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Case Study

Adverse events associated with potential drugs for COVID-19: a case study from real-world data

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Abstract

The coronavirus disease 2019 (COVID-19) has resulted as a global pandemic. The World Health Organization announced the most promising drugs in SOLIDARITY for the global trial, and several other drugs are under investigation through ongoing clinical trials to prove the effectiveness and safety of potential therapeutics. Here, we depicted the safety profile of these drugs and investigated their associated adverse events (AEs). We observed the associated AEs in different organs/systems, especially in skin and subcutaneous tissue, immune system and musculoskeletal and connective tissue. Furthermore, we observed strong bias of AEs in different groups of sex and age. Our study provides knowledge of the toxicity of potential COVID-19 drugs. While these drugs hold promise to fight the global pandemic, healthcare providers should pay attention to AEs to maximize the treatment benefit while minimizing toxicity.

Key words: COVID-19; adverse events; real-world data

Introduction

The novel coronavirus (SARS-CoV-2) is rapidly spreading as a global pandemic and has raised serious concerns [1]. The infection causes an acute respiratory illness, coronavirus disease 2019 (COVID-19) [2]. The World Health Organization announced a large global trial, SOLIDARITY, to test the four most promising therapies: remdesivir, chloroquine and hydroxychloroquine (potentially combined with azithromycin), ritonavir/lopinavir and ritonavir/lopinavir with interferon-β. Cytokine release syndrome (CRS) is common in patients with COVID-19 [3]; therefore, drugs suppressing CRS, including tocilizumab and sarilumab, have been tested in clinical trials to treat COVID-19. In addition, there are more than 300 active clinical trials for COVID-19 or SARS-CoV-2 in clinicaltrial.org [2] to investigate the clinical efficacy of more than 10 drugs. These drugs can be categorized as investigational, repurposed and adjunctive drugs. For example, a recent study reported the clinical improvement for 36/53 (68%) patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir [4]. To be noticed, 32/59 (60%) COVID-19 patients developed adverse events (AEs) [4]. Furthermore, 46/98 (46%) COVID-19 patients reported AEs with the treatment of ritonavir/lopinavir [5]. Some drugs, such as hydrochloroquine, may cause serious AEs, even death [6]. Understanding the AEs associated with these drugs in advance is critical for managing COVID-19 patients because these drugs

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may cause severe toxicity that even outweigh the benefit of the agent [2].

Materials and methods

Analysis of AE reports from FAERS database

We downloaded 808 273 individual AE reports (between 1 January 2004 and 31 December 2019) for 172 075 cases from the FDA Adverse Events Reporting System (FAERS, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard) to investigate AEs of potential COVID-19 drugs. We searched 17 drugs in FAERS and successfully obtained AE reports for repurposed agents (darunavir, ribavirin, favipiravir, oseltamivir, nitazoxanide, chloroquine, hydroxychloroquine, camostat, ritonavir/lopinavir) and adjunctive agents (sarilumab, tocilizumab, azithromycin, interferon-β, dexamethasone and melatonin) suspected of causing AEs. Chemical structure, IUPAC name and compound ID of 12 small molecule drugs were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/). We excluded non-FDA-approved drugs: favipiravir, umifenivir and camostat. The information component (IC) was calculated by comparing the observed and expected drug–AE associations in a Bayesian confidence propagation neural network [7, 8]. These AEs reported in the full FAERS database were used as the background data. IC025 is defined as the lower tail of a 95% credibility interval for the IC, and IC025 >0 is considered as statistically significant [8]. The calculation of IC and reporting odds ratio (ROR) was conducted by R package 'pvm' [7]. ROR025 >1 is considered as statistically significant. We excluded AEs with fewer than 50 reports for each drug. The preferred terms of statistically significant AEs were grouped into primary system organ classes (SOC) based on the Medical Dictionary for Drug Regulatory Activities, version 23.0. We focused on AEs that involved specific organs or systems and excluded the following SOCs: investigations, general disorders and administration site conditions, injury, poisoning and procedural complications, social circumstances, surgical and medical procedures, infections and infestations, product issues, congenital, familial and genetic disorders, pregnancy, puerperium and perinatal conditions. Serious AEs in the FAERS database means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcomes. We exclude drugs that affected less than three organs/systems in further analysis. Significantly higher reported classes of AEs were analyzed for association between sex and age for each COVID-19 drug. Patients aged 0–100 years were included. Cases for which the patient's sex was not reported were excluded. Multivariate logistic regression analysis, including age and sex, and interactions as covariates for the risk of AEs, was performed. Data processing and statistical analyses were performed using R statistical software, version 3.6.3.

