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SYSTEMATIC-REVIEW ARTICLE

Safety and Efficacy of Imatinib, Nilotinib, and Artesunate in COVID-19 Patients: A Systematic Review of Current Evidence

Ehsan Ghavimehr[1,2], Ali Zand[1,2], Seyed Ahmad SeyedAlinaghi[2], Amirali Karimi[3], Hamid Zaferani Arani[1], Pegah Mirzapour[2], Zahra Pashaei[2], Esmaeil Mehraeen[2,4,*] and Omid Dadras[2,5]

[1]School of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran; [2]Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran; [3]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [4]Department of Health Information Management, Arabdil University of Medical Sciences, Khalkhal, Iran; [5]Department of Global Public Health and Primary Care, Graduate School of Medicine, Bergen University, Bergen, Norway

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Abstract: ***Introduction*:** There is a need for better treatment options against COVID-19. This systematic review aimed to assess the safety and efficacy of imatinib and nilotinib, two tyrosine kinase inhibitors (TKIs), as well as artesunate (an anti-malarial agent), whose multilayer activities against SARS, MERS, and SARS-CoV-2 pathogenesis have been suggested in laboratory and observational studies.

***Methods*:** A comprehensive search strategy targeting relevant literature on PubMed, Scopus, and Web of Science online databases was constructed. The retrieved records were reviewed and screened by title/abstract and full text with eligibility criteria, and the most pertinent articles were included in the final qualitative synthesis. This review adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure the reliability of the results.

***Results*:** This systematic review assessed the safety and applicability of imatinib, nilotinib, and artesunate in COVID-19 patients. The results showed not only possible anti-COVID-19 effects but also acceptable safety for both generic users with comorbidities with COVID-19 and off-label use in other COVID-19 patients. Promising results were also reported enhancing the survival of COVID-19 patients.

***Conclusion*:** A double-blinded multicenter randomized controlled trial found survival benefits for imatinib with no significant treatment-related adverse events. However, no clinical trials or large observational studies exist for artesunate and nilotinib, and the evidence relies only on case reports and case series. Molecular mechanisms revealed in preclinical studies support the possible benefits of these medications in COVID-19 treatment. However, the scarcity of reliable evidence requires further studies on possible COVID-19 treatments, including but not limited to artesunate, nilotinib, and imatinib. Nevertheless, these drugs' lack of serious adverse events suggests their safe use for other indications during the COVID-19 pandemic.

Keywords: COVID-19, SARS-CoV-2, treatment, imatinib, nilotinib, tyrosine kinase inhibitor, chronic myeloid leukemia, artesunate, malaria, off-label.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2), has been the source of global concern as a pandemic and caused more than 5 million death tolls so far [1, 2]. Similar to most viral infections, there is no curative medicine for COVID-19. Hence, prevention through vaccination, social distancing, *etc*. seems the best way of controlling the pandemic [3, 4]. Nevertheless, several scientists and pharmaceutical companies have been devoting a huge budget and endeavors to develop effective medications for COVID-19 besides more efficient vaccines [5-7]. Apart from preventive measures, such as vaccines and preventive medicine, ongoing therapeutic investigations are reliable considering the substantial impact of the Coronaviridae family on human life during different periods, causing the failure of vaccines or occurring in new pandemics. Current therapeutic regimes consist of a multilayer strategy (*e.g*., inhibition of viral replication, viral neutralization, immunomodulation, immunosuppression, palliative treatment, complication treatment) [8, 9] in different

*Address correspondence to this author at the Department of Health Information Management, Khalkhal University of Medical Sciences, Khalkhal, Iran; Tel: +98-45-32426801, Fax: +98-45-32422305, E-mail: es.mehraeen@gmail.com

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phases of pathogenesis (*e.g*. presymptomatic, viral pneumonia, ARDS, cytokine storm); all of which are more based on the outcomes of treatment in clinical trials negligent of the exact pathophysiology of the disease rather than targeted specific medications. Repurposing currently available drugs is one of the cost-beneficial approaches, which, in a general sense, has a history as long as pharmacology. Regardless of being beneficial, the repurposing approach is justified due to the fact that relatively common pathogenesis pathways exist between diseases that could be reversed by the multi-potent neutralizing effects of some medicines [10].

Acute respiratory distress syndrome (ARDS) is often the primary cause of death due to COVID-19, which is underlaid by an imbalance of pro-inflammatory and anti-inflammatory mediators, where one of the endothelial or epithelial layers of alveoli is damaged and their permeability increases [11-14]. ARDS occurs in the severe extreme of acute lung injury (ALI), a spectrum of pulmonary diseases characterized by hypoxemia, non-cardiogenic pulmonary edema, and dysregulated and excessive inflammation [13]. Consequent to the damage, macrophages release cytokines in order to attract neutrophils, activate them, and increase alveolar permeability [13, 15]. Neutrophils are sequestered in vessels and egress into the alveolar space and then become activated and release enzymes (like matrix metalloproteinases) and other mediators, which, in turn, leads to the development of diffuse alveolar damage (DAD) pathologically and ALI/ARDS clinically [15].

Protein tyrosine kinases (PTKs), a group of cell receptors, play important roles not only in the chemoattraction and activation of neutrophils but also in the increase of alveolar permeability by loosening adhesions between adjacent endothelial cells, thereby facilitating the passage of fluids and leucocytes [13]. Therefore, although tyrosine kinase inhibitors (TKIs) have been initially developed as a successful anti-cancerous targeted therapy (especially for chronic myeloid leukemia [CML]) [16, 17], they have been considered as anti-SARS-CoV-2 agents [17-23]. Furthermore, some independent antiviral effects have been reported for nilotinib and imatinib [24-27], including anti-MERS, anti-SARS, and of course, anti-SARS-CoV-2 effects [20, 28-31]. On the other hand, some immunomodulatory features and mitigating activity have been shown for TKIs in acute lung injury and ARDS [32, 33].

Artesunate, like its precursor, artemisinin (derived from *Artemisia annua*), was developed as an anti-malarial agent in multidrug treatment regimes of resistant malaria, whereas its anti-cancerous [34-36], anti-viral [34, 37, 38], and immunomodulatory [39, 40] effects were revealed later. Artesunate has been shown to have some inhibitory effects on a wide variety of RNA and DNA viruses, including human cytomegalovirus (HCMV), human herpes simplex virus (HSV), hepatitis B virus (HBV), Ebola virus, polyomavirus BK, *etc*. [34, 37, 38]. Interestingly, anti-SARS-CoV-2 effects have been recently reported for artesunate *in vitro* [37]. Considering the immunomodulatory aspect, artesunate's effects on decreasing proinflammatory cytokines, especially in lungs, have been reported [39], particularly attenuating TNF and IL-6 [40], which are important in the pathophysiology of COVID-19 as mentioned above. The application of anti-malarial medicines (especially hydroxychloroquine) for the treatment of COVID-19 has been in the spotlight since the beginning of the pandemic [10, 41-43]; hence, artesunate, due to its antiviral and immunomodulatory features, has been prominent among them.

In this systematic review, we aimed to systematically investigate the available clinical evidence concerning the efficacy and safety of these controversial medications, including imatinib, nilotinib, and artesunate, which have been proposed and occasionally used in the treatment of COVID-19.

2. METHODS

In this review, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist as well as the Cochrane Handbook for Systematic Reviews of Interventions checklist to systematically review and summarize the current evidence related to COVID-19 targeted medications, including imatinib, nilotinib, and artesunate, from different therapeutic aspects, including their efficacy, side effects, preventive capacity, the possible effect on the survival, and complications in clinical settings [44, 45].

