

# How does the COVID-19 pandemic impact medication adherence of patients with chronic disease?: A systematic review

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## Abstract

**Objective:** To determine how the COVID-19 pandemic impacts patients with chronic disease medication adherence.

**Methods:** Four electronic databases, PubMed, MEDLINE, Web of Science, and CINAHL Plus Full Text, were searched for literature between 2019 and 2021. Abstracts and later full texts were independently screened by the authors of this review using inclusion and exclusion criteria to determine relevance to our study. Joanna Briggs Institute (JBI) critical appraisal tools were used to assess the quality of included texts. Relevant information and data from the included texts were extracted into tables for data synthesis and analysis.

**Results:** Ten studies met the study criteria, the most popular study design was cross-sectional design ( $n = 9$ , 90.0%), others were case series ( $n = 1$ , 10.0%). Barriers to medication adherence and facilitators of medication adherence were the major two themes that participants reported regarding the impact of COVID-19 on medication adherence. Moreover, these two main themes have been organized in sub-themes that are dealt with in-depth.

**Discussion:** Our results could heighten healthcare providers, stakeholders, and policy leaders'

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awareness of providing appropriate support for chronic disease patients, especially regarding medication adherence. Future research incorporating programs that support patients' needs is recommended.

## Keywords

COVID-19, medication adherence, chronic disease, pharmacotherapy, systematic review

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## Introduction

Chronic disease is gradually enveloping the world population, spreading to all corners of the world.<sup>1</sup> The Institute of Health Metrics and Evaluation stated that non-communicable (chronic) disorders such as coronary heart disease, stroke, cancer, chronic mellitus type 2, neurodegenerative disease, and renal failure accounted for 39.5 million of the 54.7 million deaths (72%) for which a cause was identified in 2016.<sup>2</sup> Moreover, among patients with chronic diseases, the therapy and its outcomes burden their lives and have a severe psychological effect on themselves and their caregivers.<sup>3</sup> Frequently they encounter uncertainty about the disease's nature, limited ability to control their lives, dependence on others, or disruption of their caregiver's life.<sup>3</sup>

At the beginning of December 2019, the first novel pneumonia cases of unknown origin were reported in Wuhan, Hubei province, China<sup>4</sup> and were later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19.<sup>5</sup> The ongoing COVID-19 pandemic impacts ordinary people's lives and vulnerable groups like patients with chronic diseases. Previous review literature shows that the COVID-19 pandemic has affected patients with chronic diseases such as stroke in various ways. For example, they have delayed stroke treatment, increased risk of stroke severity and disability, increased stroke mortality, and prolonged hospitalization.<sup>6</sup>

Numerous chronic disease treatments require patients to take maintenance medications, frequently more than once daily.<sup>7</sup> Previous

research stated that stroke preventive medication could reduce the recurrence of ischaemic events by about 75%.<sup>8,9</sup> However, approximately 50% of chronic disease patients are non-adherent to their respective medical therapy.<sup>10,11</sup> For stroke patients, a previous study showed that about one-third of stroke survivors are considered to be non-adherent to their medication.<sup>12</sup>

Considering the lack of study on the impact of the COVID-19 pandemic on medication adherence in patients with chronic illness, the researcher presents here, to the researcher's knowledge, for the first time a systematic review that aims to determine how does the COVID-19 pandemic impacts medication adherence of patients with chronic disease. The current review was carried out hoping that it would guide the strategy or intervention that helps improve medication adherence in patients with chronic disease who are impacted by the current outbreak of COVID-19.

## Methods

### *Identify relevant studies*

PRISMA<sup>13</sup> was applied in this systematic review to present the flow diagram of the literature's identification, screening, exclusion, and inclusion. Four electronic databases, PubMed, MEDLINE, Web of Science, and CINAHL Plus Full Text, were systematically searched on August 1, 2021, to identify preliminary studies published between January 2019 and December 2021, reporting the impact of the COVID-19 pandemic on medication adherence of patients with chronic disease. The researcher

**Table 1.** Inclusion and exclusion criteria.**Inclusion Criteria**

- Human participants of all years of age
- Original quantitative, qualitative, or mixed methods studies
- Investigated the impact of the COVID-19 pandemic on medication adherence of patients with chronic disease
- Included participants diagnosed with chronic diseases
- Chronic diseases in this review are defined as diseases that have one or more of the following characteristics: they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation, or care
- All types of settings are acceptable, including inpatient, outpatient, or home
- Described in the English language