Results

AEs associated with potential COVID-19 drugs

We investigated 17 drugs, from SOLIDARITY, a recent comprehensive review [2] and several important literatures [9–11], in the FAERS (Supplementary Table 1, Supplementary Figure 1). Remdesivir, favipiravir, umifenovir and camostat are not FDA-approved drugs, so no or only a few reports are included in FAERS. We excluded these drugs in the further analysis. We found 484 different AEs involving 18 organs/systems that were significantly increased with the administration of potential COVID-19 drugs by comparing to AEs in the full FAERS database (Supplementary Table 2). We only observed that chloroquine was associated with increased reporting of cardiac AEs, which aligns with a recent report [6]; nitazoxanide was associated with increased reporting of gastrointestinal AEs; melatonin was associated with increased reporting of psychiatric and nervous system AEs; dexamethasone was associated with increased reporting of blood and lymphatic system AEs (Supplementary Figure 2). Significantly reported AEs of chloroquine, nitazoxanide, dexamethasone and melatonin were excluded for further analysis because they involved less than three organs/tissues. The remaining drugs may cause AEs in different organs/systems (Figure 1). The highest IC of different AEs in each organ/system was presented. Ribavirin was associated with higher reporting of AEs involving the neoplasms benign, malignant and unspecified (e.g. hepatocellular carcinoma) [IC, 5.76; 95% confidence interval (CI), 5.65–5.86], metabolism and nutrition (IC, 5.17; 95%CI, 5.03–5.32) and vascular (IC, 4.62; 95%CI, 4.28–4.97). Hydroxychloroquine was associated with higher reporting of AEs involving the eye (e.g. retinal toxicity) (IC, 6.45; 95%CI, 6.23–6.67), musculoskeletal and connective tissue (IC, 5.81; 95%CI, 5.66–5.95) and skin and subcutaneous tissue (IC, 5.53; 95%CI, 5.34–5.72). Oseltamivir was associated with AEs involving the psychiatric (e.g. abnormal behavior) (IC, 4.54; 95%CI, 4.46–4.63), respiratory, thoracic and mediastinal (IC, 2.75; 95%CI, 2.51–2.99) and nervous system (IC, 2.31; 95%CI, 2.18–2.44). Ritonavir/lopinavir and darunavir were associated with AEs involving the immune system (e.g. immune reconstitution inflammatory syndrome) (IC, 6.59; 95%CI, 6.44–6.73), skin and subcutaneous tissue (IC, 6.26; 95%CI, 6.07–6.45) and metabolism and nutrition (IC, 5.68; 95%CI, 5.39–5.98). Two CRS-suppressing drugs, tocilizumab and sarilumab, were associated with AEs involving the skin and subcutaneous tissue (IC, 5.98; 95%CI, 5.85–6.10 for tocilizumab; IC, 1.89; 95%CI, 1.74–2.04 for sarilumab), musculoskeletal and connective tissue (IC, 5.68; 95%CI, 5.61–5.75 for tocilizumab; IC, 3.97; 95%CI, 3.81–4.13 for sarilumab) and immune system (IC, 5.62; 95%CI, 5.43–5.80 for tocilizumab; IC, 1.01; 95%CI, 0.79–1.23 for sarilumab). Interferon-β, was associated with AEs affecting the nervous system (IC, 4.40; 95%CI, 4.35–4.46), skin and subcutaneous tissue (IC, 3.42; 95%CI, 3.16–3.68) and psychiatric (IC, 2.41; 95%CI, 2.12–2.70). Another adjunctive agent, azithromycin was associated with AEs involving the immune system (IC, 4.04; 95%CI, 3.09–4.10), nervous system (IC, 3.68; 95%CI, 3.49–3.88) and skin and subcutaneous tissue (IC, 3.26; 95%CI, 2.96–3.57). These nine drugs are likely associated with higher reporting of AEs involving the skin and subcutaneous tissue, immune system and musculoskeletal and connective tissue (Figure 1). Despite that the AE data were not recorded for the combination treatment of hydroxychloroquine with azithromycin and ritonavir/lopinavir with interferon-β, all these drugs are more likely to induce AEs involving the skin and subcutaneous tissue, which may provide the hint for the synergistic effect for these combinations. Taken together, we demonstrated the landscape of AEs associated with potential COVID-19 drugs. We also calculated the ROR to validate our results obtained from IC. We observed similar pattern based on ROR and IC (Supplementary Figure 3), suggesting IC value is robust and reliable. We used IC only in our further analysis.