2.1. Searching Methods

A search strategy was developed combining the relevant keywords to collect all relevant literature concerning the safety and efficacy of imatinib and nilotinib (two tyrosine kinase inhibitors), and artesunate (an antimalarial agent) in COVID-19 prevention and treatment until the 12th of December, 2021 .Three online databases of PubMed, Scopus, and Web of Science (WOS) were searched in parallel to ensure an acceptable coverage of the whole literature on COVID-19. To achieve a better management entry, searching for each targeted drug was separately performed, which was considerably helpful in decreasing potential biases in grouping and evaluating articles in the next screening steps, especially for articles addressing more than one of our target drugs. Therefore, nine different queries were developed given each database's syntax format, which can be found in S1.

The queries were written carefully, considering all common/rare names and abbreviations for COVID-19 disease and each of our targeted drugs (S1). For COVID-19-related phrases, we included forty-nine different search terms, which were separated by "OR". We included all generic, codename, chemical (IUPAC), and trade names for targeted medications. Alternative terms were sought using the Medical Subject Headings (MeSH) database at NCBI, entries of drugs at Medscape, Drugbank websites, and relevant literature.

The details of the retrieved articles for each database can be found in Supplementary Table **S1**. Fig. (**1**) summarizes the screening process (PRISMA flowchart) for all drugs. Figs. (**2-4**) illustrate the review and screening process separately for imatinib, nilotinib, and artesunate, respectively.

In addition to searching databases, we included other related articles by checking the references of the included records. One study, regarding nilotinib, was included in this process [46, 47].

2.2. Screening Articles

A four-phase screen process was carried out to retrieve the relevant articles following pooling all entries from different databases in an ENDNOTE file. The researchers performed the four-phase screening process for each target drug independently and in parallel. Exclusion criteria for each are presented in each figure (Figs. **1-4**).

2.2.1. Phase 1

Duplicate entries were detected and excluded. It should be noted that based on our strategy of retaining the entries of each target drug independently, some duplicates remained in the pooled database after screening but they were analyzed separately eventually.

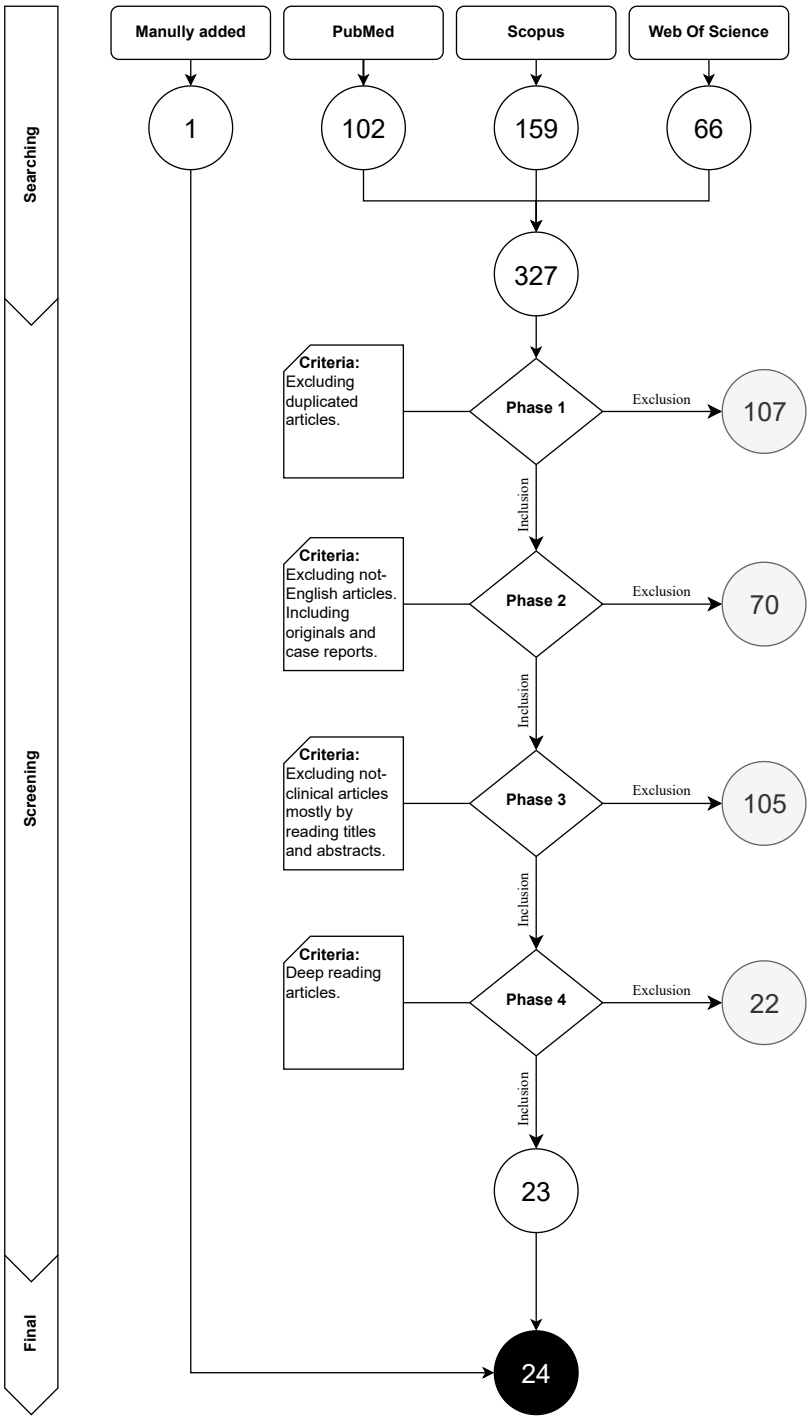

Fig. (1). PRISMA flow diagram showing screening statistics in general.

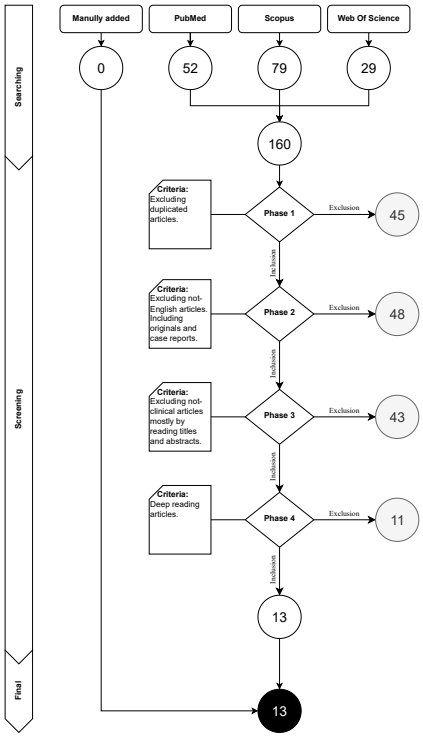

Fig. (2). Showing screening statistics for Imatinib in detail.

