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Potential clinically significant drug-drug interactions of hydroxychloroquine used in the treatment of COVID-19

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Abstract

Aims: Hydroxychloroquine (HCQ) is using as a repurposed drug in considerable proportion of COVID-19 patients. However, being a substrate of cytochrome P450 (CYP) enzymes of CYP3A4/5, CYP2C8 and CYP2D6, the safety and efficacy of this drug may be affected by the coadministration of respective CYP inhibitors, substrates or inducer drugs. It was aimed to identify potential clinically significant drug-drug interaction (DDI) pairs of HCQ.

Methods: Inhibitors, substrates and inducer drugs lists of CYP enzymes of interest from international well-recognised evidence-based drug interaction resources were used to identify potential clinically significant pharmacokinetic DDI pairs of HCQ.

Results: Among 329 identified interacting drugs that predicted to cause clinically significant DDIs of HCQ, 45 (13.7%), 43 (13.1%) and 123 (37.4%) unique DDI pairs were identified from the FDA, Stockley's and Flockhart lists, respectively. Of interest, 55 (16.7%) DDI pairs were recognised by all three resources. At least, 29 (8.8%) severe DDI pairs were identified predicted to cause severe toxicity of HCQ in patients with COVID-19. When comparing these interactions with Liverpool DDI lists, it was found that out of 423 total interactions, 238 (56.3%) and 94 (22.2%) unique DDI pairs were identified from all three resources and Liverpool DDI lists, respectively. Of interest, only three (0.7%) DDI pairs were recognised by both the three international resources and Liverpool DDI lists of HCQ.

Conclusion: Using HCQ has clinical debate whether it should or should not continue in COVID-19 patients, however, potential clinically significant DDIs identified in this study may optimise safety or efficacy of HCQ in considerable proportion of patients.

1 | INTRODUCTION

Hydroxychloroquine (HCQ) has been authorised to use in many countries for the treatment of patients with coronavirus disease-2019 (COVID-19). Also, numerous clinical trials are ongoing assessing the efficacy and safety of HCQ in patients with COVID-19.[1-5] However, because of safety or efficacy concerns, using HCQ in COVID-19 patients has recent clinical debates whether it should or should not continue in these patients. In this clinical debating situation, it is pertinent to know that, being a substrate of cytochrome P450 (CYP) enzymes as evidenced elsewhere, the metabolism of HCQ may be affected by the CYP2C8, CYP3A4/5 or CYP2D6 enzymes.[6] However, inhibitor and substrate drugs of the respective CYP enzymes may either inhibit the metabolism of HCQ or may compete with the same enzyme system, which may in turn hinders the elimination of HCQ from the body. Consecutively, blood concentrations of HCQ may accumulate and may cause serious adverse drug reactions (ADRs) because of substrate-inhibitor drug-drug interactions (DDIs) or substrate-substrate DDIs. In contrast, CYP inducer drugs may facilitate the excretion of HCQ by inducing enzymes because of substrate-inducer DDIs and are provoking the risk for therapeutic failure of HCQ while some of these pathways may

trigger the higher concentration of HCQ active metabolite which may, in turn, increase the risk of HCQ-induced toxicity.

This predictive DDIs is plausible for COVID-19 patients taking HCQ since many patients with COVID-19 had multiple comorbidities and are vulnerable to polypharmacy.[7,8] Some patients responded well to the HCQ therapy and getting improved while the clinical conditions of many others were deteriorating and even many patients were died.[2,5,9,10] Although many factors, for example age, sex, comorbidities, hypoxia, organ dysfunction, etc might trigger the clinical outcomes; however, one of the other predisposing factors of these may be partly because of the DDIs associated with the patients of COVID-19 taking multiple medications.

It had well-evidenced in numerous studies with other classes of diseases especially in older people that polypharmacy was a known risk factor for the development of clinically significant DDIs and was provoking ADRs and drug toxicities as well.[11-14] It is therefore predicted that similar effects may also exist for COVID-19 patients treated with HCQ. Being a substrate of CYP2C8, CYP3A4/5 and CYP2D6, its pharmacokinetics (PK) effects may be affected by either the inhibitor or substrate or inducer drugs of the respective CYP enzymes and are predicted to cause potential clinically significant DDIs.

It is important to recognise that the Liverpool interactions group has provided prescribing resources where they categorised the interactions of experimental COVID-19 antiviral therapies as "contraindicated medications," "potential interactions requiring dose adjustment/close monitoring," "potential interactions of weak intensity" or "no clinically significant interactions."[15] However, the lists of interacting drugs provided by the Liverpool drug interaction prescribing resource may not be comprehensive since it might miss some of the important interacting drugs. For example, in the detailed recommendations for interactions with experimental COVID-19 antiviral therapies, this COVID-19 drug interaction resource enlisted ~15 contraindicated medications for HCQ but interestingly no drugs were found to interact with HCQ that were causing toxicity of HCQ. Of these 15 contraindicated medications, 08 drugs were predicted to increase their exposure by interaction with HCQ, that is increase toxicity of co-medications and only seven drugs were predicted to decrease the exposure of HCQ, that is decrease efficacy/therapeutic failure of HCQ but no drugs were enlisted that can possibly increase the exposure of HCQ and toxicity as well. This may indicate that these lists of drugs may not cover all possible interacting drugs of HCQ.

