Journal of Applied Pharmaceutical Science Vol. 13(05), pp 041-049, May, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.105521
ISSN 2231-3354

Adverse events associated with COVID-19 treatment and their possible relationship with patient characteristics: A narrative review

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ARTICLE INFO

Received on: 24/10/2022
Accepted on: 12/02/2023
Available Online: 04/05/2023

Key words:
SARS-CoV-2, COVID-19, adverse events, drug repurposing, vaccines, patient characteristics.

ABSTRACT

The adverse events (AEs) of repurposed drugs used in coronavirus disease 2019 (COVID-19) bear a challenge in clinical practice, even though the safety profiles of these drugs are quite known for primary indications. Since it is a new virus, post-marketing surveillance of drugs' safety is of utmost clinical significance. This review aimed to investigate the patterns, incidence, and frequency of AEs of COVID-19 medications and vaccines and to explore the relationship between the occurrence of AEs and characteristics of COVID-19 patients, such as age, gender, and comorbidities. A literature search was conducted on electronic databases like MEDLINE, Google Scholar, and ScienceDirect for studies conducted on the AEs of drugs and vaccines used against COVID-19. The study found that prescription drugs for COVID-19 most commonly cause gastrointestinal symptoms, while some were associated with more severe liver, kidney, and cardiac manifestations. AEs varied among individuals, especially in elderly people with comorbidities. The known side effects of steroids and azithromycin including psychosis and prolongation of QT interval were also found to be prevalent when used in COVID-19 patients. Serious AEs such as multiple organ dysfunction syndrome (MODS) and septic shock were commonly reported among patients who required invasive ventilation. AEs reports for newly formulated vaccines showed general safety with the majority being local complaints. The reported AEs ranged from mild to severe, including MODS. Factors such as old age and comorbidities were found to be risk factors for a higher potentiality of AEs. Further studies are needed to draw evidence-based conclusions.

INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) originated from a zoonotic source in China in late 2019. Since then, the virus has taken a toll on the world. Within a short period, it transformed into a pandemic and triggered an unprecedented global public health crisis. COVID-19 was declared a Public Health Emergency of International Concern on January 30, 2020. Since then, the pandemic has had a massive global impact at all levels. As of May 28, 2022, there have been roughly 525 million cases including approximately 6.2 million deaths (World Health Organization, 2022). Although most patients with COVID-19 are asymptomatic or only have a mild form of the disease (Pascarella *et al*., 2020), the contagious nature of the condition has made it a source of great concern. In addition, the illness takes a serious turn toward septic shock or multiple organ dysfunction syndrome (MODS). As a respiratory disease that develops secondary to infection, COVID-19 patients require hospitalization (Zhou *et al*., 2020). Due to respiratory failure and the need for ventilatory support, intensive care units (ICUs) around the world became saturated. Fortunately, only 10%–20% of patients require admission to ICUs and 3%–10% require intubation (Guan *et al*., 2020). However, experts have recommended expeditious prevention and diagnosis when the pandemic struck to avert further straining of ICUs' capacities. Older men with comorbidities have been found to require intensive care more frequently. Fever, hemoptysis, and

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dyspnea are predictors of the severity of the disease (Heo *et al*., 2021). The occurrence and severity of infection depend on the age, sex, ethnicity, and medical comorbidities of an individual. Among people with pre-existing medical conditions, the severity of COVID-19 is higher, the hospitalization requirement is 6 times higher, and mortality is 12 times higher (Stokes *et al*., 2020). In addition, severity and mortality are said to be higher among men than among women (Gebhard *et al*., 2020; Jin *et al*., 2020). A meta-analysis found that Blacks, Hispanics, and Asians are prone to contracting the disease and have an increased risk of mortality (Sze *et al*., 2020).

Estimating the actual mortality related to COVID-19 is a herculean task and quite fraught with errors. Countries around the world have different ways of reporting and comparing mortality statistics. There exists a geospatial disproportionate reporting of COVID-19-associated mortalities when the African, Eastern Mediterranean, Southeast Asian, and Western Pacific regions are compared to the European demographics. For instance, registered death reports range from 98% in European countries to 10% in African countries. However, these cannot be considered absolute data due to the variations in tests and final reporting. Therefore, the World Health Organization (WHO) recommends calculating "excess mortality," which is a differential between the total number of deaths observed in a specific time point and the number expected under a no-COVID-19 scenario. Based on this index, the global excess mortality in 2020 has been estimated at 3,000,000 (World Health Organization, 2021b).