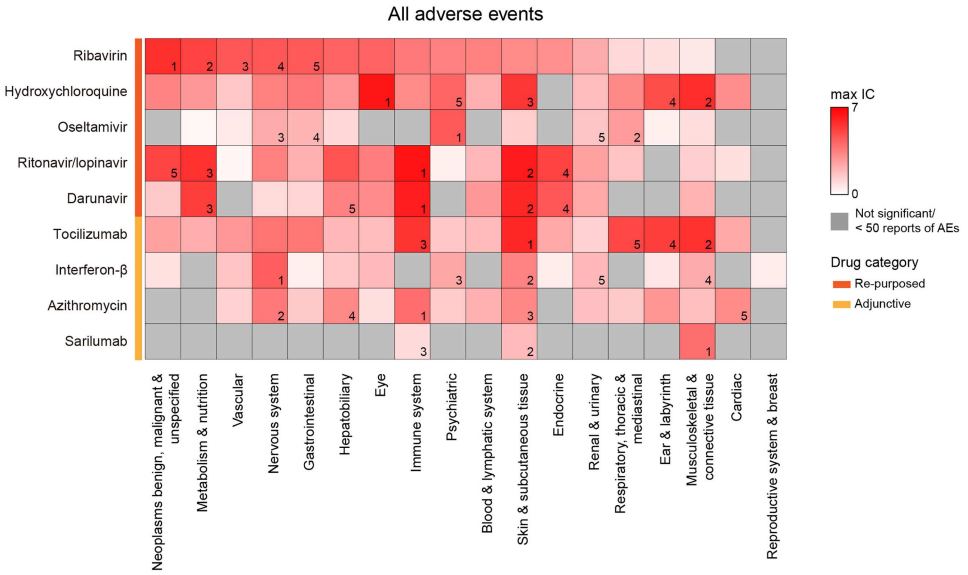

Figure 1. Landscape of all AEs associated with potential COVID-19 drugs. Heatmap of maximum IC values of significantly overreported AEs in each organ/system class for individual drugs for all AEs. Shade of the square indicates maximum IC value in each organ/system class. Gray squares indicate no significantly overreported AEs or <50 reports of AEs in that organ/system class.

