determine how and in what context COVID-19 influenced cardiac, neurological, and respiratory complications, and vascular thrombosis. For the purposes of this article, systematic reviews and meta-analyses were reported using the PRISMA method, which, although it is not an instrument for assessing the quality of systematic reviews, is useful for conducting a critical assessment. The analysis of the effects of the COVID-19 pandemic on human health became important. Due to the relatively short duration of the pandemic, there is a lack of comprehensive data that could allow for the assessment of long-term health effects.

The topic of the article regarding post-COVID complications was considered very topical, because the COVID-19 pandemic itself is the largest public health crisis in the last 100 years. It was caused by a factor previously unknown to humans. There was no population immunity to infection and no effective vaccine or specialised treatment available. This intensified the scale of threat and fear. The pandemic affected every region of the world, not only in terms of socioeconomic and political disadvantages, but perhaps the most concerning is its effects on human health. Whilst the Word Health Organisation has ended the pandemic status in many parts of the world, SARS-CoV-2 still poses a threat to health. It is and will be felt for years, even when no new infections are reported. It has far-reaching effects on health and social life, politics, and the economy. The COVID-19 pandemic is an event that tested our ability to cope with a global health crisis in an unprecedented way. It has become a huge challenge for the health system, for medical, social, and economic reasons. Some of the negative effects of the pandemic are still unknown and may only become apparent in the future. It may result from the development of diseases and health problems whose treatment, diagnosis, and rehabilitation have been limited during the pandemic. The most dangerous may be the long-term effects

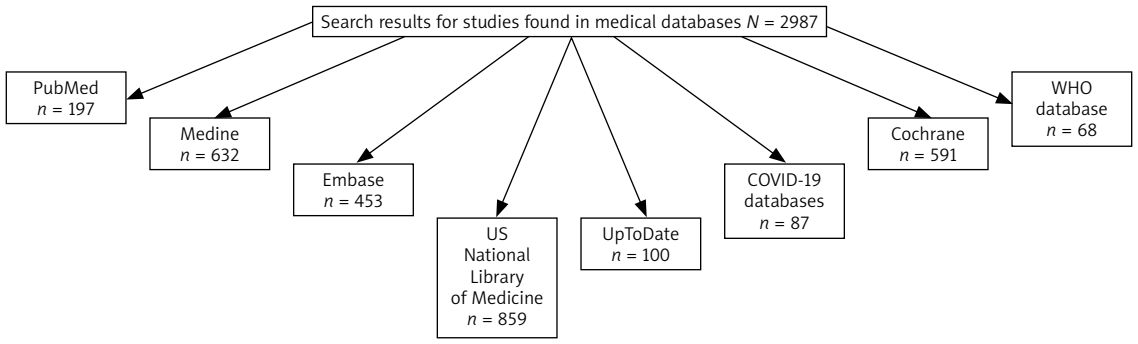

Figure 1. Characteristics of the literature search strategy

of SARS-CoV-2 infection in the form of the so-called long COVID-19. Post-COVIDovid health effects determine the need to prepare and possibly reorganise the health care system to serve rehabilitation after COVID-19 as effectively as possible, as well as the diagnosis and treatment of adult patients with long COVID-19 syndrome and children with multisystem inflammatory syndrome [3, 4]. A particular difficulty and challenge is related to the fact that long COVID, as the knowledge acquired so far indicates, is total in nature and can affect almost every system in the body and manifest themselves in the form of newly developed heart diseases, kidney diseases, diabetes, and mental health disorders [5, 6].

Material and methods

Papers published as full texts, reports, and conference reports were included in the review. The search for clinical trials followed a detailed protocol developed prior to the start of the systematic review work. The results of searches for studies found in medical databases (n = 2987) are shown in Figure 1. This incorporated the inclusion and exclusion criteria for studies in the review (Figure 2), the search strategy, the method of study selection, and the planned methodology for performing data analysis and synthesis. Inclusion criteria are presented in Table 1. To find scientific reports that could meet the inclusion criteria for the systematic review, the following were used: electronic medical information databases, to which the search strategy was implemented, references of scientific reports found, and registers of clinical trials. A description of selected studies in chronological order is included in Table 2. The selection of identified publications was performed in 2 steps at all stages: verification at the level of abstracts and titles (stage I) was performed in such a way that all reports considered useful were included in the next phase; stage II concerned the discrepancies of opinion in the course of reviewing studies based on the full texts of the reports. The following analytical tools were used to compile the results: MS Excel 2007/2010 [7] and Sophie v. 1.5.0 (meta-analysis software developed by the HTA Consulting team verified with STATA v. 10.0) [7]. The paper compiles primary and secondary studies identified through a systematic review of scientific reports to show complications as consequences after COVID-19. A systematic review of medical information databases was conducted: PubMed (197), Medline (632), Embase (453), US National Library of Medicine (859), WHO database (68), COVID-19 database (87), UpToDate (100), Cochrane (591), and COVID-19 database resources were also used (87).