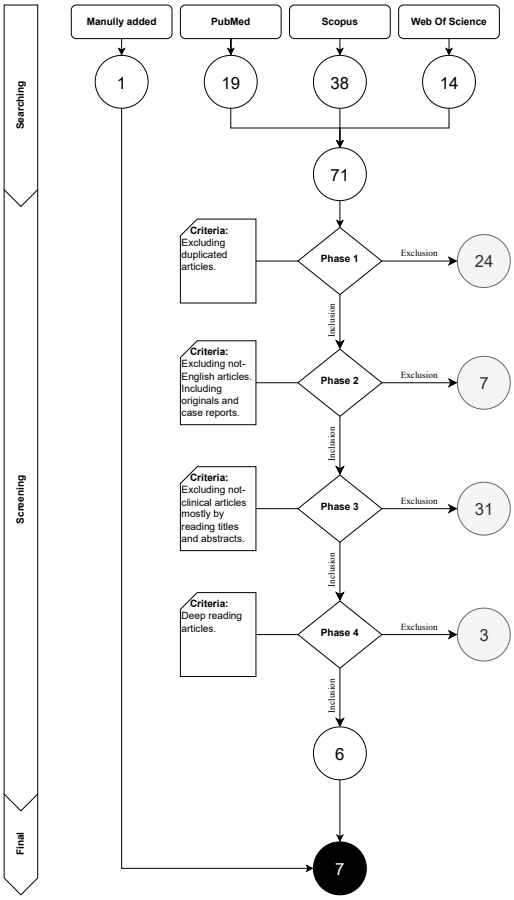

Fig. (3). Showing screening statistics for Nilotinib in detail.

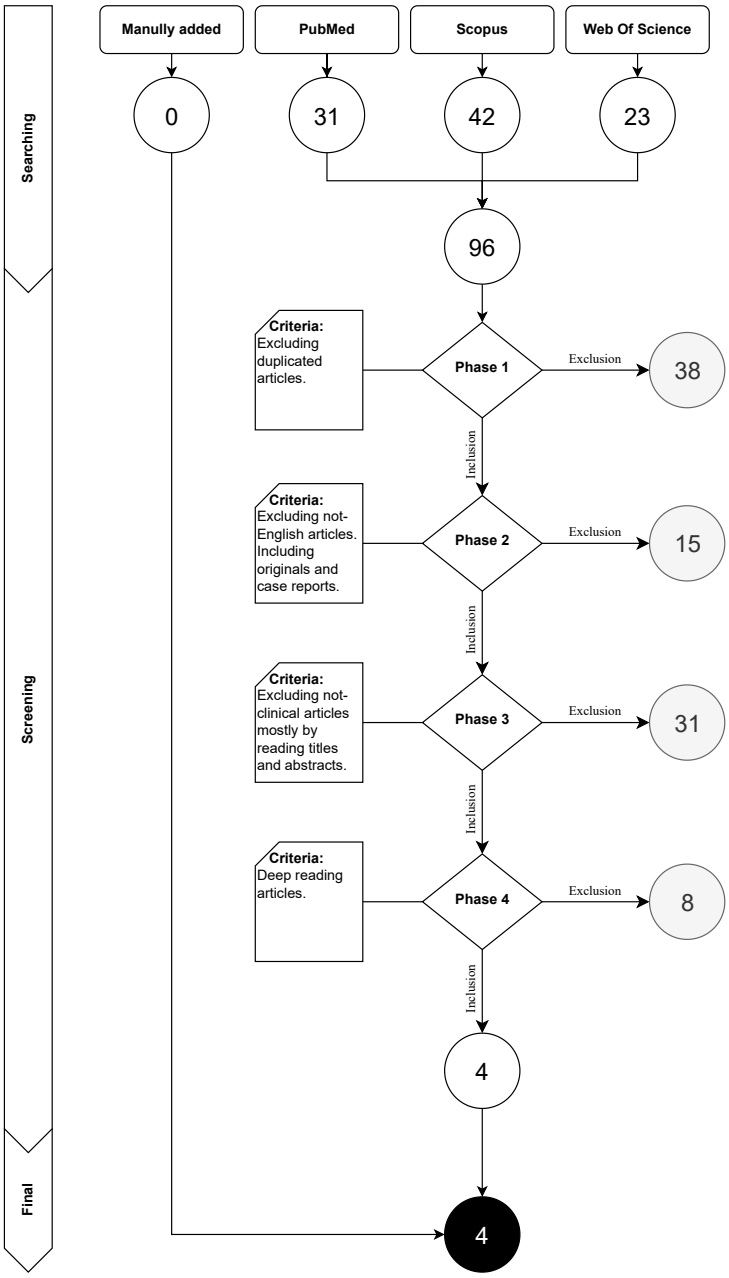

Fig. (4). Showing screening statistics for Artesunate in detail.

2.2.2. Phase 2

All articles that met the following criteria were excluded:

- Non-english articles.
- Published before the COVID-19 pandemic.
- Non-original articles and brief reports, such as thesis, dissertation, conference communication, editorial, notes, review, mini review, systematic review, meta-analysis, news design, perspective, reflection, and guidelines.

a) No case report/series, brief report, pre-proof, or article in the press were excluded due to the shortage of literature on COVID-19 and our target drugs.

b) The type of article was defined based on self-reporting on databases and assessing full text if necessary.

c) Letter articles containing case reports or primary data from clinical trials have not been excluded [7, 9, 10].

2.2.3. Phase 3

All original English articles were assessed methodologically to exclude non-clinical records. All *in vitro*, *in silico*, animal/botanical, bioinformatics/computational methods, chemical and pharmacological, social science, and engineering studies were excluded. This phase was accomplished by reading titles and abstracts, and the full texts were reviewed whenever necessary for a better understanding of the authors' methods.

2.2.4. Phase 4

The full texts of the remaining articles were reviewed to ensure that it concerns the objectives of this review. No article was excluded due to a lack of full text. The missing full texts were retrieved by reaching out to the authors. Cross-sectional studies with no reliable paraclinical tests (*i.e.*, RT-PCR, SARS-CoV-2 testing, and/or lung CT) to confirm SARS-CoV-2 infection were excluded in this step. No article was excluded because of the small study population (even being a case report/series), race of subjects, and low-quality methodology.

2.3. Data Extraction

Two approaches were taken in data extraction: firstly, predefined tables and collecting certain and unified data from every article, and secondly, a comprehensive study of articles to extract special consideration of the articles as well as their limitations. The provided data of the latter way will be reviewed in this article's text. Considering the narrow evidence on the subject, we tried to cover as much data as possible and not exclude articles due to the lack of our targeted features.

3. RESULTS

3.1. Imatinib

Observational studies have raised hopes on imatinib efficacy in COVID-19 by evaluating different aspects of SARS-CoV-2 infection in previously imatinib-receivers, including assessment of COVID-19 incidence in imatinib-administered patients considering their age and other comorbidities [46, 48-51], demonstrating fewer complications during infection course [52], and no difference in immunoglobulin (Ig) production after SARS-CoV-2 vaccination or infection [46]. However, observational studies could only be considered as primary aspects of hypotheses and further controlled clinical experiments should be conducted to collect reliable data related to imatinib administration in nonhematologic COVID-19 patients. While most of these clinical trials have not yet been published at the time of preparing this review, a trial by Aman *et al*. found considerably promising improvements in COVID-19 patients receiving imatinib during the course of the disease for the first time [53]. However, some case reports simultaneously reported some adverse events in COVID-19 patients who were or had been on imatinib [54-56]. Nevertheless, the very first clinical experiment of prescribing this medicine has been reported as a case in a letter article [47]. Although none of these negative or positive findings in case reports can be directly attributed to the drug and thereby neither in favor of nor against the primary hypothesis, further observational studies and clinical trials have been more compatible with the latter one. A summary of the three groups of clinical studies, clinical trials, observational studies, and specially reported cases, is provided as follows (Table **1**).