Serious AEs associated with potential COVID-19 drugs

We further examined the serious AEs, which lead to serious outcomes documented in the report such as death, hospitalization and life-threatening, associated with potential COVID-19 drugs. We observed overall similar pattern (Figure 2 and Supplementary Table 3). For example, the AE organ/systems with the highest IC was still neoplasms benign, malignant and unspecified (IC, 5.76; 95%CI, 5.65–5.86) for ribavirin, eye (IC, 6.44; 95%CI, 6.22–6.67) for hydroxychloroquine and psychiatric (IC, 4.37; 95%CI, 4.28–4.46) for oseltamivir. Of note, two adjunctive agents, azithromycin and interferon-β may induce serious AEs in different organs/tissues. For example, interferon-β was associated with serious AEs involving nervous system (IC, 4.39; 95%CI, 4.33–4.44), skin and subcutaneous tissue (IC, 3.40; 95%CI, 3.15–3.66) and musculoskeletal and connective tissue (IC, 2.20; 95%CI, 2.07–2.33), whereas azithromycin was associated with serious AEs involving skin and subcutaneous tissue (IC, 3.22; 95%CI, 2.91–3.53), cardiac (IC, 3.18; 95%CI, 2.90–3.47) and hepatobiliary (IC, 3.14; 95%CI, 2.98–3.31). Both hydroxychloroquine and azithromycin were associated with increased reporting AEs involving skin and subcutaneous tissue, as well as ear and labyrinth; whereas both ritonavir/lopinavir and interferon-β were associated with increased reporting AEs involving skin and subcutaneous tissue. Taken together, we demonstrated the landscape of serious AEs associated with potential COVID-19 drugs.

Sex difference of AEs associated with potential COVID-19 drugs

Considering more male COVID-19 patients are reported than female [12], we further investigated the risks of higher reported AEs in different sexes for each drug by multivariate logistic regression analysis. We observed distinct pattern for the associations of AEs and sexes (Figure 3 and Supplementary Table 4). We observed female bias of AEs in endocrine [odds ratio (OR), 3.43; 95%CI, 2.65–4.47; FDR = 1.98×10^{-19}] and metabolism and nutrition disorders (OR, 1.39; 95%CI, 1.27–1.52; FDR = 5.51×10^{-12}) and male bias of AEs in neoplasms benign, malignant and unspecified (OR, 2.72; 95%CI, 2.23–3.34; FDR = 2.94×10^{-21}) in patients receiving ribavirin. Risks of AEs involving eye (OR, 2.33; 95%CI, 1.86–2.96; FDR = 5.79×10^{-12}) and immune system (OR, 2.22; 95%CI, 1.81–2.75; FDR = 4.97×10^{-13}) are higher in female patients and risks of AEs involving vascular (OR, 2.69; 95%CI, 2.09–3.43; FDR = 4.19×10^{-14}) is higher in male patients receiving hydroxychloroquine. Female bias of AEs in gastrointestinal (OR, 1.49; 95%CI, 1.33–1.68; FDR = 2.09×10^{-10}) and male bias of AEs in musculoskeletal and connective tissue (OR, 2.09; 95%CI, 1.25–3.57; FDR = 1.18×10^{-2}) and psychiatric (OR, 1.61; 95%CI, 1.46–1.78; FDR = 1.98×10^{-19}) were observed in patients treated with oseltamivir. In contrast, we observed higher risks of 12 classes of AE, including AEs involving eye (OR, 6.45; 95%CI, 3.00–16.81; FDR = 4.88×10^{-5}), neoplasms benign, malignant and unspecified (OR, 3.71; 95%CI, 2.04–7.31; FDR = 1.40×10^{-4}) and skin and subcutaneous tissue (OR, 3.58; 95%CI, 2.25–6.00; FDR = 1.13×10^{-6}), in male patients receiving ritonavir/lopinavir. Most classes of AEs significantly associated with sexes of darunavir are male bias, such as AEs in eye (OR, 5.13; 95%CI, 2.06–17.17; FDR = 4.52×10^{-3}), gastrointestinal (OR, 2.72; 95%CI, 1.97–3.82; FDR = 1.40×10^{-8}) and immune system (OR, 2.09; 95%CI, 1.47–3.02; FDR = 1.68×10^{-4}). Female bias of AEs in endocrine (OR, 5.50; 95%CI, 3.14–10.76; FDR = 1.66×10^{-7}), psychiatric (OR, 4.85; 95%CI, 2.83–9.18; FDR = 4.51×10^{-7}) and ear and labyrinth (OR, 2.41; 95%CI, 1.63–3.75; FDR = 9.89×10^{-5}) were observed in patients treated with tocilizumab. Female bias of AEs in immune system (OR, 2.32; 95%CI, 2.04–2.64; FDR = 9.99×10^{-36}) and male bias of AEs in musculoskeletal and connective tissue (OR, 3.20; 95%CI, 2.15–4.83; FDR = 7.61×10^{-8}) were observed in patients treated with azithromycin. We observed significantly higher risks of AEs in neoplasms benign, malignant and unspecified (OR, 38.46; 95%CI, 8.62–679.82; FDR = 6.99×10^{-4}) and endocrine (OR, 4.42; 95%CI, 1.61–18.24; FDR = 2.71×10^{-2}) in female patients treated with interferon-β. Taken together, we observed a significantly sex difference of AEs associated with potential COVID-19 drugs, and this need to be take into consideration in clinical practice.