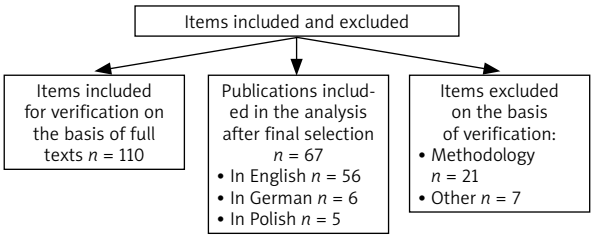

Figure 2. Characteristics of included and excluded items

To find reports not yet published in the abovementioned databases, a review of the pre-print pub-

Table 1. Presentation of inclusion criteria

Population	Patients with cardiac, neurological, and respiratory complications and vascular thrombosis
Intervention	Complication version
Comparator	Not defined
Endpoint	Defined endpoints for complications after COVID-19
Type of studies included	Single-arm studies with a group of patients who developed complications after COVID-19 Observation studies (≥ 80 persons)

Table 2. Description of selected studies in chronological order

Author, date, country of origin	Publication type	Surveyed	Research instruments	Analysis of variables	Cardiac complications	Neurological complications	Respiratory complications	Vascular thrombosis-related complications
Matrejek. *et al.* (2021), Poland	CS	N = 543	Analysis sheet, observation sheet	Types of complications	–	–	–	*N* = 321
Moroni *et al.* (2020) (2021), Italy	CS	N = 3043	Computer programs	Types of complications	–	–	*N* = 2875	–
Levi. *et al.* (2020), (2021), USA	CS	N = 1543	Observation sheet	Types of complications	*N* = 912	–	–	–
Singh *et al.* (2020)	CS	N = 722	Analysis sheet	Types of complications	–	–	–	*N* = 301
Rist *et al.*	CS	N = 100	Survey questionnaire	Types of complications	–	*N* = 421	–	–
Tomazini *et al.* (2020) (2021), Italy	CS	N = 300	Survey questionnaire	Types of complications	*N* = 601	*N* = 287	*N* = 2043	*N* = 69
Wade (2020) England	CS	N = 2298	Survey questionnaire	Types of complications	–	–	N = 1629	–
Zhau *et al.* (2020), China	CS	N = 1054	Survey questionnaire	Types of complications	–	*N* = 6148	–	–
Zhou *et al.* (2020). China	CS	N = 6213	Survey questionnaire	Types of complications	–	N = 1816	*N* = 4397	–

lication database – www.medrxiv.org – was also performed, narrowing the search to the period 1.07.2020–28.07.2020. An update search for the review version, including medical information databases: PubMed by Medline, U.S. National Library of Medicine and EMBASE, was performed on 17.12.2022. The total number of studies found in medical databases was 2987. Studies with meta-analyses published after the date of the earlier review of reports for complications as consequences of COVID-19 were included in the analysis. The process of selecting reports, with reasons for exclusion in subsequent selection steps, was presented in accordance with the recommendations of the journal [8], and it is characterised in Table 3. The systematic review allows js to perform a more accurate assessment of the severity of complications after COVID-19, as well as a broader investigation of the impact of COVID-19 on diseases such as thrombosis, myocardial infarction, respiratory disease, and neurological complications. By taking a comprehensive approach, it is believed that the collected research will allow the development of effective interventions for the treatment of post-COVID effects in the near future. For the study, 8 academic databases with published scientific articles were analysed. The authors examined 110 articles that addressed complications following COVID-19, which were narrowed down to the following: cardiovascular, neurological, respiratory, and vascular thrombosis complications. Studies that involved 7032 hospitalised patients were analysed. Initial results were traced using different combinations of keywords such as COVID-19, cardiovascular complications, myocardial infarction, cardiovascular disease, vascular thrombosis, respiratory disease, and neurological complications. In the next step, articles that met the specified criteria were analysed. A review of the literature available in the selected databases yielded 679 hits, from which 2987 papers on COVID-19 and post-COVID complications were found, some of which contained incomplete articles, even though they included key words. To eliminate unrelated publications, the search was narrowed to those that contained keyword combinations related to post-COVID complications, including: cardiovascular and cardiovascular disease (16 articles), vascular thrombosis complications (22), respiratory complications (43), and neurological complications (19). One hundred and ten articles were retrieved that were directly relevant to the issues discussed. The search results were restricted to original studies covering complications after COVID-19, and 21 articles that did not meet the authors' expectations because they did not contain comprehensive studies were excluded. Publications listed in the literature of the identified articles were assessed for relevance. For each study, the authors, year of publication, study population size, main results, and conclusions were identified. Incomplete studies in which no information on the methodol-

Table 3. Excluded secondary studies

Item	Author	Title	Description
1	Huang (2020)	Treatments Administered to the First 9152 reported Ceases of COVID-19: A systemic Review	No details of included studies
2	Ghosh (2020)	Efficacy of Corticosteroids in Non-Intensive Care Unit Patients with COVID-19 Pneumonia from the New York Metropolitan.	More recent review available
3	Majmundar (2020)	Efficacy of Corticosteroids in Non-Intensive Care Unit Patients with COVID-19 Pneumonia from the New York Metropolita	No details of included studies
4	Li (2020)	Risk Factors for Severity and Mortality in Adult COVID-19 Inpatients in Wuhan. Journal of Allergy and Clinical Immunology	Non-systematic review
5	Lopes (2020)	Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–The BRACECORONA	More recent review available
6	Rosenthal (2020)	Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19.	Non-systematic review
7	Wei (2020)	Clinical characteristics and manifestations in older patients with COVID-19.	No details of included studies

Table 4. Presentation of reliability levels

Level	Description
A	Results of ≥ 1 correctly designed RCTs, average reliability of sample representativeness results Meta-analysis of correctly designed RCTs Results of ≥ 1 RECTs supplemented with medium quality registers data
B	Correct design of RCT, average reliability of results
C	Correctly designed sample of results ≤ 2 limitations of reliability of results, modified analysis of results
D	Correctly designed clinical trial Correctly designed cohort study Correctly designed register Meta-analysis of studies
E	Randomised or non-randomised trials ≥ 2 methodological limitations Observational studies with methodological limitations