3.1.1. Clinical Trials

Aman *et al*. conducted a randomized double-blind, placebo-controlled trial to investigate the efficacy and safety of imatinib in severe COVID-19 patients who required supplemental oxygen support. The trial was done in the Netherlands. A total of 385 patients were enrolled in the study and randomized into the placebo and imatinib (800 mg loading dose on day 0, followed by 400 mg OD on days 1-9) groups. The patients, administered imatinib (197 patients), were reported to have much better clinical indexes in comparison with the patients, receiving placebo (188 patients), lower mortality in 15 (8%) *vs.* 27 (14%) until day 28 (unadjusted hazard ratio [HR] 0.51 [95% CI 0.27-0.95; $p = 0.034$], adjusted for sex, obesity, diabetes mellitus (DM), and cardiovascular disease HR 0.52 [95% CI 0.26-1.05; $p = 0.068$]), and less need for mechanical ventilation (unadjusted HR 1.07 [95% CI 0.63-1.80; $p = 0.81$], adjusted for sex, obesity, DM, and cardiovascular disease HR 1.02 [95% CI 0.80-1.30; $p = 0.87$]), as well as less duration for health cares, including fewer days of ICU admission (8 [5-13] *vs.*15 [7-21]; $p = 0.025$), and mechanical ventilation in comparison with the survivors (7 [3-12] *vs.*12 [6-25]; $p = 0.023$) and also in comparison with the whole population (7 [3-13] *vs.*12 [6-20]; $p = 0.0080$), but more days of hospital admission (7 [4-11] *vs.*6 [3-11]; $p = 0.51$), ventilator-free in ICU-admitted population (22 [14-26] *vs.*9 [0-23]; $p = 0.018$), and oxygen supplementation (7 [3-12] *vs.*5 [3-11]; $p = 0.23$), which might be caused by earlier extubation. Despite these promising findings, the researchers have declared that imatinib failed to meet their primary hypothesis of "reducing time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours". The investigators have also indicated the effect of sample size on the secondary outcomes. Regarding the safety of utilization, it was reported that none of the adverse events were imatinib-related [53].

3.1.2. Observational Studies

Since chronic myeloid leukemia (CML) is the main indication of imatinib, it would not be surprising that the subjects of all observational studies were CML or other hematologic patients, who are often of older age groups, predisposing them to comorbidities (*e.g.*, diabetes mellitus [DM] and hypertension [HT]), thereby higher symptomatic SARS-CoV-2 infection and death risks. In this review, the results from eight observational studies, including CML patients treated with imatinib, will be reviewed.

Li *et al*. conducted a cross-sectional survey with a questionnaire, followed by appropriate confirming paraclinical tests (RT-PCR SARS-CoV-2 testing and lung CT) to assess the prevalence of COVID-19 among CML patients who were on TKIs treatment as well as possible predisposing or preventive effects of their disease or treatment on the COVID-19 infection. The questionnaire was distributed among 530 non-hospitalized CML patients receiving TKIs, whose median age was 44 years. Five patients were diagnosed with COVID-19 by RT-PCR (four patients) or a typical lung CT pattern for COVID-19 (one patient), three of whom were on imatinib (two RT-PCR positive with common severity and one lung CT positive with critical severity). By considering the total number of 346 patients receiving imatinib, the prevalence of COVID-19 infection among them was 0.86% (3/346). Two of these patients were cured, while one female aged 89 years old died unfortunately. CML outpatients had a higher rate of COVID-19 (0.9% [95% CI 0.1-1.8%]) than the normal population (0.1% [95% CI 0-0.12%]), but much lower than hospitalized malignant hematological patients (10% [95% CI 6-17%]) and health-care providers (7% [95% CI 4-12%]) [48].

Table 1. The perspective of the articles on the utilization of imatinib in COVID-19 patients.

Author - Year, Country	Population, Study Design	Status of Patients on Imatinib with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Imatinib Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Clinical Trials								
Aman *et al.* - 2021, The Netherlands [53]	385 adults, randomized, double-blind, placebo-controlled, clinical trial	197 patients with severe COVID-19 and in need of supplemental oxygen who received imatinib experimentally for ten days	**Imatinib+ placebo groups:** Current or former smoker (77+76), BMI of >30 kg/m² (53+83), DM (41+54), CAD (35+48), HT (69+76), COPD or asthma (38+33), VTE history (5+5), CKD (7+7), Hepatic disease (1+1), Rheumatic disease (1+1), CHF (8+4)	800 mg loading dose on day 0, followed by 400 mg OD on days 1-9	**Before COVID-19 prescriptions in imatinib+ placebo groups:** glucose-lowering drugs (40+54), antihypertensive treatment (91+102), ACEI or ARB (51+70), statins (62+65), platelet inhibitors (42+40), oral anticoagulants (17+21) **After COVID-19 administrations in imatinib+ placebo groups:** LMWH (167+150), oral anticoagulants (6+8), antibiotics (85+77), DXM (143+133), RDV (40+40), (H)CQ (15+17)	188 patients with severe COVID-19 and in need of supplemental oxygen who received a placebo for ten days	Lower mortality: adj HR 0·52; p=0.068 Less need for mechanical ventilation: adj HR 1·02; p=0.87 Fewer days of ICU admission: p=0.025 Fewer days of mechanical ventilation in comparison with the survivors: p=0.023 Fewer days of mechanical ventilation in comparison with the whole population: p=0.0080 More days of hospital admission: p=0.51 More days of ventilator-free in ICU-admitted population: p=0.018 More days of oxygen supplementation: p=0.23	Adverse events have not been reported to be attributable to imatinib medication.
Observational Studies								
Li *et al.* - 2020, China [48]	530 adults (346 on imatinib), cross-sectional survey	3 nonhospitalized CML patients on imatinib with COVID-19	CML (3), DM (1), HT (1), CAD (1)	Not reported	Not reported	Hospitalized hematological malignant patients	Lower COVID-19 prevalence: 0.86% *vs.*10%	Not reported
						Health-care providers	Lower COVID-19 prevalence: 0.86% *vs.*7%	
						CML patients on different TKIs	Similar COVID-19 prevalence: 0.86% *vs.*1%	
						The general population	Higher COVID-19 prevalence: 0.86% *vs.*0.1%	
Başcı *et al.* - 2020, Turkey [52]	64 adults, retrospective case/control	16 CML patients on different TKIs (9 on imatinib) with COVID-19	CML (16), HT (3), CAD (2), COPD (2), DM (2), CKD (2)	Not reported	Favipiravir (3), oseltamivir (5), HCQ (8), high dose vitamin C (1)	A selected group of 48 matched patients regarding age, gender, and comorbid disease but cancer and TKIs treatment.	No mortality, mechanical ventilation, and ICU admission in the case group despite the control group.	Not reported

(Table 1) contd….