Considering the different waves of COVID-19, there appears to be a variation in deaths and severity, as well as a change in the age of the population that contracted the disease. A study in Spain found that patients were younger and mortality was low in the second wave (July 1 and October 15, 2020). Additionally, babies, children, and pregnant women showed a higher incidence (Iftimie *et al*., 2021). Another study from Japan based on the COVID-19 Registry Japan evaluated data from patients admitted during the first wave (January 26 and May 31, 2020) versus those in the second wave (June 1 and July 31, 2020) and reported 3,833 and 1,361 cases in the former and the latter periods, respectively. Japan reported a smaller number of severe patients during the second wave, the patients were younger, less likely to have comorbidities, and mortality was also lower (Saito *et al*., 2021).

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the overwhelming speed with which it spreads compelled biomedical scientists to consider repurposing available drugs (chloroquine, hydroxychloroquine, lopinavir, ritonavir, remdesivir, tocilizumab, interferon, immunoglobulins, and corticosteroids) rather than formulating newer ones. The adverse events (AEs) of the drugs used in COVID-19 bear a challenge in clinical practice, even though these drugs are repurposed and their safety is quite known. Being a new virus, post-marketing surveillance of the drugs' safety profile is of utmost concern given that undetected and unaddressed drug-related problems (DRPs) could increase mortality, morbidity, and healthcare cost (Alshargi *et al*., 2021, 2022).

METHODS

The objective of this review is therefore to investigate the patterns, incidence, and frequency of adverse drug reactions (ADRs) and AEs of COVID-19 medications and vaccines. It also aims to explore the relationship between the occurrence of AEs and the characteristics of COVID-19 patients, such as age, gender, and comorbidities. The literature search was conducted on electronic databases like MEDLINE, Google Scholar, and ScienceDirect for studies conducted on the AEs of drugs and vaccines used against COVID-19. Important keywords used to explore the studies include the following: "COVID-19," "COVID-19 pandemic," "SARS-CoV-2," "Coronavirus Disease-2019," "COVID-19 Infection," "COVID-19 Drugs," "COVID-19 Medications," "COVID-19 Therapies," "COVID-19 Treatments," "COVID-19 Vaccines," "Adverse Drug Events," "Adverse Drug Reactions," "Adverse Drug Effects," "Drug Related-Problems," "COVID-19 Patients," "Patients' Characteristics," "Patients' Parameters," and "Pharmacoepidemiology." The search was conducted within a 5-month period from August to December 2021. Relevant titles were manually identified and irrelevant studies were screened out. The included articles were reviewed and the AEs of COVID-19 therapies and vaccines were summarized under the following headings: geographic location and duration of the study, study characteristics and overall ADRs/AEs, and most common AEs and associated drugs.

RESULTS AND DISCUSSION

Drugs in the fight against COVID-19

Remdesivir was approved in October 2020 by the Food and Drug Administration (FDA) for use in adults and children older than 12 years of age, based on its immunomodulatory and antiviral properties. This is in spite of a lack of methodologically appropriate proof of efficacy (Abdelazim and Ramzy, 2022; Food and Drug Administration, 2021b). This antiviral drug is currently the only drug approved by the FDA for the treatment of COVID-19. It is a nucleoside analog with prodrug-like activity prescribed to hospitalized patients requiring additional oxygen. The European Medicines Agency (EMA) has also approved the drug for the treatment of COVID-19 in hospitalized pediatric patients (Abdelazim and Ramzy, 2022).

Chloroquine was first discovered over 70 years ago, and the COVID-19 pandemic brought its fame one more time when it showed tremendous immunomodulatory potential and antiviral efficacy against COVID-19 (Gautret *et al*., 2020; Yao *et al*., 2020). During the initial phase of the pandemic, hydroxychloroquine was repurposed alone or in combination with macrolide antibiotic (azithromycin) or the protease inhibitors antiviral drugs (lopinavir/ritonavir) (Gérard *et al*., 2020). On March 28, 2020, the FDA issued an Emergency Use Authorization (EUA) for hydroxychloroquine in the treatment of COVID-19. The win was short-term due to emerging data and the findings of the WHO Solidarity trial, and finally, in June 2020, the FDA revoked this authorization (Manivannan *et al*., 2021).