Table 5. Population characteristics including complications, age, and level of reliability

Item	Type of complications after COVID-19	Research arm (N)	Type of endpoints analysed	Reliability level
1	Cardiac	979	SoC, TOC, IRU	C
2	Neurological	1795	SoC, TOC	C
3	Respiratory system	2191	TOC, IRU	E
4	Vascular thrombosis	1181	SoC, TOC	E

ogy was provided were excluded. Seven articles were excluded because no English or German version was available. After final selection, 67 papers remained, which satisfactorily met the inclusion criteria. For the purpose of the study, reliability levels (based on the Guideline on the Primary Prevention of Cardiovascular disease approach) are presented in Table 4 to obtain the highest possible results. In contrast, population characteristics including complications, age, and credibility level are included in Table 5.

Narrowing down the results based on analyses of the methods used in the articles provided 24 search results. The studies were grouped according to the occurrence of the most common complications (Table 6).

Figures 1 and 2 describe the process of selecting publications for a systematic review according to PRISMA (search 12–22/12/2022).

???????????????????????? Population (P) – patients after COVID-19 treatment. Population (P) – patients after COVID-19. Intervention (I) complications af-

Table 6. Population presentation: age, complications, and course of disease

Age [years]	Complications following COVID-19 (studied on a population of *N* = 7032)											
	Complications investigated				Severe course				Mild course			
	CC *N* (%)	NC *N* (%)	RC *N* (%)	VTC *N* (%)	CC (*N*)	NC (*N*)	RC (*N*)	VTC (*N*)	CC (*N*)	NC (*N*)	RC (*N*)	VTC (N)
30-40	65 (0.92)	561 (7.97)	5519 (78)	884 (12.57)	21	39	101	43	863	522	5418	22
40-50	1556 (22.1)	754 (10.72v	3590 (51.05)	1132 (16.09)	100	73	1086	641	1456	681	2524	491
50-60	397 (5.64)	602 (8.56)	5008 (71.21)	1025 (14.57)	364	121	3214	165	661	481	1794	232
60-70	687 (9.48)	250 (3.52v	1874 (26.64)	2143 (30.47)	412	73	158	498	273	48	287	1645
≥ 70	1461 (20.77)	896 (12.74)	3197 (45.46)	1478 (21.01)	953	253	2265	1007	508	643	932	471

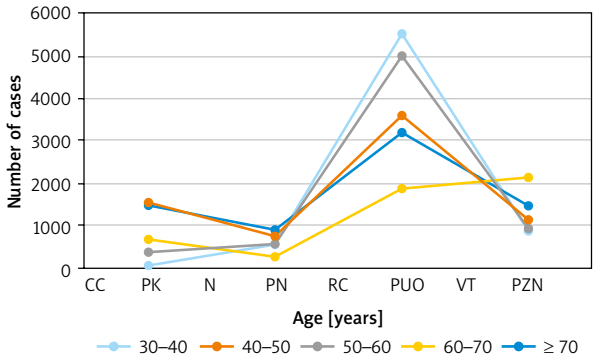

Figure 3. Chart of complications after COVID-19 for a specific age range

ter COVID-19. Intervention types of complications. Comparator (C) – limited to 4 complications. Systematic reviews, meta-analyses, clinical trials. A total of 18 systematic reviews from the search (Kattar 2020, Rooney 2020??????????????????????) were included in the analysis; 2 RCTs/single-arm studies from the search (Puncher 2021??????????????????, Liu 2020) and RCTs/single-arm studies from the secondary evidence bibliography (Hermann 2020, Sinha 2020, Altundag 2015, Konstantinidis 2020?????????????????? ??????????????????????).

Method description

To find the optimal method or tool to study complications after COVID-19, the authors used the PRISMA method (preferred reporting items for systematic and meta-analyses). It allowed presentation of reviews evaluating the effects of interventions and was used to report systematic reviews with objectives other than the evaluation of interventions. The PRISMA method became helpful for the correct reporting of systematic reviews, meta-analyses, and randomised trials related to complications after COVID-19. Its application was limited to the following research stages: formulation of research questions, development of a literature search strategy and search of bibliographic databases, selection of studies for review based on predefined inclusion and exclusion criteria (in the first stage, on the basis of titles and abstracts; in the second stage, on the basis of analysis of full texts of publications), data extraction, analysis, and interpretation. All studies of information needs, related to complications after COVID-19, in which the assessed population consisted of patients in the selected age ranges, were included in the review: 30–40, 40–50, 50–60, and ≥ 70 years old between 2020 and 2021. The predominant complications after COVID-19 in the defined age range are presented in Figure 3. The characteristics of the population, taking into account the age of the patients, the type of complications, as well as its course after COVID-19, are included in Table 6. Table 7, on the other hand, characterises the population, type of complications, type of endpoints analysed, and level of reliability. Both primary studies (studies of a qualitative and quantitative nature) and those based on secondary data analysis were included in the review. Studies had to accurately describe the method used or created to gather information on complications related to COVID-19. However, studies that addressed complications other than cardiovascular, neurological, or respiratory or vascular thrombosis were eliminated from the review. The following information was extracted in detail from each study: author of the publication, year of the publication, country in which the study was conducted, research method and data collection technique, and technique/method of meta-analysis of results. In addition, the rationale and purpose for conducting the study and the theories and methodological approaches used were analysed. The synthesis of the data from the independent primary studies allowed the conclusions from the single