**Exclusion Criteria**

- The study did not include the population of interest or concerned animal subjects
- Conference proceedings, abstracts, review articles, theoretical papers, pilot study, protocol, dissertation, letter to the editor, opinion (viewpoint), statement paper, government documents, or working papers

combined the search terms: (stroke OR cerebrovasc\* disorders OR cerebrovasc\* disease OR cerebrovasc\* accident OR brain isch?emi\* OR isch?emi\* cerebral attack OR brain attack OR intracranial h?emorrhage\* OR CVA) AND (Medication Adherence OR Medication Nonadherence OR Medication Noncompliance OR Medication Persistence OR Medication Compliance OR Medication Non-Compliance) AND (severe acuterespiratory syndrome coronavirus 2 OR 2019-nCoV OR Wuhan coronavirus OR SARS-CoV-2OR 2019 novel coronavirus OR COVID-19 virus OR coronavirus disease 2019 virus OR ncovOR COVID-19 OR SARS-CoV-2) using Boolean phrases. In addition, reference lists of the included studies were manually searched to obtain relevant studies. All references identified were stored in EndNote. The detailed search strategy is shown in Supplementary Table 1.

**Study selection**

Two of this systematic review's authors independently screened titles and abstracts of eligible studies. Subsequently, the full text was also assessed to decide whether or not it was relevant. A third anonymous researcher was required to resolve disagreements when discrepancies

occurred. Inclusion criteria were implemented to guarantee that only studies considered relevant to our objective were included. Similarly, exclusion criteria were used to eliminate literature not affiliated with the review (Table 1).

**Quality assessment**

Two researchers assessed the methodological quality of studies independently to evaluate the design, conduct, and analysis of the studies, using the Joanna Briggs Institute (JBI) critical appraisal tools designed for systematic review, including JBI critical appraisal checklist for analytical cross-sectional studies<sup>14</sup> and JBI critical appraisal checklist for case series.<sup>15</sup> The assessment of cross-sectional studies consisted of the following aspects: inclusion criteria, descriptions of subjects and the setting, measurement of exposure, criteria used for measurement of the condition, confounding factors, strategies against confounding factors, outcomes measurement, and statistical analysis. The evaluation of the case series included the following domains: inclusion criteria, measurement of condition, identification of the condition for participants, consecutive inclusion, completeness of inclusion, demographics of the participants, clinical information of the

participants, outcomes or follow-up results, site(s) demographic information and statistical analysis.

### **Data extraction**

The standardized chart for data extraction (Supplementary Table 2) developed for this review included the following data for each study: reference, country, year, design and quality score, target population and sample size (n), participant socio-demographics, medication adherence (MA) measurement, key findings (the impact of COVID-19 on MA), themes on the impact of COVID-19 on MA, and summarize/further research implication. Two reviewers completed data extraction and were checked by a third reviewer.

### **Data synthesis**

The convergent integrated analysis framework suggested by Joanna Briggs Institute (JBI) for systematic reviews was adopted for the data synthesis of the included studies.<sup>14</sup> This framework, specialized for the simultaneous analysis of qualitative and quantitative data, transforms data of different categories into the same format to facilitate data integration.<sup>16</sup> Since transforming qualitative data to quantitative data, namely “quantitizing,” is more error-prone than “qualitizing,” the latter is preferred when conducting the data synthesis.<sup>14,17</sup> Qualitizing the quantitative data also facilitates the presentation of the studies’ risks and the way they were mitigated, such as sample sizes, attritions of participants, etc. Therefore, in this review, the “qualitizing” method, converting quantitative data into “qualitized” data, was adopted. The “qualitizing” process included transforming the quantitative results into “qualitized” data, which were narrative interpretations or textual descriptions that answered the review question. Afterwards, the “qualitized” data was assembled with the qualitative data. Assembled data were categorized and pooled together based on similarity in

meaning to produce a set of integrated findings in the form of a line of action statements.

In this review, this process means that themes were extracted from the key findings of the included studies by examining the similarities and differences between the key findings, and sub-themes were then abstracted according to the more specific target of the corresponding findings, similar to the way that qualitative researchers produce themes (Supplementary Table 2). For example, one of the key findings by Gul & Atakli, 2021,<sup>18</sup> “two patients (1.8%) stated that they had difficulty accessing drugs during the pandemic period,” was coded as “difficulty in accessing drugs”, forming the theme “barriers to medication adherence”, and then was further identified as the sub-theme “medication shortage” falling under the theme “barriers to medication adherence”. This process was conducted by two researchers independently. A third researcher was required when there was a discrepancy.