Corticosteroids, such as dexamethasone, improve survival in hospitalized patients requiring additional oxygen (RECOVERY Collaborative Group, 2020; Tomazini *et al*., 2020). The RECOVERY group trial reported significantly low mortality at 28 days among dexamethasone-treated patients compared to the routine care group of patients with COVID-19. Patients on invasive mechanical ventilation were found to be more beneficial

(RECOVERY Collaborative Group, 2020). However, the study did not provide evidence to support its beneficial effect in patients who were not on respiratory support. The dosage of steroids, associated medical comorbidity, and severity of the disease are important parameters that physicians should keep in mind when prescribing dexamethasone. The RECOVERY trial also found that patients who started the drug after the first week of the illness showed better responses. Thus, researchers hypothesize that at this stage viral replication is secondary to the immunological response of the body, allowing the steroid to dominate and produce a positive response (RECOVERY Collaborative Group, 2020).

An adjunctive drug to dexamethasone therapy is tocilizumab. It is a recombinant humanized anti-interleukin-6 receptor monoclonal antibody. Tocilizumab has been found to improve survival among patients who require external respiratory support (Gordon and Danilov, 2021). The EMPACTA trial showed lower mortality at 28 days in patients who received tocilizumab and were mechanically ventilated (Salama *et al*., 2021). In contrast, the COVACTA trial did not report significant differences in mortality at 28 days or clinical improvement between the tocilizumab and placebo groups, while the hospital stay was shorter in the former (Rosas *et al*., 2021).

The antiparasitic drug, Ivermectin, received FDA approval as a treatment against COVID-19 due to its ability to inhibit viral replication (Caly *et al*., 2020). However, following increasing evidence showing no benefit from the use of the drug, it is not currently used for COVID-19 (Lim *et al*., 2022; Reis *et al*., 2022).

According to the guidelines of the American National Institute of Health (2021) for COVID-19 patients who are not hospitalized (mild to moderate disease), a combination of bamlanivimab plus etesevimab and casirivimab plus imdevimab can be used in an emergency, if patients show a risk of progression of the disease. However, for critically ill patients, interleukin-6 receptor antagonists (tocilizumab, sarilumab) are equally effective compared to glucocorticoids. The clinical response is faster and the mortality is lower. However, the authors of the trial insist that to improve the efficacy of therapy, it should be started within 24 hours after starting organ support (Brown *et al*., 2021).

AEs associated with COVID-19 drugs

AEs can arise due to therapeutic interventions and may be related to the patient's age or comorbidities. These incidences are of concern because they are associated with increased morbidity and mortality and add to the cost of treatment (Alshargi *et al*., 2021, 2022). In situations such as the present pandemic, when most healthcare systems are already strained, AEs manifestations would further aggravate the whole scenario. In practice, it is not clear how to define a drug reaction because the associated condition, like the disease itself, may be a confounder (Mota and Kuchenbecker, 2017). However, drug safety should not be ignored or treated equally to drug efficacy.

Pharmacovigilance (PV) and drug monitoring programs are more relevant now because the currently reprofiled drugs for COVID-19 had hitherto not been used against the new SARS-CoV-2. It is therefore difficult to estimate the efficacy and gauge the response *in vivo* without having robust experimental data. There is no time to spare because millions of lives are at stake, and hence post-marketing trials are the source of additional drug safety information. Even the rarest of AEs can be known if a drug is administered to a large population. During unprecedented times when health regulatory bodies release drugs under EUA aimed at verifying their effectiveness or safety profile, these drugs must be under long-term surveillance (Food and Drug Administration, 2021a). The WHO PV Team has been supporting low- and middle-income countries in spontaneous reporting of AEs through a smartphone-based adverse reaction reporting application (Med Safety App). The application was launched in collaboration with the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom and the WHO Collaborating Centre, Uppsala Monitoring Centre. During the COVID-19 pandemic, the application has been updated to support the AEs associated with the drugs and vaccines used for infection (Falcão *et al*., 2021; Grein *et al*., 2020; Izcovich *et al*., 2020; Jing *et al*., 2021; Melo *et al*., 2021; Ramireddy *et al*., 2020; Ramírez *et al*., 2020; Sun *et al*., 2020; Wang *et al*., 2020; World Health Organization, 2021a; Zekarias *et al*., 2020).