Table 7. Description of methodology, number of primary studies, and quality assessment

Methodology	Number of primary studies	Quality assessment acc. to PRISMA
A systematic review with meta-analysis. Inclusion criteria: randomised clinical trials (RCTs), cohort studies and case-control studies comparing COVID-19 patients with cardiac, neurological, thrombotic and respiratory complications. The included studies were assessed with the use of: Cochrane risk-of-bias tool for RCT studies, NOS Scale for observational studies, ROBIS risk-of-bias tool for systematic reviews. The quality of evidence was assessed using the PRISMA tool.	Only results relating to COVID-19 are analysed and described in this paper. Of the studies included in the review, 16 involved population with COVID-19, all of which were cohort studies 2020: for population N = 7032	Moderate quality
Meta-analysis - patients suffering from COVID-19. Inclusion criteria: separate results for patients with post-COVID complications, COVID-19 infection study; vascular thrombosis occurred due to coronavirus infection. Review publications, single case reports and publications that did not report separate results were not included in the study. The Cochrane Collaboration tool was used to assess the included studies. Risk of bias was assessed using 'funnel plots' and PRISMA.	In this paper, only the results related to COVID-19 were analysed and described. Forty-five studies were found that met the inclusion criteria and were included in the review. Of these, four studies did not sufficiently address complications after COVID-19 (cohort studies, N = 4111).	Moderate quality
A systematic review with meta-analysis. Inclusion criteria: Patients diagnosed with COVID-19. Respiratory complications including duration of pneumonia, duration of hospitalisation, duration of fever and other adverse events. Only studies published in English or German, full-text publications were included. Conference abstracts and studies in which necessary information was omitted were not included in the review. The quality of evidence was assessed using the Prisma tool.	In this paper, only results related to COVID-19 were analysed and described. Forty-three studies meeting the inclusion criteria were found and included in the review. Of these, five studies (cohort studies) involved patients with COVID-19: 2020 all grades of disease, N = 6906, mild disease course N = 2002. Severe disease course: N = 3432 including very severe disease course: N = 1472	High quality
A systematic review with meta-analysis. Inclusion criteria: randomised clinical trials (RCTs), cohort studies and case-control studies comparing COVID-19 patients with cardiovascular complications. To assess the included studies, the following were used: Cochrane risk-of-bias tool for RCT studies, NOS scale for observational studies, ROBIS risk-of-bias tool for systematic reviews. The quality of evidence was assessed using the PRISMA tool.	In this study, 16 articles were analysed and only results related to COVID-19 were described. Of the studies included in the review, six were on populations with COVID-19, all of which were cohort studies: the 2020 study for the COVID-19 population (N = 2979). The analysis included hospitalised patients with COVID-19 between 1 February 2020 and 30 April 2021.	Moderate quality
A review with meta-analysis regarding patients with neurological diseases and complications due to COVID-19 infection. Inclusion criteria: No access to the appendix where the description was provided. No information available on the tools used to assess the included studies.	In this study, nineteen articles were analysed and only results related to COVID-19 were described. Ten of the studies included in the review focused on the COVID-19 population, all of which were cohort studies: the 2020 study for the COVID-19 population (*N* = 1795). The analysis included patients hospitalised from 23 March 2021 to 23 March 2022.	Moderate quality

studies to be extended to the wider population. This method allowed us to perform a critical appraisal against the correct reporting of systematic reviews.

Presentation of accepted scientific evidence. A – Results of > 1 correctly designed RCT, medium to high reliability of results (sample representativeness, ITT, blinding, appropriate method for meta-analyses); meta-analysis of correctly designed RCTs. Results of ≥ 1 RCT supplemented with data from medium and high-quality registers. B – Correctly designed RCTs, high reliability of results (representativeness of sample). Meta-analysis of correctly designed RCTs. C – RCTs with few (≤ 2) methodological limitations (lack of blinding, small sample size, limitations of randomisation method, modified analysis of meta-analysis results). D – Correctly designed controlled clinical trial without randomisation. Correctly designed prospective cohort study. Correctly designed register. Meta-analysis of the aforementioned primary studies. E – Randomised or non-randomised clinical trials with numerous (> 2) methodological limitations (lack of blinding, small sample size, inappropriate randomisation method, lack of ITT). Prospective observational studies with numerous methodological limitations.

Presentation of the levels of reliability adopted on the basis of the Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [9].

- A – Results of > 1 correctly designed RCT, medium to high reliability of results (sample representativeness, ITT, blinding, appropriate method for meta-analyses). Meta-analysis of correctly designed RCTs. Results of ≥ 1 RCT supplemented with data from medium- and high-quality registers.
- B – Correctly designed RCTs, average reliability of results (sample representativeness. Meta-analysis of correctly designed RCTs).
- C – RCT with few (≥ 2) methodological limitations (lack of blinding, small sample size, limitations of randomisation method, modified analysis of meta-analysis results).
- D – Correctly designed controlled clinical trial without randomisation. Correctly designed prospective cohort study. Correctly designed register. Meta-analysis of the primary studies mentioned above.

E – Randomised or non-randomised clinical trials with numerous (> 2) methodological limitations (lack of blinding, small sample size, inappropriate randomisation method, no ITT). Prospective observational studies with numerous methodological limitations.