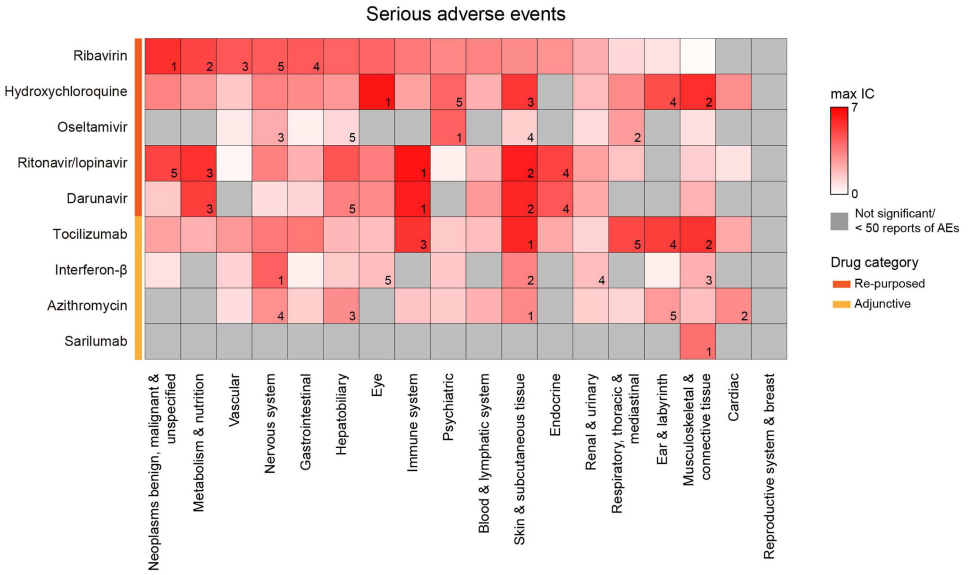

Figure 2. Landscape of serious AEs associated with potential COVID-19 drugs. Heatmap of maximum IC values of significantly overreported AEs in each organ/system class for individual drugs for serious AEs. Shade of the square indicates maximum IC value in each organ/system class. Gray squares indicate no significantly overreported AEs or <50 reports of AEs in that organ/system class.