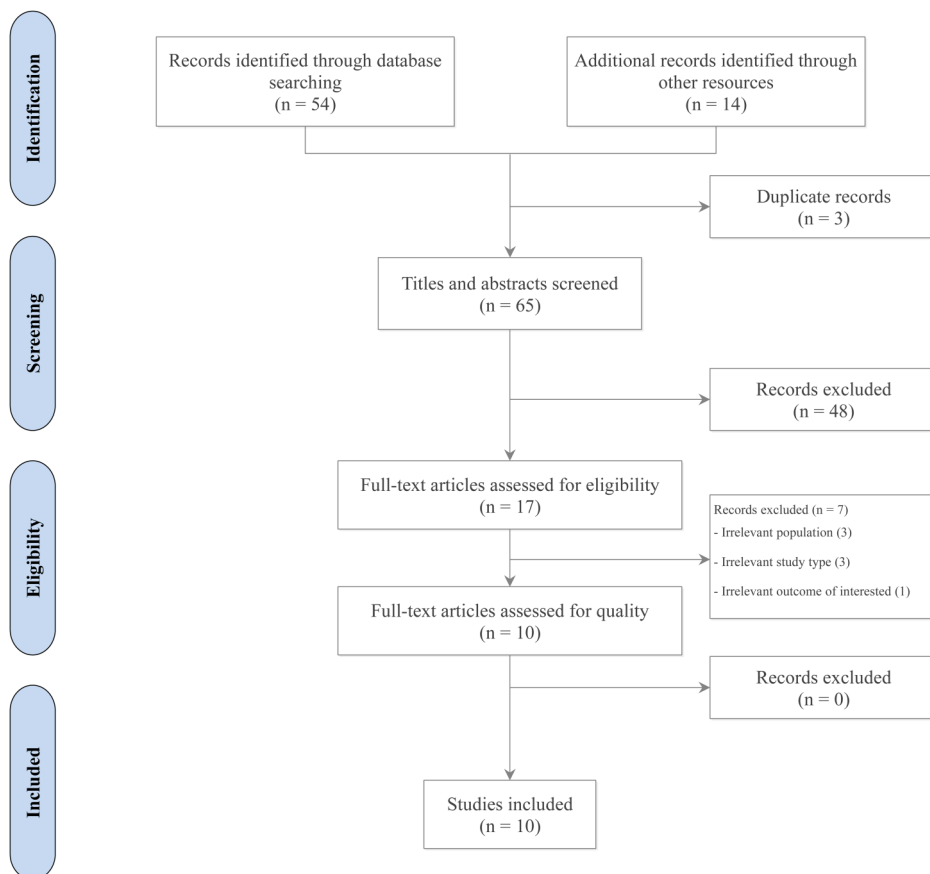
## **Results**

### **Search results**

A total of 68 articles were identified initially, with 14 found from other resources. Three duplicates were identified by Endnote X8 and removed. Afterward, the rest articles were screened by title and abstract according to the inclusion and exclusion criteria (Table 1), leaving 17 articles eligible for the full-text screening. During the full-text screening phase, seven articles were excluded, three for irrelevant population, three for irrelevant study type, and one for not the outcome of interests. Ten studies were included for final analysis after quality appraisal. Finally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>13</sup> was applied to outline the retrieval process (Figure 1).

### **Description of included studies**

It is shown in Table 2 that all included studies were published between 2020 (n = 2, 20.0%) and 2021 (n = 8, 80.0%). The included



**Figure 1.** PRISMA flow chart.

studies were carried out mostly in India ( $n = 2$ , 20.0%). Each with one study, other countries are China, Turkey, Saudi Arabia, French, Ireland, Switzerland, Ethiopia, and Australia. The most popular study design was cross-sectional design ( $n = 9$ , 90.0%), others were case series ( $n = 1$ , 10.0%). The target population of the included studies was patients with hypertension ( $n = 3$ , 17.7%), diabetes mellitus ( $n = 3$ , 17.7%), rheumatic musculoskeletal disease, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, asthma, epilepsy, glaucoma, stroke, atrial fibrillation, COPD, and inflammatory bowel disease (all  $n = 1$ , 5.9%). Sample size ranged from 1 to 50, 50 to 100, 100 to 200, 200 to 300 (all  $n = 1$ , 10.0%), and more than 300 ( $n = 6$ , 60.0%). Participants were

primarily those over 45 years old. Some studies reported the COVID-19 test status of the participants (not tested, negative, positive, highly suspicious) while others did not. The 8-item Morisky Medication Adherence Scale (MMAS), the Modified Morisky Scale (MMS), and the 10-item the Medication Adherence Rating Scale (MARS) was adopted as medication adherence measurement tools (all  $n = 1$ , 10.0%), with most studies not reporting the tools for assessing medication adherence (all  $n = 7$ , 70.0%).

### Assessment of methodological quality

In accordance with the JBI critical appraisal checklist for analytical cross-sectional studies<sup>14</sup>