- RCT – (randomised controlled trial) – a clinical trial with randomisation, that is a random selection of patients into a control group and an experimental group.
- ?????????????????????????? SoC – standard of care; TOC – tocilizumab; MICU – medical intensive care unit; IRU – intensive recovery unit.
- ??????????????????CC – cardiac complications, NC – neurological complications, RC – respiratory complications, VTC – vascular thrombosis complications

Results and discussion

In this analysis, no attempt was undertaken to make a substantive assessment of the studies included in the review. Some shortcomings in the reporting of the method of observation were identified, such as the omission of information in several studies about the type of sampling or the method of text analysis used, which did not allow for an assessment of the quality of the study. A weakness of the quantitative studies included in the review is the fact that specially designed questionnaires with untested parametric properties were used in them, which raises questions about the accuracy and reliability of the results of these studies [10]. In addition, as recognised in McCarthy's review of patients with complications after COVID-19 [11], while designing a questionnaire specifically for the use of a particular study allows the questionnaire questions to be tailored to the characteristics of the population under study, it also makes it difficult to compare the results with other information. The fact that this systematic review of studies was limited to those published between 2020 and 2021 can be considered a limitation of this systematic review. The lack of critical assessment of the quality of the studies included in the review should also be considered a limitation of the analysis. At this stage of the research work, it was rather sought to establish how and in what context COVID-19 affected complications: cardiovascular, neurological, respiratory, and vascular thrombosis. It was then sought whether there was any dominant method to study these complications [12]. The study conducted confirms that SARS-CoV-2 infection pertaining to the aforementioned complications significantly affected them. In cardiac complications, the most important pathomechanisms arise from hypoxia, activation of the systemic inflammatory process, hypercoagulability, adrenergic stimulation, direct infection, and myocardial necrosis [13, 14]. The highest percentage estimated in the age group 40–50 years (f = 1556) accounted for 21.1% among other complications. The second age group with a high percentage involved patients in the population ≥ 70 years old (f = 1461), which accounted for 20.77%. The lowest proportion of these complications was in the 30–40 years age group (f = 65), 0.92%. Cardiovascular complications associated with SARS-CoV-2 infection were initially perceived in the context of myocardial infarction and myocarditis, exacerbation of heart failure, cardiac arrhythmias, and thromboembolic complications. Observations regarding the possibility of myocardial ischaemia in the course of COVID-19 appeared very early, when it was found that a large percentage

of hospitalised people manifested laboratory tests that showed increased concentrations of proteins (including troponins) that may indicate heart damage [15, 16]. It is now known that this is true about myocardial overload, and increased troponin concentration does not necessarily result from this from ischaemic damage to cardiomyocytes [13].

Myocardial ischaemia and infarctions occur at different stages of infection. In the acute hospital period, cardiological presentations of COVID-19 as the leading diagnoses are rare, limited to a few per cent of patients [17, 18]. The incidence of cardiovascular complications has not been definitively established, but the latest systematic reviews indicate that they concern a large percentage of patients [19, 20]. The most frequently described clinical consequences of COVID-19 within the cardiovascular system include acute coronary syndromes, heart failure, myocarditis, cardiac arrhythmias, and inflammatory changes in vessels [21]. The presence of cardiovascular diseases preceding the infection in a given patient, including the most common form of hypertension, is of great importance. Both the involvement of the cardiovascular system during infection and earlier occurrence of diseases within it are associated with a more severe clinical course of COVID-19 and a worse prognosis [14, 22]. Cardiac arrhythmias, as well as the severity of previously diagnosed arrhythmias, may accompany the acute phase of COVID-19 and post-COVID conditions. Patients complain of tachycardia (accelerated heart rate), paroxysmal palpitations, and attacks of atrial fibrillation may also occur more frequently. In the course of COVID-19, other proarrhythmic factors (promoting uneven heartbeat) are also activated, so it seems reasonable to actively search for atrial fibrillation in people who have had COVID-19, especially in people with risk factors for arrhythmia and periodically experiencing abnormal heart function already during the recovery period after COVID-19 [23].