A non-systematic literature search revealed quite a few studies that aimed primarily at finding drug-associated AEs among COVID-19 patients and those who reported drug-related AEs as secondary outcomes. These studies are summarized in Table 1. Large clinical trials, systematic reviews, meta-analyses, and retrospective patient chart reviews found gastrointestinal disorders, renal and hepatic complications, cardiac manifestations, and rarely endocrine disorders as common AEs associated with COVID-19 drugs. Liver damage in patients with COVID-19 is said to be often transient and can return to normal (Aggarwal *et al*., 2020). On the other hand, elevated levels of D-dimer, a marker of thromboembolic disease and disseminated intravascular coagulation, on admission are associated with mortality among patients with COVID-19 (Zhang *et al*., 2020). Iatrogenic thromboembolic diseases are associated with drugs such as dexamethasone, baricitinib, sarilumab, interferon beta-1b, and intravenous immunoglobulins (Ramírez *et al*., 2020). Table 2 lists the common side effects (SEs) of the drugs used in the treatment of COVID-19 while the classification of the reported AEs based on the affected body system is presented in Figure 1.

AEs of COVID-19 drugs and patient characteristics

The occurrence of unintended drug responses varies among the population and depends on the age, sex, race, and comorbid condition(s) of an individual. The literature is replete with findings supporting the association of demographic characteristics with the appearance of an unexpected reaction to a drug, which is due to altered pharmacodynamics and pharmacokinetics. Older patients represent a considerable population who visit emergency departments and are twice as prone to ADRs as their younger counterparts (Alshargi *et al*., 2021; Budnitz *et al*., 2006). Aging causes changes in drug metabolism, and the presence of multimorbidity and polypharmacy, among others, contribute to such iatrogenic diseases (Calderón-Larrañaga *et al*., 2017). Consequently, the biological differences between a man and a woman also result in varied responses to a drug (Alomar, 2014).

In particular, drugs used for the treatment of COVID-19 have also shown a disparity in the incidence of adverse drug events. For example, ribavirin-related AEs are found to be

Table 1. Studies reporting AEs/ADRs in patients with COVID-19.