**Table 2.** The characteristics of the included studies.

Characteristic	Number (n)*	Percentage (%)
Publication year		
2021	8	80.0%
2020	2	20.0%
Country		
India	2	20.0%
China	1	10.0%
Turkey	1	10.0%
Saudi Arabia	1	10.0%
French	1	10.0%
Ireland	1	10.0%
Switzerland	1	10.0%
Ethiopia	1	10.0%
Australia	1	10.0%
Study design		
Cross-sectional study	9	90.0%
Case series	1	10.0%
Target population		
Hypertension	3	17.7%
Diabetes mellitus	3	17.7%
Patients with rheumatic musculoskeletal disease	1	5.9%
Spondyloarthritis	1	5.9%
Rheumatoid arthritis	1	5.9%
Psoriatic arthritis	1	5.9%
Asthma	1	5.9%
Epilepsy	1	5.9%
Glaucoma	1	5.9%
Stroke	1	5.9%
Atrial fibrillation	1	5.9%
COPD	1	5.9%
Inflammatory bowel disease	1	5.9%
Sample size (n)		
1–50	1	10.0%
> 50–100	1	10.0%
> 100–200	1	10.0%
> 200–300	1	10.0%
> 300	6	60.0%
Participant socio-demographics		
Age (year)		
18–25	4	14.8%
26–44	7	26.0%
45–59	8	29.6%
60 or above	8	29.6%
Sex		
Male	10	50.0%
Female	10	50.0%

(continued)

**Table 2.** Continued

Characteristic	Number (n)*	Percentage (%)
<i>COVID-19 test status</i>		
Not tested	2	12.5%
Negative	2	12.5%
Positive	2	12.5%
Highly suspicious	1	6.3%
N/A	9	56.3%
<i>Medication adherence measurement</i>		
The 8-item Morisky Medication Adherence Scale (MMAS)	1	10.0%
The Modified Morisky Scale (MMS)	1	10.0%
The 10-item Medication Adherence Rating Scale (MARS)	1	10.0%
Not specify**	7	70.0%

\*The number of included studies in which one study may contribute to > 1 characteristic.

\*\*Adherence to the ongoing rheumatological therapy and any changes in the rheumatology treatment plan since the beginning of the COVID-19 pandemic questionnaire (not specify the name of the measurement),<sup>19</sup> Ask the following questions: Do you have a chronic disease that forces you to go to the hospital? (Yes/No), Do you take specific medications/drugs for this disease? (Yes/No), Are you adherent to these treatments during this COVID-19 pandemic? (Yes/No), Do you hesitate to go to the hospital during the current pandemic? (Yes/No) (not specify the name of the measurement),<sup>20</sup> Compliance to pharmacological and routine physical activity during the last one month of lockdown was assessed using a dichotomous question,<sup>21</sup> A multidimensional Questionnaire consisting of 1) Demographic and clinical data including age, gender, district of residence, diagnosis, and medication advised, which were extracted from electronic medical record 2) Questions pertaining to barriers for a hospital visit, and barriers for medication adherence during the pandemic,<sup>22</sup> The researchers calculated three medication adherence metrics with three formulas and Two questions were asked during the regular follow-up interviews,<sup>23</sup> Adherence was determined by the following formula: dose compliance (%) = number of days with right dose in 30 days/30 × 100%.<sup>24</sup>

COPD: Chronic obstructive pulmonary disease.

N/A: Not applicable.

and JBI critical appraisal checklist for case series,<sup>15</sup> not taking the unapplicable ones into account, most contents about the methodological quality was clearly reported in the included studies (all above 50%), thus leading to less risk of bias (Table 3). Nevertheless, as to the measurement of exposure, two out of the nine cross-sectional studies did not report clearly.<sup>20,25</sup> In addition, three out of the nine studies failed to identify confounding factors.<sup>18,19,25</sup>

### *Description of the COVID-19 pandemic impact on medication adherence of patients with chronic disease*

A summary of the findings from the included studies is provided in Supplementary Table 2. Scrutiny of Table 4 can be placed into two major themes: 1) Barriers to medication

adherence and 2) Facilitators of medication adherence. These two main themes have been organized in sub-themes that are dealt with in-depth hereunder.

#### *Barriers to medication adherence*

*Concern of COVID-19 infection.* Six studies reported that concern of COVID-19 infection is the factor associated with non-medication adherence among chronic disease patients.<sup>19,20,22,24,25,27</sup> The concern of going to the hospital and health facilities during the pandemic, the concern of contagion; COVID-19 infection or symptoms, not returning to the hospital for a prescription, missed doses, or dose reduction of medications due to psychological affection (e.g. stress) due to the pandemic were majority reported as factors that contribute to medication non-

**Table 3.** The methodological quality of the included studies.

Appraisal questions/ Reference	Murray et al. (2021) <sup>25</sup>	Costantino et al. (2021) <sup>19</sup>	Zakaria et al. (2020) <sup>20</sup>	Gul and Atakli (2021) <sup>18</sup>	Gautam et al. (2021) <sup>21</sup>	Subathra et al. (2021) <sup>22</sup>	Dietrich et al. (2021) <sup>23</sup>	Shimels et al. (2021) <sup>26</sup>	Zhang et al. (2020) <sup>24</sup>	Barnes et al. (2021) <sup>27</sup>
<b>JBICRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES</b>										
1. Were the criteria for inclusion in the sample clearly defined?	+	+	?	+	+	+	+	+	+	+
2. Were the study subjects and the setting described in detail?	+	+	\	+	+	+	+	+	+	+
3. Was the exposure measured in a valid and reliable way?	?	+	?	+	+	+	+	+	+	+
4. Were objective, standard criteria used for measurement of the condition?	+	+	+	+	+	+	+	+	+	+
5. Were confounding factors identified?	-	-	+	-	+	+	+	+	+	+
6. Were strategies to deal with confounding factors stated?	\	\	+	\	+	\	+	+	\	\
7. Were the outcomes measured in a valid and reliable way?	+	+	+	+	+	+	+	+	+	+
8. Was appropriate statistical analysis used?	+	+	+	+	+	+	+	+	+	+
<b>JBICRITICAL APPRAISAL CHECKLIST FOR CASE SERIES</b>										
1. Were there clear							+			