Among the most commonly described clinical consequences of COVID-19 are acute coronary syndromes, heart failure, and myocarditis [21]. The presence of cardiovascular conditions, including the most common – hypertension, preceding the infection is of great importance. Both cardiovascular system involvement during infection and pre-existing cardiovascular disease are associated with a more severe clinical course of COVID-19 and a poorer prognosis [14, 22]. A study conducted in the UK showed that out of 100 hospitalised patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of ICU patients and 60% of hospital ward patients experienced fatigue and dyspnoea between 4 and 8 weeks after hospital discharge [2, 24]. In a study conducted in Germany involving 100 patients who underwent COVID-19, magnetic resonance imaging (MRI) of the heart was performed an average of 71 days after diagnosis, revealing changes in cardiac imaging in 78% and ongoing myocarditis in 60% of patients [25]. In a retrospective study from China including 26 patients who recovered from COVID-19 and initially had cardiac symptoms, cardiac MRI abnormalities were found in 15 patients (58%) [26]. However, these data should be treated with caution, and the prevalence of cardiac abnormalities in post-COVID-19 patients should be assessed, because these results are likely to be biased by including only patients with cardiac symptoms. In contrast, the results of the Metcovid study (Jeronimo 2020)??????????????????? [39], on the basis of clinical and/or radiological images, proved an increase in cardiac problems in each age group, regardless of comorbidities [27]. Among the neurological complications, the consequences of COVID-19 included strokes, seizures, and Guillain-Barré syndrome, accompanied by temporary paralysis. It is noted that a previous coronavirus infection may also increase the risk of developing Parkinson's disease and Alzheimer's disease [28, 29]. SARS-CoV-2 virus infection causes new, previously unseen symptoms of damage to the nervous system and neurological diseases. It is emphasised that recurrence or exacerbation of previously diagnosed disorders and symptoms is also possible. There are various mechanisms that cause damage to the nervous system during SARS-CoV-2 virus infection [30]. First, there may be significant damage to nerve cells as a direct result of the virus. Secondly, as a result of the inflammatory reaction, nerve cells may be damaged by antibodies and/or activated lymphocytes [19, 31]. The possibility of a stroke occurring during COVID-19, especially in patients with coexisting disorders of the blood supply to the central nervous system (i.e. brain), is quite high. Stroke occurs in 1–6% of patients with infection, which is much more common than in the general population [32]. It also depends on the severity of COVID-19 [33]. In more than half, the mechanism of infection-related stroke involves the development of inflammation in the course of an immune reaction and direct vascular damage by the virus [11, 33]. Headache usually affects 10–15% of COVID-19 patients, but according to some researchers it may affect up to 70% of patients [34]. It often accompanies other symptoms of infection, such as fever, a feeling of exhaustion, runny nose, and sore throat, but it can also be a spontaneous symptom. The nature of the headache may also vary, from constant, pressing pain to unilateral or bilateral pulsating pain [35]. Possible mechanisms of headache development include stimulation of nerve endings (including the trigeminal nerve, innervating most of the face and front of the head) directly by the SARS-CoV-2 virus or by circulating inflammatory mediators (chemical compounds produced in the body that contribute to the development of inflammation), or as a result of damage to blood vessels or hypoxia [12, 33].

Neurological, neuropsychiatric complications occurred in patients who experienced acute COVID-19.

High rates of anxiety and depression were reported in some subjects using self-assessment scales for psychiatric stress. Younger patients were reported to have more psychiatric symptoms than patients aged > 70 years. Patients experienced headaches, visual disturbances, hearing loss, loss of taste or smell, impaired mobility, numbness in limbs, tremor, muscle pain, memory loss, cognitive impairment, and mood changes up to 3 months after COVID-19 diagnosis. The highest proportion with this complication were patients in the ≥ 70 years age group (f = 896), 12.74%. The second highest percentage age group was the population studied aged 40–50 years (f = 754), 10.72%. The lowest neurological complications were observed in the 60–70 years group (f = 250) at 3.52% [15]. In a publication by Lopez from 2021 [40], a total of 55 long-term effects associated with COVID-19 were identified from retrieved documents. Measurable parameters included 6 elevated laboratory parameters, i.e. interleukin-6 (IL-6), procalcitonin, serum ferritin, C-reactive protein (CRP), BNP hormone (NT-proBNP), and D-dimers [24]. It is emphasised that fatigue (present in 58% of patients assessed) is the most common symptom of long-term and acute COVID-19. In this case, symptoms are similar to those of acute respiratory distress syndrome (ARDS), in which it was observed that even after as long as 1 year, more than two-thirds of patients reported clinically significant symptoms of fatigue [35]. The cause of respiratory symptoms in the course of COVID-19 is the binding of the SARS-CoV-2 virus to the type II angiotensin-converting enzyme (ACE-2), abundantly present on the surface of the cells that make up the mucous membranes of this system [36, 37]. The SARS-CoV-2 virus binds to and penetrates alveolar pneumocytes (cells that build the alveoli), and binds to ciliated respiratory epithelial cells [37]. The severity of COVID-19 disease and its symptoms in the respiratory system depends on the course of the immune response to the infection. It can be concluded that not the infection itself, but an excessive reaction to it causes the progression of the disease to a severe form. Symptoms caused by SARS-CoV-2 in the respiratory system are not specific only to COVID-19, but their severity and effects, especially in the lower respiratory tract respiratory and lung parenchyma, determine the severity of the disease [38]. Respiratory symptoms suggesting a connection with SARS-CoV-2 infection include cough (most often dry), chest pain or discomfort, decreased exercise tolerance, and then shortness of breath at rest [39]. In a few patients, symptoms related to the upper respiratory tract predominate, such as runny nose, sneezing and sore throat. A retrospective study in China [32, 40] revealed that lung function (measured by spirometry) was impaired after COVID-19 (54.4%). Dyspnoea and cough were found in 24% and 19% of patients, respectively. In addition, abnormalities on CT lung scans persisted in 35% of patients, even 60–100 days after the first scan. The findings conclude that the age group with the highest rate of respiratory complications was the population between 30 and 40 years (f = 5519), 78%. The second group with a high percentage of complications were patients aged 50–60 years (f = 5008), 71.21%. The lowest percentage was observed in the age group ≥ 70 years (f = 3197), 45%. Based on a study conducted at Massachusetts General Hospital (USA), which included patients admitted to the ICU in March and May 2020 for acute respiratory distress syndrome (ARDS), the incidence rate of respiratory-related complications was ≥ 54% in each age group analysed [41]. It is noted that antithrombotic prophylaxis should be recommended in all hospitalised patients with COVID-19 due to the nature of pneumonia in the course of COVID-19 [42]. In vascular thrombosis-related complications, the most commonly described clinical consequences (Tang 2021 – medium study reliability: small sample size, Asian population, short follow-up period), show an increase in vascular thrombosis-related diseases after COVID-19 in all age ranges analysed [16]. Similarly, in another study by Ranjbar 2020–2021 (medium study reliability), an increase in vascular thrombosis complications was demonstrated [43]. Results of identified experimental studies: CAPE COVID, REMAP-CAP [3] also confirm an increase in thrombotic complications after COVID-19 ≥ 30% [44]. Thus, the highest rate of thrombotic complications was noted in the 60–70 years age group (f = 2143), with 30.47%, followed by the ≥ 70 years group (f = 1478), with 21.01%, and the least in the 30–40 years group (f = 884), which gave 12.57%.