Geographic location and duration of the study	Study characteristics and overall AEs or ADRs	Most common ADRs/AEs and associated drugs
Brazil (Melo *et al*., 2021); March–August, 2020	631 ADRs reported among 402 patients	*Drugs:* Chloroquine, hydroxychloroquine, and azithromycin. *Events:* Prolongation of the QT interval followed by diarrhea, itching, and an increase in transaminases. Chloroquine and hydroxychloroquine were the only drugs linked with severe ADRs.
Spain (Ramírez *et al*., 2020); March 1–April 30, 2020	204 severe ADRs among 2,682 patients. 201 adults (>18 years) and 3 children	*Drugs:* Dexketoprofen, dexamethasone, azithromycin, lopinavir, ritonavir, tocilizumab, and chloroquine/hydroxychloroquine. *Events:* Blood dyscrasia including agranulocytosis, pancytopenia, and thrombocytopenia. Drug-induced liver injury was the most common event.
China (Sun *et al*., 2020), January 17–February 29, 2020	217 patients; prevalence of ADR was 37.8%	*Drugs:* lopinavir/ritonavir, and umifenovir. *Events:* Increased serum glutamic pyruvic transaminase levels, nausea, vomiting, and diarrhea.
Sweden (Zekarias *et al*., 2020), reports until June 7, 2020	2,573 reports from the global ADR database (VigiBase)	*Drugs:* Hydroxychloroquine, azithromycin, and lopinavir/ritonavir. *Events*: Prolongation of QT interval, diarrhea, nausea, hepatitis, and vomiting (in order of decreasing frequency in males). Diarrhea, QT prolongation, nausea, vomiting, and upper abdominal pain (in order of decreasing frequency in females).
A systematic review (preprint) (Izcovich *et al*., 2020) on RCTs from December 2019 to October 2021	16 randomized trials in the WHO COVID-19 database and 6 Chinese databases (total 32 databases) encompassing a total of 8,226 patients	*Drugs:* Hydroxychloroquine, lopinavir/ritonavir, and remdesivir. *Events*: Amplified risk of nausea, vomiting, and diarrhea were attributed to lopinavir/ritonavir and hydroxychloroquine. Cardiotoxicity, delirium/cognitive dysfunction (for lopinavir/ritonavir and hydroxychloroquine), cardiac toxicity, and cognitive dysfunction/delirium (for hydroxychloroquine). Remdesivir may not be associated with the risk of AKI or cognitive dysfunction/delirium (based on two studies only).
China (Jing *et al*., 2021), reports from January 1, 2004 to December 31, 2019	484 AEs involving 18 organs/SOC specific to COVID-19. Data from the FDA AERS	*Drugs:* Seventeen drugs, repurposed (darunavir, ribavirin, favipiravir, oseltamivir, nitazoxanide, chloroquine, hydroxychloroquine, camostat, lopinavir/ritonavir, and adjunctive (sarilumab, tocilizumab, azithromycin, interferon-β, dexamethasone, and melatonin). *Events:* Ribavirin: Higher risk of neoplasms, AEs involving endocrine, and musculoskeletal and connective tissue. Hydroxychloroquine: higher risk of neoplasms, AEs involving ear, labyrinth, and eye. Oseltamivir: AEs involving renal and urinary, musculoskeletal and connective tissue, and metabolism and nutrition.
Los Angeles (Ramireddy *et al*., 2020), February 1–April 4, 2020	490 cases of COVID-19-positive/suspected patients	*Drugs*: Azithromycin, hydroxychloroquine, or a combination of both drugs. *Events*: A total of 12% of patients reached critical QTc prolongation; changes in QTc were highest with the combination compared with either drug, greater prolongation with combination against azithromycin.
China (Wang *et al*., 2020), February 6–March 12, 2020	237 patients (158 to remdesivir and 79 to placebo)	*Drugs:* Concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. *Events: Remdesivir*: constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased TB; there were 28 serious AEs. Placebo: hypalbuminemia, constipation, anemia, hypokalemia, increased AST, increased blood lipids, and increased TB; there were 20 serious AEs.
Portugal (Falcão *et al*., 2021), March 16–August 15, 2020	Chart review of 149 patients 101 were on hydroxychloroquine (20 single drugs, 52 in combination with azithromycin, 22 in combination with lopinavir/ritonavir, and 7 with both lopinavir/ritonavir and azithromycin), while the remaining 48 took remdesivir	*Drugs:* Hydroxychloroquine, remdesivir, azithromycin, lopinavir, ritonavir. *Events:* Higher incidence with hydroxychloroquine than remdesivir. Hepatobiliary disorders (most commonly transaminase increase) were the most common AEs, followed by GI, renal, and cardiac disorders. Hydroxychloroquine + lopinavir/ritonavir subgroup had higher hepatobiliary and renal disorders.
Patients enrolled in the US, Japan, Italy, Austria, France, Germany, Netherlands, Spain, and Canada (Grein *et al*., 2020); January 25–March 7, 2020	Total 53 patients received remdesivir	*Drug:* Remdesivir *Events:* Thirty-two patients reported AEs including increased liver enzymes, hypotension, renal impairment, and rash. Patients receiving invasive ventilation experienced more AEs. Serious AEs including AKI, MODS, septic shock, and hypotension were reported in 12 patients receiving invasive ventilation.

Geographic location and duration of the study	Study characteristics and overall AEs or ADRs	Most common ADRs/AEs and associated drugs
Meta-analysis (Sterne *et al*., 2020); February 26–June 9, 2020	It included 7 RCTs from 12 countries and evaluated the efficacy of corticosteroids in 1,703 critically ill patients	*Drugs:* Dexamethasone, hydrocortisone, and methylprednisolone. *Events:* Serious AEs were reported in six trials; 64 AEs were observed in 354 patients randomized to corticosteroids; 80 AEs were reported in 342 patients randomized to usual care or placebo. However, there was no evidence to indicate that the risk of serious AEs was higher in patients randomized to corticosteroids.