(continued)



**Table 3.** Continued

Appraisal questions/ Reference	Murray et al. (2021) <sup>25</sup>	Costantino et al. (2021) <sup>19</sup>	Zakaria et al. (2020) <sup>20</sup>	Gul and Atakli (2021) <sup>18</sup>	Gautam et al. (2021) <sup>21</sup>	Subathra et al. (2021) <sup>22</sup>	Dietrich et al. (2021) <sup>23</sup>	Shimels et al. (2021) <sup>26</sup>	Zhang et al. (2020) <sup>24</sup>	Barnes et al. (2021) <sup>27</sup>
criteria for inclusion in the case series?										
2. Was the condition measured in a standard, reliable way for all participants included in the case series?						+				
3. Were valid methods used for identification of the condition for all participants included in the case series?							+			
4. Did the case series have consecutive inclusion of participants?							+			
5. Did the case series have complete inclusion of participants?							+			
6. Was there clear reporting of the demographics of the participants in the study?							+			
7. Was there clear reporting of clinical							+			

(continued)

Table 3. Continued

Appraisal questions/ Reference	Murray et al. (2021) <sup>25</sup>	Costantino et al. (2021) <sup>19</sup>	Zakaria et al. (2020) <sup>20</sup>	Gul and Atakli (2021) <sup>18</sup>	Gautam et al. (2021) <sup>21</sup>	Subathra et al. (2021) <sup>22</sup>	Dietrich et al. (2021) <sup>23</sup>	Shimels et al. (2021) <sup>26</sup>	Zhang et al. (2020) <sup>24</sup>	Barnes et al. (2021) <sup>27</sup>
information of the participants?										
8. Were the outcomes or follow-up results of cases clearly reported?							+			
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?							+			
10. Was statistical analysis appropriate?							+			
Percentage of yes* (%)	62.5%	75%	62.5%	75%	100%	87.5%	100%	100%	87.5%	87.5%

+ : yes; " - " : no; " ? " : unclear; " ! " : not applicable.

\*The number of "yes" / total items in the checklist x 100.

**Table 4.** The impact of the COVID-19 pandemic on medication adherence of patients with chronic disease .

Reference*/Themes and subthemes	Barriers to medication adherence (MA)						Facilitators of MA		
	The concern of COVID-19 infection	Medication shortage	Travel restriction	Financial restriction	Substance use	Compliance with health guidelines	Health information		
Murray et al. (2021) <sup>25</sup>	+					+			
Costantino et al. (2021) <sup>19</sup>	+	+	+						
Zakaria et al. (2020) <sup>20</sup>	+		+						
Gul and Atakli (2021) <sup>18</sup>		+						+	
Gautam et al. (2021) <sup>21</sup>	+	+	+			+			
Subathra et al. (2021) <sup>22</sup>			+	+					
Dietrich et al. (2021) <sup>23</sup>			+						
Shimels et al. (2021) <sup>26</sup>		+	+	+	+				
Zhang et al. (2020) <sup>24</sup>	+	+						+	
Barnes et al. (2021) <sup>27</sup>	+								
<b>Total (n, %)</b>	<b>6 (60%)</b>	<b>5 (50%)</b>	<b>6 (60%)</b>	<b>2 (20%)</b>	<b>1 (10%)</b>	<b>3 (30%)</b>		<b>1 (10%)</b>	

\*One study can report ≥ one impact.

adherence among chronic disease patients. The most prominent example of this theme comes from a study by Costantino et al., 2021,<sup>19</sup> which reported that more than 30% of patients with spondyloarthritis, rheumatoid arthritis, and psoriatic arthritis suspended or decreased the dosage of one of their medications and medication modifications were mainly due to fear of contagion (79.3%) or symptoms suggestive of infection (17.8%).

**Medication shortage.** Five studies revealed that COVID-19 impacts the availability of medications (medication shortage), perception of medicine out of stock, difficulty in accessing drugs, and non-availability of medical care and medication.<sup>18,19,22,24,26</sup> For example, a cross-sectional study by Subathra et al., 2021<sup>22</sup> aimed to analyze the barriers encountered by the glaucoma patients during the follow-up visit and medication adherence during the pandemic found that non-availability of medication (54.81%) was the top barrier to medication adherence.