Amid this emergency situation, details of the treatment provided in COVID-19 patients were not available and was therefore unable to assess the potential clinically significant DDIs of the patients with COVID-19. However, the present study was aimed to predictively identify potential clinically significant DDIs pairs from the international resources so as to aware clinicians regarding the probability and severity of these interactions.

What's known

- Hydroxychloroquine (HCQ) may potentially interact with the cytochrome P450 (CYP) inhibitor, substrate or inducer drugs affecting its metabolism.

What's new

- In total, 423 interacting drugs predicted to cause clinically significant drug-drug interaction (DDIs) of HCQ involving CYP3A4/5, CYP2C8 and CYP2D6 was identified using three international evidence-based drug interaction resources.
- At least 55 DDI pairs should be taken into clinical considerations to optimise safety and efficacy of HCQ. Of interest, 29 severe DDI pairs were identified that may cause toxicity of HCQ and should be highly prioritised to optimise safety of HCQ.

2 | METHODS

This is a predictive original research aimed to identify potential clinically significant DDI pairs, this study used the US Food and Drug Administration (FDA) clinical table of CYP enzyme of interest for strong, moderate or weak inhibitors. This is because the FDA is a reputable internationally recognised body that provides clinical tables of CYPs that are evidence-based and systematically categorise the inhibitor drugs according to their strength and are updated on a regular basis.[16] The tables classify "strong," "moderate" or "weak" inhibitors which give an indication of the severity of putative interactions leading to safety or efficacy concerns greater than those present when the drugs are administered alone. For example, "strong, moderate and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively."

Secondly, this study used clinical tables of Flockhart CYP DDI interactions in which inhibitors were also categorised as strong, moderate and weak as done by the FDA CYP clinical tables.[17] For this reason, the present study has predictively categorised the potential interactions of HCQ as identified from the FDA and Flockhart lists as severe, moderate or weak interactions in which HCQ was predictively paired with strong, moderate or weak inhibitor drugs, respectively.

Thirdly, potential clinically significant DDI pairs were also identified from the Stockley's drug interactions since this is also an internationally well recognised evidence-based drug interactions resource.[18] Of note, Stockley's lists of CYP substrates, inhibitors and inducers of interest were not provided any severity categorisation. Also, Flockhart lists had no severity categorisation for CYP substrate and inducer drugs.

For uniformity, all inhibitor, substrate and inducer drugs identified from the FDA, Stockley's or Flockhart lists were putatively

paired with HCQ called DDI pairs predicted to cause clinically significant DDIs. At the end, severities of DDIs were determined only for the inhibitor drugs identified from either the FDA or Flockhart lists.

Finally, the identified potential clinically significant DDIs were compared with the lists of interacting drugs of HCQ as provided by the Liverpool COVID-19 drug interaction resource. Liverpool interactions group had provided prescribing resources where they categorised the interactions of experimental COVID-19 antiviral therapies as "contraindicated medications," "potential interactions requiring dose adjustment/close monitoring," "potential interactions of weak intensity" or "no clinically significant interactions."[15] The list of interacting drugs of HCQ was extracted from this prescribing resource and compared with the lists of drugs identified from the FDA, Stockley's drug interactions and Flockhart lists.

3 | RESULTS

As shown in Figure 1 and as detailed in the Methods section, there were in a total of 254 DDI pairs were identified from the FDA, Stockley's and Flockhart clinical tables comprising inhibitors, substrates and inducers of CYP3A4/5 enzyme and were predicted to cause clinically significant DDIs of HCQ affecting safety or efficacy. Of which, 40 (15.7%), 42 (16.5%) and 97 (38.2%) unique (without being duplicated with two/three-way combination) DDI pairs were identified from the FDA, Stockley's and Flockhart lists, respectively. However, 11 (4.3%), 12 (4.7%) and 18 (7.1%) DDI pairs were recognised by both the FDA and Stockley's; FDA and Flockhart; Stockley's and Flockhart lists, respectively. Of interest, 34 (13.4%) DDI pairs were recognised by all three resources.

In total, 20 DDI pairs were identified from the FDA, Stockley's and Flockhart clinical tables comprising inhibitors, substrates and inducers of CYP2C8 enzyme and were predicted to cause clinically significant DDIs of HCQ affecting safety and efficacy, as shown in Figure 2. Of which, 02 (10.5%), 01 (5.3%) and 08 (42.1%) unique (without being duplicated with two/three-way combination) DDI pairs were identified from the FDA, Stockley's and Flockhart lists, respectively. However, 02 (10.5%), 03 (15.8%) and 01 (5.3%) DDI pairs were recognised by both the FDA and Stockley's; FDA and Flockhart; Stockley's and Flockhart lists, respectively. Of interest, 03 (15.8%) DDI pairs were recognised by all three resources.