Author - Year, Country	Population, Study Design	Status of Patients on Imatinib with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Imatinib Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Crolley *et al*. 2020, UK [49]	68 adults, retrospective study	18 patients on targeted treatments for cancer (one on imatinib) with COVID-19	CML and many other forms of malignancies	Not reported	Not reported	46 patients on chemotherapy with COVID-19	Decreased likelihood of death in patients on targeted treatment (including imatinib) *vs.*on chemotherapy (adj OR 0.53 *vs.*9.84).	Not reported
Yılmaz *et al*. - 2021, Turkey [51]	243 adults, single-center survey	3 CML patients on imatinib (upheld in one) with COVID-19	CML (3), CKD (1), HT (2), BPH (1), CAD (1)	400 mg OD	**Before COVID-19:** losartan (1), hydrochlorothiazide (1), ASA (1), terazosin (1), metoprolol (1), olmesartan (1), amlodipine (1) **After COVID-19:** HCQ (1), clarithromycin (1), enoxaparin (3), ceftriaxone (1), favipiravir (1), oseltamivir (1)	A 243-patient CML population regardless of COVID-19	All 3 patients recovered.	Imatinib was withheld in one patient due to concerns about QTc prolongation
Wang *et al*. - 2021, USA [50]	62 adults, single-center retrospective study	One patient with CML on imatinib and COVID-19	CML, FL, lymphopenia (ALC <1,000 B/L), former smoker	Not reported	rituximab, AlloSCT	Other hematologic malignant patients with COVID-19	Death after intubation and PE.	Not reported
Bonifacio *et al*. - 2021, Italy [46]	564 adults; cross-sectional study (serology)	2 CML patients on imatinib with positive serology for anti-SARS-CoV-2 Ig	CML (2)	Not reported	Not reported	205 patients with CML on imatinib regardless of positivity to anti-SARS-CoV-2 Ig	Prevalence of COVID-19 based on serology was 0.98% among imatinib receivers while the seropositivity was 1.95% in the whole CML population (similar to the general population) and 3.5% among nilotinib receivers.	Not reported
Pimpinelli *et al*. - 2021, Italy [60]	92 adults, prospective cohort study	7 CML patients on imatinib (w/o COVID-19)	CML (7)	Not reported	BNT162b2 mRNA vaccine	42 MM patients (w/o COVID-19)	MPM [20 out of 50 had CML; among whom 7 were on imatinib] had a better response to BNT162b2 mRNA vaccine *vs.*MM patients (88% *vs.*76.6%) but lower than the nonmalignant control group (88% *vs.*100%).	Not reported
Morales-Ortega *et al*. - 2021, Spine [57]	30 adults; primary reports of a clinical trial	30 non-hematologic patients with COVID-19 receiving imatinib experimentally	Smokers (3), previous alcohol consumption (5), dyslipidemia (12), HT (9), DM (5)	400 mg OD (for 7 days)	DXM (21), TCZ (9), RDV (2)	None	IgG production was not impaired.	Not reported
Case Reports								
Morales-Ortega *et al*. - 2020, Spain [47]	38-year-old woman, case report	A non-hematologic patient with COVID-19 who was administered imatinib experimentally	Not reported	400 mg OD day 12 afterward (after relapse) for 5 days	HQC, LPV/r, ceftriaxone	None	After receiving imatinib, the patient's clinical status improved, and was discharged.	Not reported

(Table 1) contd….

Author - Year, Country	Population, Study Design	Status of Patients on Imatinib with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Imatinib Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Ibrahm *et al*. - 2020, Saudi Arabia[54]	57-year-old man, case report	A CML patient on imatinib	CML, DM, DKA, metabolic acidosis	Imatinib 400 mg OD, except for 5 days of mechanical ventilation (due to drug interaction with ritonavir, a modified dose of imatinib on someday).	HQC, azithromycin, ceftriaxone, enoxaparin (1 mg/kg/BID), methylprednisolone (40 mg BID), LPV/r (400/100 mg BID 14 das), ribavirin (400 mg BID 14 days), interferon beta 1-b (8MIU 3 days), paracetamol, glucose−lowering drugs	None	The patient recovered successfully.	Not reported
Lagziel *et al*. - 2020, USA [55]	58-year-old woman, case report	A CML patient on imatinib with COVID-19	CML, morbid obesity, HT, gout, CKD	Not reported	Levofloxacin, oseltamivir, vancomycin, piperacillin, tazobactam, prednisone, hydrocortisone	None	The patient recovered successfully.	Possible role of imatinib in the development of the skin presentation, which was supposed as SJS/TEN, after AKI and COVID-19 complications.
Ranganathan *et al*. - 2021, USA [56]	Three adults, case series	A 69-year-old black woman with CML and COVID-19	CML, CAD, HT, DM, obesity, dyslipidemia, persistent encephalopathy	Not reported	HQC, methylprednisolone, low dose of fentanyl, TPE (5 total exchanges in 10 sessions)	None	The patient's neurological manifestations improved.	Not reported

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor, adj HR: adjusted hazard ratio, adj OR: adjusted odds ratio, AKI: acute kidney injury, ALC: absolute lymphocyte count, AlloSCT: allogeneic stem cell transplant, ARB: angiotensin receptor blocker, ASA: acetylsalicylic acid, BID: twice a day, BPH: benign prostatic hyperplasia, CAD: coronary artery disease, CHF: congestive heart failure or heart failure, CKD: chronic kidney disease or renal failure, CML: chronic myeloid leukemia, COPD: chronic obstructive pulmonary disease, CQ: chloroquine, DKA: diabetic ketoacidosis, DM: diabetes mellitus, DXM: dexamethasone, FL: follicular lymphoma, HCQ: hydroxychloroquine, HR: hazard ratio, HT: hypertension, LMWH: low-molecular-weight heparin, LPV/r: lopinavir/ritonavir, MM: multiple myeloma, MPM: myeloproliferative malignancies, OD: daily, OR: odds ratio, PE: pulmonary embolism, RDV: remdesivir, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SJS/TEN: Steven Johnson syndrome/toxic epidermal necrolysis, TCZ: tocilizumab, TPE: therapeutic plasma exchange, VTE: venous thromboembolism, w/o: without.

Başcı and colleagues conducted a retrospective study to compare the outcome of COVID-19 in 16 CML patients taking TKIs (9 on imatinib, 4 on dasatinib, and 3 on nilotinib) with a selected group of 48 patients matched with respect to age, gender, and comorbidities except for cancer (1/3 ratio). Patients on TKIs were less likely to be admitted to ICU, undergo mechanical ventilation support, or stay long in the hospital in comparison with the non-cancer patient sample. None of the patients on imatinib were reported neither to need ICU admission, or mechanical ventilation support, nor to die. A shorter hospital stay was also reported for TKI-receivers/imatinib-receivers *versus* the control group (9 [2-18]/8 [6-18] *vs.*18 [4-46]). Nonetheless, this study failed to show statistical significance for any of these findings and suggested further and larger studies [52].

A large-scale study by Crolley and colleagues included 2791 cancer patients on systemic anticancer treatment (SACT), 68 of whom were COVID-19 positive while 2723 of them were COVID-19 negative. Interestingly, it was shown that although chemotherapy increased the likelihood of death (adjusted odds ratio [OR] 9.84 [95% CI 5.73-16.9]), targeted treatments for cancer, in general, had a protective effect (adjusted OR 0.53 [95% CI 0.30-0.95]). However, only one of the patients on targeted treatments was receiving imatinib in their regimen [49].

Yılmaz *et al*. assessed 243 CML regarding the likelihood of SARS-CoV-2 infection and management of their comorbidities. Five patients (2%) tested positive, which was higher than the general population rate (0.25%). Three out of the five patients were on imatinib (400 mg OD) before the infection

and two of them continued it during COVID-19 treatment. All three patients recovered successfully with no complications in 4-10 days [51].

In the study by Wang and colleagues, a single-center experience on hematologic malignancies, three CML cases with concomitant COVID-19 infection (confirmed by RT-PCR SARS-CoV-2 testing) among 6000 patients were diagnosed. One of them aged 60 years old and died after intubation and pulmonary embolism while receiving imatinib [50].