**Travel restriction.** Six included studies show that travel restrictions contribute to medication non-adherence.<sup>19–23,26</sup> Decreased access to health professionals due to delayed consultation, appointments, or medical exams. Quarantine causes difficulty obtaining medications and treatment and communicating with health care providers. The hospital restrictions for non-emergency services during the initial phases of lockdown and transportation problems such as lack of public transport facility, which patients usually use to go to the hospital and do the follow-up visits, were reported in the six included studies mentioned above as travel restrictions contributing to medication non-adherence.

**Financial restriction.** One barrier patients with chronic disease encountered during the pandemic for medication adherence was financial restriction. Two included studies found that financial difficulties due to the pandemic are

the top barrier to medication adherence, and COVID-19 negatively impacts the financial status.<sup>22,26</sup> Notably, the study by Subathra et al., 2021,<sup>22</sup> which aimed to analyze the barriers encountered by 363 glaucoma patients for the follow-up visit and medication adherence during the pandemic, found that 57.3% of the patients were found to be non-adherent to medication and financial difficulties are one of the main factors contributed to it. Consistently, the study from Shimels et al., 2021<sup>26</sup> aimed to assess the magnitude and associated factors of poor medication adherence among diabetic and hypertensive patients also found that from overall 409 participants, about 57% of them reported that the COVID-19 pandemic had posed negative impacts on their affordability of prices.

**Substance use.** Substance use is one factor that was found to be the factor associated with medication non-adherence during the pandemic of COVID-19. One of the included studies that assessed the magnitude and associated factors of poor medication adherence among diabetic and hypertensive patients during the COVID-19 pandemic found that current substance use history significantly predicted high odds of poor adherence.<sup>26</sup> It suggested that all concerned health authorities should consider and set multidisciplinary strategies to prevent the impacts of the COVID-19 pandemic on medication adherence of patients with chronic illnesses, especially those with current substance use history.

**Facilitators of medication adherence.** Although the COVID-19 pandemic situation is intense, some patients reported silver linings during the pandemic regarding medication adherence as the following;

**Compliance with health guidelines.** Three studies revealed that during the COVID-19 pandemic, patients with chronic diseases who comply with health guidelines are more likely to adhere to their medication.<sup>21,24,25</sup> For

instance, Murray et al., 2021<sup>25</sup> found that medication adherence rates are reported to be highest among patients with the rheumatic musculoskeletal disease who cited health authority guidelines. Moreover, a study aimed to investigate the potential role of health literacy in determining adherence to COVID-19 preventive behavior, pharmacological, and lifestyle management among diagnosed patients with diabetes mellitus and hypertension during nationwide lockdown shows that health literacy was a significant predictor of adherence to medical management.<sup>21</sup> Similarly, Zhang et al., 2020<sup>24</sup> also reported that following health-care professional supervision was significantly related to medication adherence in patients with chronic obstructive pulmonary disease (COPD) during the pandemic.

**Health information.** One study by Gul & Atakli, 2021<sup>18</sup> aims to investigate how the COVID-19 pandemic can impact patients with epilepsy on drug compliance found that during the pandemic period, patients had higher motivation and knowledge than before the pandemic ( $p=0.048$ ). This study explained that the accessibility of intensive training and information about COVID-19 in visual and printed media could help patients with epilepsy manage their medication compliance. Therefore, it is suggested that the effectiveness of this strategy could be potentially tested with other chronic diseases.

## Discussion

As far as medication adherence's impact is concerned, this review expands the knowledge about the COVID-19 pandemic impacts on medication adherence in patients with chronic disease, including two main themes: (1) Barriers to medication adherence with sub-theme; the concern of COVID-19 infection, medication shortage, travel restriction, financial restriction, and substance use. (2) Facilitators of medication adherence with sub-theme; compliance with health guidelines and

health information, which will be discussed further below.

The concern of going to the hospital and health facilities during the pandemic, the concern of contagion, not returning to the hospital for a prescription, missed doses or dose reduction of medications due to psychological affection such as stress due to the pandemic were the majority reported in our included studies as factors that contribute to medication non-adherence among chronic disease patients.<sup>19,20,22,24,25,27</sup> Our results are consistent with the previous study aimed to determine the adherence rates to systemic treatments in patients with psoriasis and identify the causes of non-adherence during the COVID-19 pandemic. The result shows that during the COVID-19 pandemic, among 342 patients with psoriasis, one of the most frequent reasons for non-adherence to treatment was concern about the COVID-19 infection (16.3%).<sup>28</sup> Similarly, a study from Polat Ekinci et al., 2021 reported that during the COVID-19 pandemic, among 133 patients with psoriasis, 52 of them (39%) suspended their biological treatments for short ( $n=33$ ) or long ( $n=19$ ) periods without medical advice due to reasons of fear, worry, and anxiety.<sup>29</sup> Nevertheless, a study by Kaye et al., 2020 shows the different perspectives regarding this aspect. The researcher reported that patients with asthma and COPD who were advised to closely adhere to their prescribed inhaler medication therapy and track their adherence to their controller medications during the COVID-19 pandemic are more motivated and achieve higher medication use.<sup>30</sup> The strategy to encourage patients with chronic diseases to adhere to their medication should be developed and implemented. However, more study is needed as the findings from included studies may not be generalizable to all patients due to the heterogeneity of the sample size.