The studies that concern reports of hospitalised patients are worthy of attention due to inflammatory diseases in the head and neck. Trybek *et al.* [45] noticed a worsening of the underlying disease in the case of co-infection with the SARS-CoV-2 virus. They suggested, among other things, that COVID-19 probably significantly affects the course of the disease and the results of treatment in patients with neck phlegmon. They also proposed further research to clarify the mechanism of the impact of SARS-CoV-2 infection on the course of phlegmon in the head and neck. During the COVID-19 pandemic, many procedures were performed with restrictive procedures, where medical staff were largely exposed to infection with the SARS-CoV-2 virus. Lichota *et al.* [46] stated in their reports that the principles of conduct during otolaryngological procedures during the SARS-CoV-2 pandemic are constantly being improved to protect both medical staff and patients. The rapidly changing epidemiological situation and the availability of personal protective equipment make it possible to perform ENT procedures relatively safely in the era of the SARS-CoV-2 pandemic.

It is stated that the diagnosis and treatment of disease syndromes initiated or intensified by COVID-19 will constitute a basic element of diagnosis and treatment in the coming years. Both doctors and patients will learn about and become familiar with the appearance of new symptoms in clinical teams, age groups, and subpopulations different than before. Over time, knowledge related to COVID-19 will increase, making both therapy and prevention more effective. Clinicians' recommendations and experiences will allow for a reliable assessment of the frequency, severity, and duration of reported COVID-19 symptoms.

Survey selection form

The 67 articles selected for analysis included surveys of 11,874 patients who underwent COVID-19 and acquired various complications either during or shortly after the viral infection, which were narrowed down to cardiovascular, neurological, respiratory, and vascular thrombosis-related. Patients with at least one complication were included in the analysis. Most authors presented the 4 most characteristic complications, which were used in this meta-analysis. It is highlighted that some studies included more than those presented and described by the authors of the article. Sample sizes varied from 40 to 2806 participants, averaging 158 respondents per survey. Some authors did not specify the response rate from the surveys. The following scientific reports were found for cardiovascular, neurological, respiratory, and vascular thrombosis complications after COVID-19: (16) studies with RCTs- Recovery Horby 2020 (9) [3] and Coral 2020 (7) [44], (12); retrospective studies – Wang 2020 [47], Wu 2020 (6) [27], Bani- Sadr 2020 (15) [48], Shang (11) [17]. Studies of secondary systematic reviews were found with meta-analysis – Gangopadhyay 2020 (18) [34], Lu 2020 (19) [32] and without meta-analysis – Singh 2020 (4) [15]. It is emphasised that not all primary studies were included in the systematic reviews found, due to their lesser fulfilment of the criteria for inclusion in the meta-analysis of a review using the Prisma method. As part of the update review conducted, the following were found: 20 primary studies: o 5 RCTs - Metcovid (Jeronimo 2020) (22) [29], CoDEX Tomazini 2020 (23) [29], CAPE COVID Dequin 2020 (24) [6], REMAP-CAP (25), Edalatifard 2020 (26) [49], o 15 observational studies: Hu 2020 (27) [49], Liu 2020(28) [31], Bartoletti 2020 (29) [23], Keller 2020 (30) [35], Li 2020 (31) [50], Ma 2020 -2021(32) [51], Ruiz-Irastorza 2020 (33) [52], Yang 2020 (34) [53], CHIC Ramiro 2020 (35) [43], Wei 2020 (36) [54], Rubio-Rivas 2020 (37) [55], SAM-COVID-19 Rodríguez-Bano 2020 (38) [39], Narain 2020 (39) [56], and Wu 2020 (40) [57] (accepted manuscript-type publication found; a preprint publication was previously available [58]), and 5 secondary studies: WHO REACT 2020 (9) (41), Chen X 2020 (7) [59], Salton 2020 (13) [60], and Thachil 2020 (44) [16]. In addition, in an unsystematic search, a WHO document (68) was found, representing data related to post-COVID complications. In the update review conducted (version primary and secondary studies), the following were found: 6 RCTs, of which 2 represent updates of publications included in the version review – Horby 2021 (46) (RECOVERY; Horby 2020 update - preliminary results and Corral-Gudino 2021 (47) Corral 2020 update – publication previously only available in a pre-print form) [26]; and 4 RCTs – Jamaati 2021 (48) [1]. The 24 reviewed articles present the results of cross-sectional studies. In the review, articles published in Polish, English, and German were used. The authors of the studies came from different countries and represented different models of health care system. The researchers took into account the age rather than the gender of the patient. Thus, due to the association of complications with gender, no general conclusions were drawn.