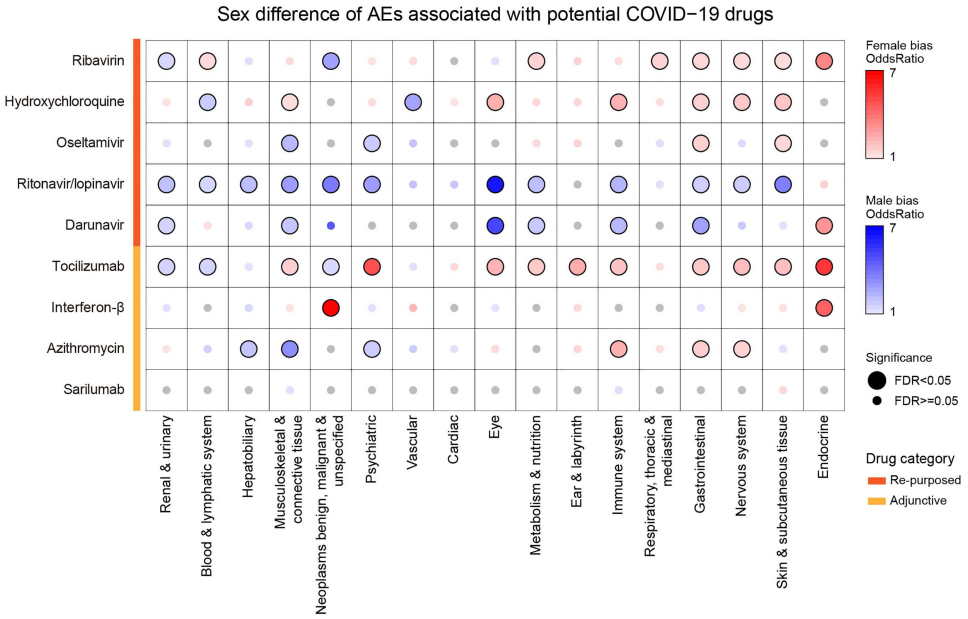

Figure 3. AEs associated with COVID-19 drugs in different sexes groups. Heatmap of OR for difference of AEs between male and female patients treated by nine potential COVID-19 drugs. Red indicates female bias; blue indicates male bias; shade of the dot indicates OR; bigger dots indicate FDR < 0.05.

Age difference of AEs associated with potential COVID-19 drugs

Age is a key risk factor for COVID-19 patients [13], so we further investigated the risks of significantly higher reported AEs in different age groups by comparing patients <65 years old (yo) versus patients ≥65 yo [14] (Figure 4 and Supplementary Table 5). Patients ≥65 yo had higher risk of AEs involving neoplasms benign, malignant and unspecified (OR, 2.36; 95%CI, 1.97–2.82; FDR = 7.95×10^{-20}), and patients <65 yo had higher risk of AEs involving endocrine (OR, 4.30; 95%CI, 2.72–7.32; FDR = 3.42×10^{-8}) and musculoskeletal and connective tissue (OR, 3.35; 95%CI, 2.26–5.22; FDR = 6.30×10^{-8}) when receiving ribavirin. Patients ≥65 yo had higher risk of AEs involving neoplasms benign, malignant and unspecified (OR, 4.58; 95%CI, 2.75–7.79; FDR = 4.25×10^{-8}), ear and labyrinth (OR, 3.05; 95%CI, 2.19–4.26; FDR = 3.21×10^{-10}) and eye (OR, 1.83; 95%CI, 1.59–2.10; FDR = 1.42×10^{-16}) when receiving hydrochloroquine. They also had higher risk of AEs in renal and urinary (OR, 4.53; 95%CI, 3.34–6.14; FDR = 5.00×10^{-21}), musculoskeletal and connective tissue (OR, 3.15; 95%CI, 1.85–5.27; FDR = 1.54×10^{-5}) and metabolism and nutrition (OR, 2.10; 95%CI, 1.34–3.22; FDR = 2.81×10^{-3}) when receiving oseltamivir. Patients ≥65 yo also had higher risk of AEs in renal and urinary (OR, 3.86; 95%CI, 2.65–5.49; FDR = 2.70×10^{-12}) when receiving ritonavir/lopinavir.