It is shown in this study that 50% of the included studies reported medication shortage due to the COVID-19 pandemic, which impacted medication adherence. The COVID-19 shortage

dilemma can lead to the discontinuation of medication therapy, posing a threat to the well-being of the patients, especially the chronically ill, since this population commonly requires long-term medication. It is found by the Canadian Hydroxychloroquine Study Group that for people with quiescent disease, interrupted hydroxychloroquine intake is associated with a 2.5-fold increased risk of new clinical manifestations or a recurrence or aggravation of the illness.<sup>31</sup> This underlines the significance of ensuring sufficient medication for chronically ill patients. In order to mitigate the negative effect that COVID-19 brought on medication supplements and medication adherence for the chronically ill, certain measurements are to be taken into consideration by the government, healthcare organizations, and medical institutions. It is reported in an international survey targeting pulmonary hypertension patients that during the COVID-19 crisis, people discontinuing medication in the middle-income countries is twice the number of that in high-income countries,<sup>32</sup> which suggests that international organizations could give more assistance to low and middle-income countries with medication storage, and these countries themselves should put more attention to medication shortage issues. Additionally, some medication administering equipment can be properly collected, sterilized, and reused, such as metered-dose inhalers.<sup>33</sup> Moreover, as recommended in the American College of Rheumatology's guideline, tailored dose reductions and extended dosing intervals can be a solution to the medication shortage caused by COVID-19.<sup>34</sup>

Our findings indicate that the travel restriction against COVID-19 resulted in insufficient access to healthcare providers, medical treatment, and medicine, thus hurting medication adherence for those with chronic conditions. Though travel restriction is an effective action to delay the COVID-19 epidemic progression,<sup>35,36</sup> it has also rendered the care for the chronically ill and other patients more inaccessible, the extent of which is beginning to be recognized recently.<sup>37</sup> Umar et al., 2021<sup>38</sup> found that inaccessibility to hospitals caused

by COVID-19 travel restrictions resulted in a 15 times more likelihood of care delay, and every additional hour of travel time to hospitals led to a 20% increase in the chance of care delay. Several promising actions have been put forward to tackle this problem, benefiting chronically ill patients' medication adherence. Firstly, telemedicine, including audio and video equipment permitting two-way, real-time interactive communication between the patient and distant site physician,<sup>39</sup> has been recommended by the World Health Organization (WHO) and the Centre for Disease Control (USA) as a first-line tool to confront this dilemma. Nevertheless, certain obstacles need to be settled for the wide acceptance of this sustainable solution, of which one main impediment is insufficient political support and understanding of the usefulness and applications of telemedicine.<sup>40</sup> More investigations on necessary resources and costs are required for effective implementation in low and middle-income countries.<sup>40</sup> Secondly, the provision of transportation and uninterrupted access to chronic care and medicines is needed, such as enabling patients and caregivers to travel through block posts or past curfew time, financial assistance, and introducing patient navigators.<sup>38</sup> Thirdly, for rural and remote areas, some essential equipment needs to be 24/7 and specialist-led, ambulance capacity and service capacity (e.g. availability of specialist cardiovascular nurses) are to be ensured, and remote monitoring can be a great choice for people with chronic diseases.<sup>41</sup> Furthermore, strategies should be planned in advance to adapt to the possible future when restrictions are progressively waived and the post-COVID-19 scenario.<sup>37</sup>

Two included studies reported that financial restriction was associated with non-adherence to medication during the COVID-19 pandemic.<sup>22,26</sup> Our result was consistent with the recent study that examined the effect of COVID-19 on medication compliance among patients with glaucoma in Egypt. This study revealed that the financial restriction (21.5% of participants) was the biggest barrier to non-

medication adherence among 200 patients with glaucoma.<sup>42</sup> In general, people with chronic diseases are often prescribed different long-term types of medication, so the high costs of their medication regimens are common. Thus, the affordability of medication has become an issue since insurance policy and coverage for medications are different at the individual and healthcare system levels. Therefore, identifying financial restrictions is important although it does not guarantee medication adherence, it is the first step to examining one of the potential problems that may be associated with non-medication adherence. Additionally, this may allow healthcare providers to provide available resources to patients before prescribing medication that patients cannot afford or do not plan to refill.