AEs: Adverse Events, ADRs: Adverse Drug Reactions, GI: Gastrointestinal, WHO: World Health Organization, AKI: Acute Kidney Injury, COVID-19: Coronavirus Disease 2019, SOC: System Organ Class, FDA: Food and Drug Administration, AERS: Adverse Event Reporting System, TB: Total Bilirubin, AST: Aspartate Aminotransferase, MODS: Multiple Organ Dysfunction Syndrome, RCTs: Randomized Controlled Trials.

Table 2. Drugs used for the treatment of COVID-19 and their SEs.

COVID-19 drug	Common SEs
Chloroquine, hydroxychloroquine (Khosa *et al*., 2018; Krzeminski *et al*., 2018; Parmar *et al*., 2000)	QT interval extension, parkinsonism, psychosis, seizures, and myopathy
Azithromycin (Kim, 2014)	Diarrhea, nausea, abdominal cramps, QT interval prolongation, and torsade de pointes
Lopinavir/Ritonavir (Cornelius, 2021; Ghasemiyeh *et al*., 2020)	Diarrhea, nausea, vomiting, headache, drowsiness or dizziness, and moderate to severe elevations in serum aminotransferase (lopinavir)
Tocilizumab (Koryürek and Kalkan, 2016)	Hypertension, demyelinating disorders, leukoencephalopathy, peripheral neuropathy, and increased risk of fungal and bacterial infections
Corticosteroids (Campbell *et al*., 2017; Khan and Gillani, 2018)	Psychosis, seizure, anxiety, and myopathy