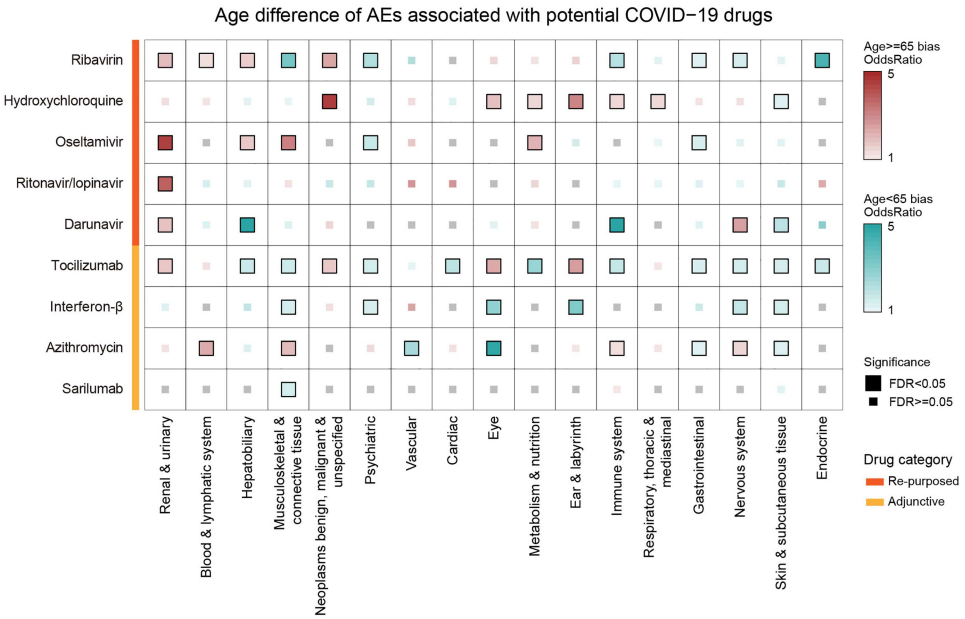

Figure 4. AEs associated with COVID-19 drugs in different age groups. Heatmap of ORs for difference of AEs between age < 65 and age ≥ 65 patients treated by nine potential COVID-19 drugs. Brown indicates age ≥ 65 yo bias; light green indicates age < 65 yo bias; shade of the square indicates OR; bigger squares indicate FDR < 0.05.

Patients ≥65 yo had higher risk of AEs in nervous system (OR, 2.50; 95%CI, 1.30–4.45; FDR = 8.31×10^{-3}), and patients <65 yo had higher risk of AEs in immune system (OR, 6.83; 95%CI, 2.17–41.42; FDR = 1.73×10^{-2}) and hepatobiliary (OR, 6.00; 95%CI, 2.27–24.36; FDR = 5.89×10^{-3}) when receiving darunavir. Strikingly, AEs for adjunctive drugs are reporting higher in almost all organs/systems in age < 65 yo. For example, patients <65 yo had higher risks of AEs in metabolism and nutrition (OR, 2.67; 95%CI, 2.15–3.37; FDR = 1.06×10^{-16}), cardiac (OR, 1.89; 95%CI, 1.33–2.77; FDR = 2.29×10^{-3}) and immune system (OR, 1.72; 95%CI, 1.55–1.91; FDR = 7.60×10^{-23}) when receiving tocilizumab. They had higher risk of AEs of ear and labyrinth (OR, 3.17; 95%CI, 1.33–10.37; FDR = 4.92×10^{-2}), eye (OR, 2.77; 95%CI, 1.97–4.04; FDR = 1.14×10^{-7}) and nervous system (OR, 1.76; 95%CI, 1.56–1.98; FDR = 7.95×10^{-20}) when receiving interferon-β. They had higher risk of AEs in eye (OR, 4.90; 95%CI, 1.77–20.30; FDR = 1.89×10^{-2}), vascular (OR, 2.35; 95%CI, 1.35–4.44; FDR = 1.13×10^{-2}) when receiving azithromycin. They also had higher risk of AEs in musculoskeletal and connective tissue (OR, 1.41; 95%CI, 1.05–1.92; FDR = 4.98×10^{-2}) when receiving sarilumab. Taken together, we observed a significantly age difference of AEs associated with potential COVID-19 drugs, and this need to be taken into consideration in clinical practice.