Substance use is defined as patients' self-reported use of alcohol, Khat, and or cigarettes within the last three months.<sup>26</sup> An Ethiopia study found only one out of the 33 diabetic or hypertensive participants with substance use managed to take his or her medication as prescribed during the pandemic.<sup>26</sup> Although little was discussed in the study on the potential causes of the poor medication adherence rate, substance use as a risk factor for medication nonadherence was not new before the pandemic. A study in 2006 showed around 50% of diabetic patients reported alcohol consumption.<sup>43</sup> In comparison to those without substance use (alcohol consumption and smoking), coexisting of substance use and diabetes was associated with poorer clinical outcomes and lower medication adherence rate.<sup>44</sup> Previous study also found substance use types and patterns significantly predict anti-retroviral treatment compliance in people living with HIV.<sup>45</sup> Furthermore, the impact of substance use on functionality could range from controlled use with maintaining health behaviors to heavy use with impairing health behaviors.<sup>46</sup> Individuals with support from family members, significant others, or healthcare providers and stable housing stated they were more motivated to abstain and prioritize health over substance

use.<sup>46</sup> Reduced social connection from physical distancing during the pandemic is likely to cause psychological distress and triggers a substantial increase of substance use.<sup>47</sup> This emphasizes the important role of social support plays to regulate substance use and the importance to screen patients' history of substance use and level of social support. Future research is needed in interventions that delivers social support remotely, and digital therapeutics such as an internet-based intervention to address substance use disorder<sup>48</sup> is a potential intervention that could be tested on improving medication adherence in patients with chronic disease.

Three included studies noticed some unexpectedly positive behaviors during the COVID-19 pandemic. For instance, patients with chronic diseases who comply with health guidelines are more likely to adhere better and manage medications.<sup>21,24,25</sup> However, our results were contrary to previous studies that found a negative effect of COVID-19 on behaviors such as physical activity. For example, a recent study found that physical activities have declined among Vietnamese patients who comply with restrictions on outside activities to minimize COVID-19 exposure.<sup>49</sup> Other previous studies also found that COVID-19 has harmful impacts on physical activities and exercise; these studies indicated that 40% of the general population have physical inactivity due to fear of exposing COVID-19.<sup>50,51</sup> Thus, as the COVID-19 pandemic continues its infection and deadly path, dramatic changes in behaviors should be examined to embrace medication adherence behaviors to prevent complications among patients with chronic disease.

The increased availability of health information to patients during the COVID-19 pandemic was determined to be a supporting factor in medication adherence in one of the included studies.<sup>18</sup> Our findings are consistent with previous literature studying 20 residents in a resource-limited setting in the Cape Coast metropolis in Ghana, which found that health knowledge improved during the

pandemic in terms of access to health information and increased understanding of health issues led to an increase in health-seeking behaviors.<sup>52</sup> To this point, another study examining the causes of poor medication adherence in patients with cardiovascular disease found that the most significant patient-related factors included a lack of understanding of both their disease and the treatment decision-making process and suboptimal medical literacy.<sup>53</sup> Similarly, a study of 172 patients discharged from a hospital found that 34% and 36% of patients could not identify the schedule or purpose of their medication, respectively.<sup>54</sup>

However, our findings come in contrast to previous literature findings that people engaged in riskier behaviors and fewer preventative behaviors as a result of online misinformation spread throughout the pandemic.<sup>55</sup> Additionally, the study analyzed 112 million posts on social media related to COVID-19 and found that over 40% of posts contained information from unreliable sources, 42% were circulated from bots, and 67.78% of adults have been exposed to COVID-19 related misinformation. Therefore, further study should be conducted to determine the extent to which the rise of COVID-19 misinformation translates to a rise in misinformation on chronic disease treatments. Strategies to improve health literacy should be taken to empower patients to utilize health information in their medication regimes properly. Moreover, it is necessary to determine the proper course of action to increase health literacy as well as accurate and available health information while at the same time educating patients to be less susceptible to misinformation.

This systematic review has potential limitations that need to be acknowledged. First, since this systematic review is conducted in a retrospective manner, new data published after the data collection period may be underreported, affecting the results. Second, the limitations involved the inclusion criteria that only English studies were to be included. Excluding non-English studies may change the results. Lastly, identifying relevant studies among the

many potential sources of information is usually a laborious process. However, the researchers have comprehensively searched relevant studies from the most common databases indexed.

## Conclusion

This systematic review provided a better understanding of how the COVID-19 pandemic impacts chronic disease patients' medication adherence. In addition, the results could heighten healthcare providers' awareness of providing appropriate support for them. Therefore, future research incorporating programs that support patients' needs is recommended. Moreover, more studies that aim to determine the impact of COVID-19 on medication adherence of chronically ill patients by disease type during COVID-19 need to be conducted, especially longitudinal research with robust design and sampling and analytic strategies.

## Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Not applicable, because this article does not contain any clinical trials.

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## Supplemental material

Supplemental material for this article is available online.

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