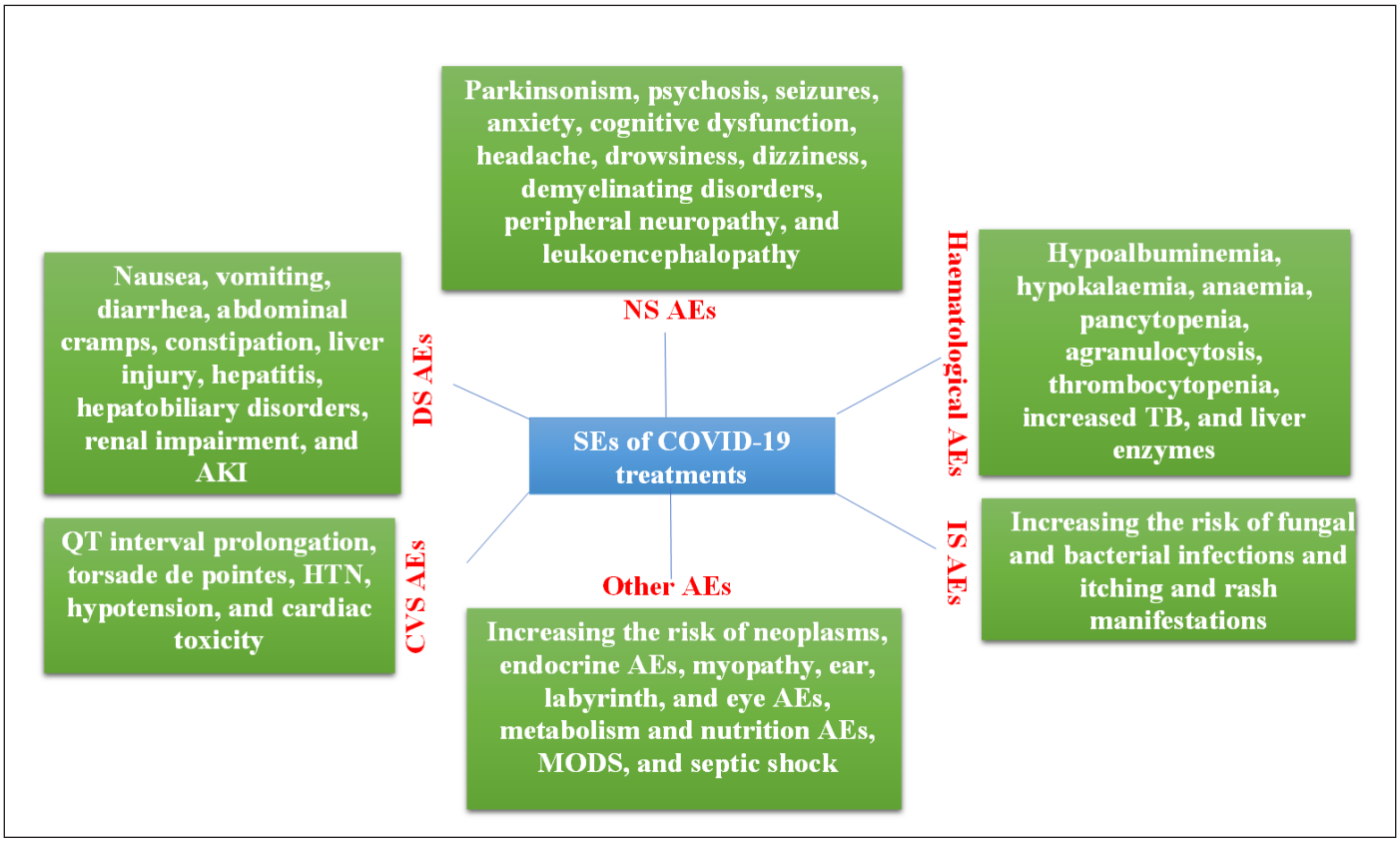

Figure 1. AEs of COVID-19 treatment. AEs: Adverse events, NS: Nervous system, IS: Immune system, TB: Total bilirubin, MODS: Multiple organ dysfunction syndrome, CVS: Cardiovascular system, HTN: Hypertension, DS: Digestive system, AKI: Acute kidney injury.

more common among women and those over 65 years of age; tocilizumab and sarilumab cause AEs involving the endocrine system among patients under 65 years of age; women over 65 years of age are prone to hydroxychloroquine-associated AEs involving the eye and immune systems; men under 65 years of age show AEs associated with ritonavir/lopinavir plus interferon-β involving the eye, skin, and subcutaneous tissue (Jing *et al*., 2021; Melo *et al*., 2021). In general, COVID-19 patients over 65 years of age are said to be more associated with severe ADRs than younger patients (Melo *et al*., 2021).

Another analysis of adverse drug reports based on VigiBase (until June 2020) revealed 2,773 adverse drug reports, the majority from Europe. The gender data showed a lower proportion of AEs among women (39%) than among men (55%), while 6% did not report the gender of the patient. However, this trend was the opposite in the case of chloroquine and oseltamivir, although the data were found to be from two countries. The most frequently reported AEs with COVID-19 treatments were prolonged QT electrocardiograms in both sexes, diarrhea being the second most common among men and nausea among women (Zekarias *et al*., 2020).

A group of Chinese authors studied AEs reported in the FDA Adverse Event Reporting System (AERS) from January 2014 to December 2019 that involved 17 repurposed drugs for COVID-19. It was found that these drugs accounted for up to 484 AEs reports. Overall, there was a significant variation in AEs depending on the age of the patients. For example, there was a higher risk of neoplasm among older people (>65 years of age) using the repurposed drug ribavirin and hydroxychloroquine, while there were more endocrine and musculoskeletal AEs among those younger than 65 years (Jing *et al*., 2021).

AEs associated with COVID-19 vaccine

The COVID-19 pandemic has been a challenge for biomedical researchers, and it should be acknowledged that the researchers emerged winners with laurels. The speed at which the COVID-19 vaccines were formulated was rather fascinating. Phase III trials began to report results within 1 year after COVID-19 was declared a pandemic. Since then, the EMA, FDA, and MHRA have authorized various vaccines and global immunization programs.

Most vaccines have obtained EUA, which means that trial data are limited and that further safety and efficacy issues must be cleared prior to general use. Thus, vaccine safety must be monitored, and post-marketing surveillance outcomes would improve our knowledge beyond what was known during clinical development (Li *et al*., 2021). As of January 20, 2021, 173 vaccines were in preclinical development and 64 in clinical trials, while emergency approval was granted to 9 vaccines by regulatory authorities in different parts of the world (Kaur *et al*., 2021).

There is some evidence showing that AEs are higher among people previously infected with the SARS-CoV-2 virus (Menni *et al*., 2021; Wise, 2021). It would not be wise to generalize the AEs related to vaccines around the world because demographic disparity plays a major role. Furthermore, data are heterogeneous with studies recruiting different age groups of the population, involving individuals with and without a history of COVID-19, and variation in antibody titers, among others. The reassuring aspect is that the researchers found fewer incidences of severe AEs, and the majority of these were mild to moderate, which weaned away on their own.