Serological investigations have always provided valuable epidemiologic insights. Bonifacio *et al*. benefited from this methodology to conduct a cross-sectional study on CML patients on imatinib (and nilotinib) by comparing the prevalence of COVID-19 between these patients and the general population. The study assessed the serological positivity of SARS-CoV-2 among 564 CML patients (most of whom [n=467] were on TKIs and 205 patients were on imatinib), leading to a COVID-19 prevalence of 1.95% (95% CI 1.09-3.46) which was similar to the general population. The study population was based on outpatients, and none represented any COVID-19 symptoms. Eleven patients were SARS-CoV-2 IgG positive (three of whom were also SARS-CoV-2 IgM positive) with different histories of having COVID-19 symptoms or previously confirmed infection. Two out of those 11 patients were on imatinib with no previously confirmed COVID-19 but self-limited symptoms some weeks ago. Based on their reports, the prevalence of COVID-19 among imatinib users was <1% (2/205), which was lower than the general population [46].

In a prospective cohort study, Pimpinelli and colleagues studied the efficacy of COVID-19 vaccination by serological methods in hematologic patients. They compared the neutralizing anti-SARS-CoV-2 IgG titers in 42 multiple myeloma (MM) cases and 50 myeloproliferative malignancy patients (MPM; including 20 CML, 11 essential thrombocythemia, 8 myelofibrosis, and 11 polycythemia vera patients) with its level in 36 non-cancer elderly controls, all of whom had been vaccinated with two doses of BNT162b2 mRNA vaccine (2 weeks interval) and tested negatively for COVID-19. All CML patients were on TKI treatments (7 on imatinib, 7 on nilotinib, 4 on dasatinib, and 2 on bosutinib). Unfortunately, no data was reported for the TKI-treated patients by the authors and the study failed to conclude neither in favor of nor against holding TKIs before vaccination. Nevertheless, the seroprotection rate (>15 AU/mL) of the MM group three weeks after the second dose was 78.6% in comparison with the 100% in the control group (p=0.003); although this rate was better in MPM patients (88%), it was still significantly less than the control group (p=0.038). The same was true about the geometric mean concentrations (GMCs), where it was decreased significantly in both MM and MPM patients (from 353.3 AU/mL in the control group in comparison with 106.7AU/mL in the MM patients and 172.9 AU/mL in the MPM patients [p=0.003 and p=0.049 respectively]) [48].

Although the clinical trial of David Bernal *et al*. has not finished, a preliminary published letter article reported that imatinib (400 mg OD) did not reduce IgG production in non-hematologic COVID-19 patients who were receiving it experimentally [57].

3.1.3. Case reports and Case Series

Morales-Ortega and colleagues reported a case of a 38-year-old woman with COVID-19 taking hydroxychloroquine (QCH), lopinavir/Ritonavir (LPV/r.), and ceftriaxone. After a short improvement interval, signs and symptoms relapsed and the condition continued being deteriorated. Oxygen supplementation was required, radiologic findings were not promising, and she developed a hyper-inflammatory state despite treatment with HCQ and lopinavir/ritonavir. Imatinib was experimentally initiated on day 12 of symptoms (without any hematologic/oncologic indication), while ceftriaxone was held up. Three days later, the patient's clinical profile improved, and she was discharged on day 5 of the initiation of imatinib. The patient was on imatinib for five days and on HCQ and LPV/r for 9 days. Later, she was also enrolled in an ongoing clinical trial. This case is the first case of experimentally using imatinib in a non-hematologic patient for COVID-19 [47].

In another case report by Ibrahm and colleagues, a CML patient developed ARDS during SARS-CoV-2 infection. The patient continued to receive imatinib during the COVID-19 treatment except for five days of mechanical ventilation (during the administration of ritonavir, the dosage of imatinib was modified due to drug interaction). Eventually, he improved clinically and fully recovered [54].

Lagziel and colleagues described COVID-19 in a complicated CML case of a 58-year-old woman suffering from morbid obesity, hypertension (HT), gout, and chronic kidney disease (CKD), with four years history of imatinib treatment. Although her two first COVID-19 tests were negative despite respiratory signs and symptoms, acute kidney injury (AKI) and severe dermatologic presentations developed. The skin presentations, which were later interpreted as Steven Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), started with rashes, developed into vesicles and bullae with desquamation, and finally formed widespread large open wounds (dermatopathological biopsy result was erythema multiform-like reaction). Eventually, the third COVID-19 test resulted positive in another center, and despite all complications, she recovered successfully [55].

Ranganathan *et al*. evaluated the reversing effects of therapeutic plasma exchange (TPE) on the complication of persistent encephalopathy after COVID-19 in three patients. One of the patients, whose outcome of undergoing TPE treatment for post-COVID-19 encephalopathy was assessed, appeared to be on imatinib treatment due to a recent diagnosis of CML. The authors reported a considerable improvement in the patient's neurological signs and symptoms after TPE. However, it was not clear whether imatinib was continued after COVID-19 diagnosis and if so, whether it has contributed to the development of persistent encephalopathy after COVID-19 or reversed it by TPE, or neither of them [56].

3.2. Nilotinib

No study was found related to the use of nilotinib in COVID-19 patients, although studies on CML patients have again provided insight to continue with TKIs in the post-COVID-19 period. Similar to imatinib, all evidence related to

the use of nilotinib in COVID-19 infection emerged from the studies concerning CML patients (Table **2**). Except for a complicated case of multiple cranial nerve palsy due to a blast crisis which might be irrelevant to the prescription of nilotinib [50], we have not found any other adverse event report. Four studies have expressed promising outcomes of nilotinib-administered CML patients or a lower prevalence of infection among them [46, 48, 51]. Immunological investigations have implicated that although humoral reactions might be important in COVID-19 patients, T-cell-mediated responses are required to be studied more in future endeavors [48].

As it has been described in the cross-sectional survey by Li and colleagues for imatinib, although the imatinib-receiving CML sample had some cases of COVID-19 (3 out of 345), no infection was reported in the nilotinib group (0 out of 59) [48].

A retrospective study by Başcı and colleagues was also summarized earlier in the imatinib section. The promising findings of improved clinical outcomes in TKI receivers were again reflected by no ICU admission and mechanical ventilation in the three on-nilotinib patients. Although the total hospital stay was longer than imatinib-receivers (12.5 *vs.* 8), it was still shorter than the control group (12.5 *vs.*18). However, it was not statistically significant [52].

Yılmaz *et al*. whose study was also previously described, presented two cases of chronic CML receiving nilotinib for years (nilotinib was withheld in both during their COVID-19 course). Like the three on-imatinib patients, the two nilotinib receivers also recovered successfully (one developed acute kidney injury [AKI]), while it has been declared that they have not been using nilotinib during COVID-19 treatment due to QTc prolongation [51].

CML could have different phases and complications, as Bouchlarhem *et al*. presented a 35 years old male case of accelerated CML on nilotinib, who was also later diagnosed with a severe SARS-CoV-2 infection requiring hospitalization and non-invasive ventilation. Unfortunately, he developed multiple cranial nerve palsy due to a blast crisis, which is a known, but rare, CNS complication of CML. Regarding CML and blast crisis, appropriate chemotherapy treatment was added to nilotinib intravenously and intrathecally. Eventually, he was discharged after curing COVID-19 and multiple cranial nerve palsy [58].