Discussion and conclusion

In summary, we present AEs for potential COVID-19 drugs based on real-world data from FAERS. FDA revoked emergency use authorization for hydroxychloroquine and chloroquine for treatment of COVID-19 patients on 15 June 2020. However, there is still heated argument for the treatment with hydroxychloroquine and chloroquine [15–18]. These drugs may cause AEs involving many organ/systems, especially skin and subcutaneous tissue, immune system and musculoskeletal and connective tissue. We also observed disparity bias of AEs based on sexes and ages for different potential COVID-19 drugs. Although it is known that some classes of AEs associated with specific drugs, such as chloroquine/hydroxychloroquine is associated with cardiac disorder based on individual cases [6, 19], we provided the most comprehensive landscape of AEs of these potential drugs. Based on our large-scale analysis, the frequency of cardiotoxicity associated with chloroquine/hydroxychloroquine treatment is relatively low. This is also consistent with a recent prospective observational study [15] and an open-label, randomized controlled trial [20]. In addition, we also provided evidences of personalized management of COVID-19 patients receiving these drugs according to gender and age. For example, female patients and patients <65 yo should be closely monitored for AEs involving endocrine when receiving ribavirin; patients <65 yo receiving tocilizumab and sarilumab, two drugs suppressing CRS, should be closely monitored for AEs involving musculoskeletal and connective tissue; female patients with age ≥ 65 yo should be closely monitored for AEs involving eye and immune systems when receiving hydrochloroquine; male patients with age < 65 yo should be carefully monitored for AEs involving eye and skin and subcutaneous tissue when receiving ritonavir/lopinavir plus interferon-β and vascular toxicities when receiving hydrochloroquine plus azithromycin. Older patients are undergoing changes (e.g. reduction in renal clearance, liver size and lean body mass) that could impact biological processes and subsequently altered drug distribution, metabolism and pharmacodynamic responses [21, 22]. Higher body fat, greater plasma volume and organ perfusion, sex hormone–related regulation of drug-metabolizing enzymes are reported to contribute to the sex differences of AEs [23, 24]. While these drugs hold promise to fight the global pandemic, healthcare providers should pay attention to AEs to maximize the treatment benefit while minimizing toxicity.

The limitation of our study is that the safety reports are not from COVID-19 patients and information in the FAERS database is based on spontaneous reports. Analyses of safety data from clinical trials should be undertaken to further investigate the toxicities of these drugs in the COVID-19 setting. Furthermore, FAERS is a postmarketing safety surveillance program for FDA-approved drugs and therapeutic biologic products [25]

and essentially based on spontaneous reports thus provide limited information about patients' characteristics, treatment and disease histories [26–28]. Some confounding factors, such as drug–drug interaction, prior diseases and coexisting illness, are lacking from FAERS. Further studies to integrate COVID-19 patients' risk factors, such as diabetes [29–31], cancer [32, 33], hypertension [34], cardiac disease [14, 35] and cerebrovascular diseases [14], are necessary to better understand the AEs associated with these drugs.

Key Points

- A comprehensive survey from real-world data for AEs.
- A landscape of associated AEs with potential drugs for COVID-19.
- Sex and age differences of AEs associated with potential COVID-19 drugs.
- Analysis from safety data may be taken into consideration in clinical practice.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

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Data availability

All the datasets we used in our analysis are publicly available and all web links are described in the methods. All data supporting the findings of the current study are listed in Supplementary Tables 1–5.

Author contributions

L.H. conceived and supervised the project. Y.J. and L.H. designed and performed the research. Y.J. and L.D. performed data analysis. Y.J. and L.H. interpreted the results. Y.J. and L.H. wrote the manuscript.

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