A systematic review pooled the results of 11 studies reporting AEs of COVID-19 vaccines between December 2019 and 2020. Most of the reactions were resolved in 3–4 days. Common local AEs were pain at the injection site, swelling, and redness, while systemic AEs were fever, fatigue, myalgia, and headache (Kaur *et al*., 2021). An interim analysis of a phase 3 trial in the United Arab Emirates and Bahrain studied AEs associated with inactivated vaccines, developed from SARS-CoV-2 WIV04 and HB02 strains against a control group (aluminum hydroxide). AEs after 7 days of injection occurred in the range of 41.7%–46.5%, including all groups; serious AEs were rare but similar in all groups; the most common AEs were pain at the injection site and headache (Al Kaabi *et al*., 2021). The Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines have also been reported to be safe. Sub-analysis of the data showed that there is no significant variation in the type or severity of AEs among patients who received one or both doses (Menni *et al*., 2021). Safety monitoring in the United States Vaccine AERS and v-safe reported between December 14, 2020 and January 13, 2021 have indicated 6,994 reports of AEs associated with the Pfizer-BioNTech vaccine out of which 9.2% were serious. There were 113 deaths, although the available information did not reveal any causal relationship between deaths and vaccination. Thus, it was concluded that the study provided "reassurance" and that the said vaccine has a good safety profile (Gee *et al*., 2021). A preprint published on medRxiv on March 2021 analyzed severe ADRs reported in VigiBase following COVID-19 vaccinations. It found a female preponderance (80%) in the reporting system. Also, the regional data have shown that Europe reported a majority of the AEs in females between 18 and 64 years of age. The older generation (more than 65 years) reported more serious AEs related to vaccination (Dutta *et al*., 2021).

CONCLUSION

COVID-19 has not been proven to be deadly to most infected patients, but its contagious nature and breathtaking spread speed have engulfed nations around the world in no time. Furthermore, reports of drug-related AEs added to the concern. During the initial days of the pandemic, drugs such as hydroxychloroquine and dexamethasone were in widespread use. Later, evidence surfaced against the efficacy and potential hazards of these drugs, and regulatory bodies cautioned the medical fraternity. At the same time, antivirals such as remdesivir, lopinavir, and ritonavir were found to be effective against SARS-CoV-2. Regarding the SEs of these drugs, there is a lack of consistency between reports. Also, the spontaneous reporting systems do not provide comprehensive data because of the absence of uniform participation across the globe. Overall, from this review, it can be concluded that since most of the drugs were already being used, clinicians should keep in mind the known SEs of these drugs. The study found that COVID-19 therapies have some risk of aggravating AEs such as increasing the risk of neoplasms, seizures, immunosuppressive effects, and cardiovascular disorders, which are undoubtedly life-threatening disorders (Al-Shargi *et al*., 2020).

These findings have substantial implications for safe and effective pharmacotherapy in COVID-19 and can help clinicians

predict, diagnose, avoid, minimize, and control AEs. The revealed relevant clinical differences in AEs of COVID-19 medications and vaccines across different groups of patients suggested that there are patients at higher risk of experiencing AEs. Such outcomes provide useful information to help clinicians shift away from a one-size-fits-all approach and stratify the risk of AEs by patient depending on a variety of factors since personalization of pharmacotherapy has been found to be effective in reducing the DRPs and their consequences (Alshargi *et al*., 2022).

The presence of multimorbidity and advanced age appears to be the main areas of concern. Prescription patterns for patients with COVID-19 should be based on the individual health condition. Since these conclusions are drawn based on a descriptive review of published literature, they should be considered with caution. Furthermore, a systematic review and meta-analysis may be needed to draw more comprehensive and evidence-based conclusions.

AUTHORS' CONTRIBUTIONS

O. A. contributed to the conception and designing of the work and drafting and writing the manuscript, S. A. contributed to designing and writing of the manuscript and revising the whole manuscript, B. A. contributed to writing, revision, and proofreading of the manuscript, and A. A. contributed to the writing of the manuscript and substantially revised the whole manuscript. All the authors have read and approved the manuscript.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:
Al-Shargi OY, Alzaid S M, Al-Dosari B S, Alzubaidi A S. Adverse events associated with COVID-19 treatment and their possible relationship with patient characteristics: A narrative review. J Appl Pharm Sci, 2023; 13(05):041–049.