Immunological assessment of COVID-19 in CML patients has been evaluated in the studies of Mansi and colleagues and Bonifacio *et al*. As described earlier among the 11 serologically positive patients in the study of Bonifacio and colleagues, four patients were on nilotinib. While the prevalence of the seropositivity to SARS-CoV-2 in CML patients (1.95%) was similar to the general population, it was higher among the nilotinib-users (3.5% [4/114]), contrary to imatinib takers (<1%) [46].

Mansi *et al*. evaluated acquired immune responses in a 52-year-old woman, who was in the early stages of CML and being treated by nilotinib, 52 months after SARS-CoV-2 infection. The humoral immune response was positive while the T-cell mediated response (to CoV-S, M, and N proteins) was not detected (no history of cancer in which T-cells are less responsive to the three proteins with 33.3%, 33.3%, and 14.3% prevalence). In general, the studied population demonstrated that serological reactions can stay positive for months after COVID-19 in malignant patients, and T-cell response is more prone to be impaired in comparison with non-cancer individuals [59].

Although the unique study of Pimpinelli and colleagues has also considered nilotinib-administered in addition to imatinib-prescribed patients, the detailed data of these groups have not yet been published; hence, comparison between groups was not possible. The general findings of this study indicated that MPM patients are at least better than MM patients regarding immunoglobulin production [60].

3.3. Artesunate

In three case reports and one case series study [61-64], artesunate has been prescribed for the treatment of four patients with SARS-CoV-2 and malaria/dengue co-infection. The age range of the patients was 24-38 years and none of them had chronic disease except one patient who had a recurrent malarial infection. All three patients who were discussed in the case reports were male and the other one presented in the case series was a pregnant woman. There were four pregnant women co-infected with COVID-19 and malaria in the case series study while only one of them received artesunate [63]. In all the case reports [61, 62, 64], the patient who received artesunate (intravenously or orally) was fully recovered and no death was reported. In the case series, although artesunate appeared to be safe for the mother and the fetus and no complication was reported in this group, an abortion occurred in one of the three patients who did not receive artesunate. In addition to artesunate, other oral and injectable treatments were used for all four patients, as described in Table **3** in detail. No side effects were reported in these four studies.

4. DISCUSSION

Pre-clinical studies and molecular mechanisms support the possible benefits of artesunate and nilotinib for the treatment of COVID-19; however, the clinical evidence is limited, and no conclusive evidence is available for these two treatments. On the other hand, the clinical evidence is more promising for imatinib. Besides, several observational studies and a double-blinded placebo-controlled randomized clinical trial have demonstrated longer survival and improved clinical severity, decreased duration of ICU stay, and duration of mechanical ventilation in patients with COVID-19 receiving imatinib [53]. Small studies on imatinib have also reported that patients on imatinib may represent a favorable vaccination outcome with BNT162b2 and a lower risk for SARS-CoV-2 infection.

Regarding the side effects, none of the studies on artesunate and nilotinib have reported adverse events. Nevertheless, the existing evidence points to an acceptable safety profile for imatinib. The aforementioned clinical trial demonstrated that none of the adverse events were directly related to imatinib [53]. One study observed some possible skin reactions with unclear relation to imatinib [55], and another study discontinued imatinib due to the patient's QTc prolongation [51]. Possible interactions for imatinib have been suggested

with anticoagulants and some COVID-19 treatments, such as Ritonavir [54].

Possible mechanisms are suggested for the benefits of these medications; however, further studies are recommended to explain the exact mechanism.TKIs, such as nilotinib and imatinib, may protect against SARS-CoV-2 infection and severe COVID-19 mainly through the inhibition of viral entry [31]. Previous studies have demonstrated the ability of TKIs to prevent some viruses' entry into cells, including human immunodeficiency virus (HIV), hepatitis C, coxsackievirus, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) [25, 26, 31]. Sisk *et al*. showed that TKIs block both virus-cell and cell-cell fusion as well as viral entry is denied before the initiation of hemifusion [24]. Cagno *et al*. found that only nilotinib inhibits COVID-19 replication *in vitro*, but such effects are not observed with imatinib and dasatinib (another TKI) [28].

Table 2. The perspective of the articles on the utilization of nilotinib in COVID-19 patients.

Author - Year, Country	Population, Study Design	Status of Patients on Nilotinib with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Nilotinib Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Li *et al*. - 2020, China [48]	530 adults (346 on imatinib), Cross-sectional survey	59 nonhospitalized CML patients on nilotinib	CML (59)	Not reported	Not reported	Hospitalized hematological malignant patients Health-care providers CML patients on different TKIs The general population	No COVID-19 was reported. 0% prevalence of COVID-19 in nilotinib receivers, which was lower than in all other groups.	Not reported
Başcı *et al*. - 2020, Turkey [52]	64 adults, Retrospective case/control	16 CML patients on different TKIs (3 on imatinib) with COVID-19	CML (16), HT (3), CAD (2), COPD (2), DM (2), CKD (2)	Not reported	Favipiravir (3), oseltamivir (5), HCQ (8), high dose vitamin C (1)	A selected group of 48 matched patients regarding age, gender, and comorbid disease but on cancer and TKIs treatment.	No mortality, mechanical ventilation, and ICU admission in the case group despite the control group.	Not reported
Yılmaz *et al*. - 2021, Turkey [51]	243 adults, Single-Center Survey	2 CML patients on nilotinib with COVID-19 (nilotinib withheld in both)	HT (1), hypothyroidism (1), IFG (1)	600 mg OD / 800 mg OD	Before COVID-19: telmisartan, hydrochlorothiazide, levothyroxine, ASA, paracetamol After COVID-19: HCQ, azithromycin, enoxaparin	A 243-patient CML population regardless of COVID-19	Both patients recovered	AKI in one patient.
Bouchlarhem *et al*. - 2020, Morocco [58]	35-year-old man, Case report	A CML patient on nilotinib with COVID-19	CML (accelerated phase, blast crisis), multiple cranial nerve palsy (considered as a complication of blast crisis)	Not reported	Regarding COVID-19: vitamin C2 g OD, Zinc 45mg BID, DXM 6mg OD, LMWH (therapeutic or prophylactic dose), PPI 20 mg OD, ceftriaxone, levofloxacin Regarding CML and multiple cranial nerve palsy: methotrexate (intrathecal), cytarabine(intrathecal), HYPER-CVAD chemotherapy protocol	None	The patient recovered successfully	Multiple cranial nerve palsy (considered as a complication of blast crisis)

(Table 2) contd….

Author - Year, Country	Population, Study Design	Status of Patients on Nilotinib with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Nilotinib Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Bonifacio *et al.* - 2021, Italy [46]	564 adults, cross-sectional study (serology)	4 CML patients on nilotinib with positive serology for anti-SARS-CoV-2 Ig	CML (4)	Not reported	Not reported	114 patients with CML on imatinib regardless of positivity to anti-SARS-CoV-2 Ig	The prevalence of COVID-19 based on serology was 3.5% among nilotinib receivers, while the seropositivity was 1.95% in the whole CML population (similar to the general population) and 0.98% among imatinib receivers.	Not reported
Mansi *et al.*, 2021, France [59]	39 adults, Prospective monocentric trial	A CML patient on nilotinib with positive serology for anti-SARS-CoV-2 Ig	CML (1)	Not reported	Not reported	38 patients with a different cancer history, a group of patients w/o cancer history (data of another similar article)	Negative T-cell response but positive serology for anti-SARS-CoV-2 serology	Not reported
Pimpinelli *et al.* - 2021, Italy [60]	92 adults, prospective cohort study	7 CML patients on nilotinib (w/o COVID-19)	CML (7)	Not reported	BNT162b2 mRNA vaccine	42 MM patients (w/o COVID-19)	MPM [20 out of 50 had CML; among whom 7 were on imatinib] had a better response to BNT162b2 mRNA vaccine *vs*.MM patients (88% *vs*.76.6%) but lower than the nonmalignant control group (88% *vs*.100%).	Not reported

Abbreviations: AKI: acute kidney injury, ASA: acetylsalicylic acid, BID: twice a day, CAD: coronary artery disease, CKD: chronic kidney disease or renal failure, CML: chronic myeloid leukemia, COPD: chronic obstructive pulmonary disease, CQ: chloroquine, DM: diabetes mellitus, DXM: dexamethasone, HCQ: hydroxychloroquine, HT: hypertension, IFG: impaired fasting glucose, LMWH: low-molecular-weight heparin, MM: multiple myeloma, MPM: myeloproliferative malignancies, OD: daily, PPI: proton pump inhibitors, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, TCZ: tocilizumab, w/o: without.