The compiled description of methodology and conclusions of the identified studies are an analysis of the results of medium-quality studies (observational - mainly cohort, retrospective). It should be highlighted that not all primary studies included in the systematic reviews found met the inclusion criteria for the systematic review. The results of the meta-analysis indicate statistical differences in complications caused by COVID-19. On the other hand, the authors of the systematic review with meta-analysis request further observations and studies related to cardiovascular, neurological, respiratory, and vascular thrombosis complications in patients who contracted COVID-19 and, in the long term, systematic follow-up of patients with these complications. In the context of clinical trials, systemic therapy for COVID-19-related complications should be acceptable. The conclusions of the systematic review suggest that most complications were related to the respiratory system. In patients with severe (but not critical) course of COVID-19, the results of the meta-analysis of 2 studies did not reach the threshold for statistical significance. The authors of this paper suggest that it is essential to confirm the results of the study with meta-analysis in further methodologically correct clinical trials to draw definitive conclusions regarding post-COVID complications. The systematic review with the PRISMA meta-analysis included only randomised studies; the other reviews also included lower-quality studies, including observational studies. The authors also indicate that post-COVID complications in the population were frequent and independent of age or previous medical history. Thanks to the PRISMA meta-analysis, a high heterogeneity of the included primary studies was achieved. Based on the results of the meta-analysis, in which 8 retrospective observational studies were included, it is indicated that complications related to vascular throm-

bosis occurred much more frequently than before COVID-19. At the same time, attention is drawn to the high heterogeneity of the included studies, which led to conclusions.

Measurement instruments

The most frequently chosen questionnaires were the St. George's Respiratory Questionnaire (SGRQ), which allowed complications after COVID-19 to be singled out. They were applied in 49 studies; these questionnaires were mainly used by researchers from the USA, UK, Italy, Australia, and China. The Male Sexual Health Questionnaire – Ejaculatory Dysfunction (MSHQ-EjD) was used by 10 researchers from Portugal, France, and Spain. Premature Ejaculation Diagnostic Tool (PEDT) was chosen by 14 researchers mainly from Germany and the UK. Paper and Pen Personal Interviews (PAPI) were used by 26 researchers mainly from the USA, Australia, China, Italy, Sweden, and Poland. In the statistical study, many researchers used more than one questionnaire: Taylor ≥ 2 [40], Tomazini ≥ 1 [29], Zhou ≥ 2 [21], Lu ≥ 1 [32], and Jamerson ≥ 1 [14]. Thus, measurement scales allow the results of measurements obtained in studies to be systematised. The most commonly used scales in research are ordinal, which allows values to be determined in a specific order due to some characteristic (individual cases can be ordered according to the indicated criterion).

Evaluation

In the analysed publications included in the review, the specific complications that occurred after COVID-19 were investigated. The population of patients who underwent COVID-19 were also examined (the population was presented in age ranges) and the course/intensity of the analysed complications. Due to the varied research methods that were useful for assessing complications after COVID-19, a comprehensive review of selected articles was developed. The individual results presented in the articles are worth noting. Regardless of the countries in which the authors studied complications after COVID-19, the conclusions were consistent regarding cardiovascular, neurological, thrombotic, and respiratory complications. Many study authors described their results very similarly. There were minor discrepancies in 19 studies on neurological complications, and the same was true for 43 studies on respiratory complications. Identical conclusions were found in 46 articles covering studies related to respiratory complications and 16 to cardiac complications. Most of the researchers emphasised the correlation between COVID-19 and the consequences caused by the virus. The PRISMA meta-analysis contributed to a systematised presentation of post-COVID complications.

Conclusions

The purpose of the review presented here was to analyse articles published between 2020 and 2022. However, the analysis was limited to studies conducted between 2020 and 2021. The limitation was because many studies are ongoing and have not been completed. Data collection was an important aspect in preparation for the review that was developed. Eight academic databases with keywords on COVID-19 and cardiovascular, neurological, respiratory, and vascular thrombosis complications were examined. Articles of similar structure and scope have been narrowed down to key terms. The review is comprehensive in nature, as reflected by the number of articles published. The data from the literature on complications following COVID-19, although quite limited because research is ongoing and regularly updated, provide evidence that SARS-CoV-2 infection affects respiratory, neurological, and cardiovascular functions and causes blood thrombosis. Attention is drawn to the fact that, after COVID-19, the complications discussed in the paper showed a significant increase. After analysis, it can be concluded that respiratory-related complications were the most common. Next in order were complications related to vascular thrombosis, followed by cardiovascular complications, and the least frequent were neurological complications. The results of the primary studies identified, showed that patients with complications required hospitalisation and the inclusion of multiple therapies until their health improved. Analysis of the results found in observational studies did not clearly suggest additional factors causing the complications presented, because not all patients had comorbidities prior to contracting COVID-19. The intensity of the complications, as well as their course, varied. At present, it is difficult to conclude why some patients developed these and not other complications (excluding comorbidities). The studies found have a number of limitations (short follow-up time, retrospective nature, heterogeneity in terms of baseline characteristics of patients, lack of subgroup analyses to address pre-existing comorbidities) that contribute to the low or moderate reliability of the evaluations. It can be argued that only comprehensive studies of the effects of COVID-19 will allow mechanisms to be developed to prevent and mitigate post-COVID complications. In the context of clinical trials, systemic therapy for COVID-19-related complications should be acceptable.

Funding

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Arkadiusz Żurawski
Collegium Medicum
Jan Kochanowski University
Kielce, Poland
Phone: +48 787339222
E-mail: azurawski@onet.eu

Received: 10.09.2023
Accepted: 1.03.2024
Online publication: 30.06.2024