Table 3. The perspective of the articles on the utilization of artesunate in COVID-19 patients.

Author - Year, Country	Population, Study design	Status of patients on Artesunate with COVID-19	Comorbidities, Chronic Disease, and Risk Factors	Artesunate Dosing	Co-interventions	Comparator	Outcomes	Adverse Events
Mahajan *et al.* - 2020, India [63]	4 pregnant women, Case series	A 27-year-old pregnant woman with malaria and SARS-CoV-2 co-infection	Malaria infection, post-dates, previous CS	120 mg BID injection on the first day, followed by 120 mg OD injection for 5 days	QC (500 once a week)	3 other pregnant patients co-infected by SARS-CoV-2 and malaria (2)/dengue virus (1)	Uneventful emergency CS for the on-artesunate patients despite some complications in other pregnant patients (IUFD, retained POC, low birth weight, PROM).	None
Pusparani *et al.* - 2021, Indonesia [62]	24-year-old man, case study	A case of malaria and SARS-CoV-2 co-infection	Malaria (non-falciparum), history of 4 other times of infection with malaria (recurrent non-falciparum malaria)	40 mg QID for three days	Oseltamivir (75 mg BID, 10 days), azithromycin (500 mg OD, 7 days), piperaquine (325 mg QID, 3 days), primaquine (15 mg OD, 14 days)	None	The patient recovered successfully.	None
Sardar *et al.* - 2020, Qatar [61]	34-year-old man, Case series	A case of malaria and SARS-CoV-2 co-infection	None	2.4 mg/kg IV BID for two days	Artemether-lumefantrine PO after treatment with artesunate	None	The patient recovered successfully.	None
Caglar *et al.* - 2021, Turkey [64]	38-year-old man, Case report	A case of malaria and SARS-CoV-2 co-infection	None	2.4 mg/kg IV BID for five days	Favipiravir, enoxaparin (4,000 U BID), vitamin D (20,000 U/day), QC (0.5 mg PO TIP; before artesunate initiation), artemeter-lumefantrine PO after treatment with artesunate for three days	None	The patient recovered successfully.	None

Abbreviations: BID: twice a day, CS: caesarean section, IUFD: intrauterine fetal demise, IV: intravenous, PO: by mouth, POC: products of conception, PROM: premature rupture of membranes, QC: chloroquine, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, TID: three times a day, OD: once a day.

Artesunate can also protect against COVID-19 through several pathways. First, artesunate has anti-inflammatory characteristics presented by both *in vitro* and *in vivo* studies [65]. Artesunate suppresses the production of proinflammatory cytokine TNFα from macrophages by preventing NF-κB nuclear translocation [34, 66]. Artemether, an artemisinin derivative, can also inhibit T-cell activation *in vitro* and *in vivo* by suppressing IL-2 production [67]. Another artemisinin derivative also enhances the production of IL-10, an anti-inflammatory cytokine [68]. Second, some studies suggest antiviral properties for artemisinin derivatives against CMV [69], HSV, HCV, *etc*. [34, 37, 38]. In fact, studies have suggested a better activity of artesunate against HSV in comparison with natural artemisinin [70]. While these antiviral properties of ar-

tesunate could also be related to its anti-inflammatory characteristics [69], some other mechanisms have also been suggested, including interference with the regulatory processes of virus-infected cells and depriving them of metabolic requirements for their replication [70]. Interestingly, Paeshuyse *et al*. found the dose-dependent inhibitory effect of artemisinin on HCV replicon replication. Its combination with an iron donor hemin had synergistic anti-HCV effects without affecting the host cells [71]. An *in vitro* study on artemisinin derivatives demonstrated the highest anti-SARS-CoV-2 efficacy for arteannuin, followed by artesunate and dihydro-artemisinin with similar anti-SARS-CoV-2 activity. This study has raised hopes in artemisinin derivatives due to their anti-SARS-CoV-2 ability, including artesunate [37].

While such mechanisms support the possible benefits of artesunate, nilotinib, and imatinib for the treatment of COVID-19, little evidence exists for the two former medications, which is the major limitation of this study. The design of the studies was mostly case reports and case series on artesunate and nilotinib. No statistical analysis could also be performed due to the scarcity of evidence. Nevertheless, we believe that this systematic review has its own value as it presents evidence for these medications and encourages future researchers to help with building upon the current knowledge related to the efficacy and safety of artesunate, nilotinib, and imatinib in COVID-19 treatment [72-76].

CONCLUSION

Molecular mechanisms and preclinical studies support the possible benefits of artesunate, nilotinib, and imatinib. We found no clinical trials or large observational studies for artesunate and nilotinib and all available evidence was derived from case reports and case series for these two treatments, which could limit their clinical applicability. On the other hand, a double-blinded multicenter randomized controlled trial found lower severity, days of ventilation, and ICU admission risk as well as higher survival with no major adverse events in the imatinib group. Nevertheless, these drugs have been demonstrated to have acceptable profiles of adverse events during the COVID-19 pandemic. Their use can be continued for other possible indications, including CML, gastrointestinal stromal tumor (GIST), malaria, *etc*. This systematic review also pinpointed the scarcity of available evidence and consequently the need for further investigations on possible drugs that could be repurposed as candidates for COVID-19 treatment, including but not limited to artesunate, nilotinib, and imatinib.

AUTHORS' CONTRIBUTION

Esmaeil Mehraeen, SeyedAhmad SeyedAlinaghi, and Hamid Zaferani Arani contributed to the conception and design of the study. Ehsan Ghavimehr participated in the acquisition of data.

Pegah Mirzapour, Ali Zand, and Ehsan Ghavimehr contributed to the analysis and interpretation of the data. Ehsan Ghavimehr, Ali Zand, Amirali Karimi, Pegah Mirzapour, and Zahra Pashaei drafted the article. SeyedAhmad SeyedAlinaghi, Esmaeil Mehraeen, and Amirali Karimi revised it critically for important intellectual content. Esmaeil Mehraeen, Omid Dadras, and SeyedAhmad SeyedAlinaghi gave the final approval of the version to be submitted.

LIST OF ABBREVIATIONS

ALI	=	Acute Lung Injury
ARDS	=	Acute Respiratory Distress Syndrome
COVID-19	=	Coronavirus Disease 19
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TKIs	=	Tyrosine Kinase Inhibitors

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

PRISMA check list is available on publisher website.

AVAILABILITY OF DATA AND MATERIALS

The authors stated that all the information provided in this article could be shared.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article. Supplementary material is available on the publisher website.

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