As shown in Figure 3, in a total of 108 DDI pairs were identified from the FDA, Stockley's and Flockhart clinical tables comprising inhibitors, substrates and inducers of CYP2D6 enzyme and were predicted to cause clinically significant DDIs of HCQ affecting safety or efficacy. Of which, 07 (6.5%), 08 (7.4%) and 53 (49.1%) unique (without being duplicated with two/three-way combination) DDI pairs were identified from the FDA, Stockley's and Flockhart lists, respectively. However, 02 (1.9%), 10 (9.3%) and 10 (9.3%) DDI pairs were recognised by both the FDA and Stockley's; FDA and Flockhart; Stockley's and Flockhart lists, respectively. Of interest, 18 (16.7%) DDI pairs were recognised by all three resources.

Since substrate, inhibitor and inducer drugs of CYP enzymes of interest may overlap between various two or three-way combinations of the FDA, Stockley's and Flockhart lists, therefore it was important to investigate the correlations among these lists. As shown in Figure 4, in total of 329 drug pairs were identified from the FDA, Stockley's and Flockhart clinical tables comprising inhibitors, substrates and inducers of CYP3A4/5, CYP2C8 and CYP2D6 enzymes and were predicted to cause clinically significant DDIs

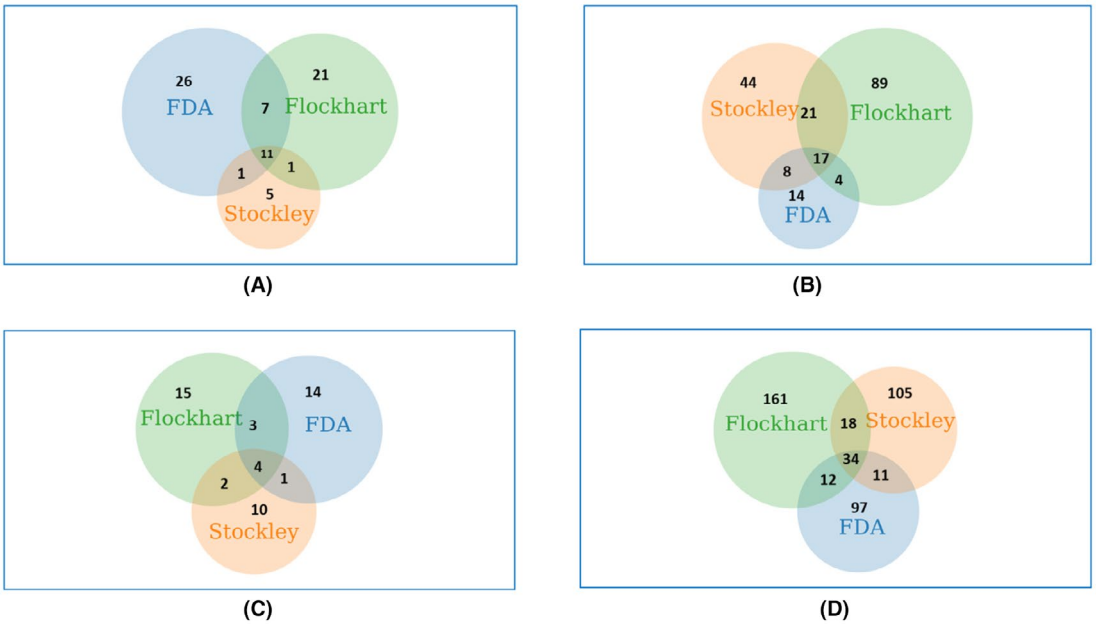

FIGURE 1 Potential clinically significant drug-drug interaction (DDI) pairs of hydroxychloroquine (HCQ) involving CYP3A4/5 enzyme identified from the FDA, Stockley's and Flockhart lists of CYP3A4/5 inhibitors, substrates and inducer drugs. A, DDI pairs involving HCQ and CYP3A4/5 inhibitors interactions. B, DDI pairs involving HCQ and CYP3A4/5 substrates interactions. C, DDI pairs involving HCQ and CYP3A4/5 inducers interactions. D, Cumulative DDI pairs involving HCQ and CYP3A4/5 inhibitors/substrates/inducers interactions

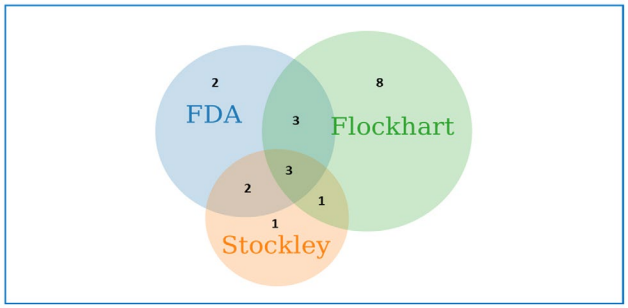

FIGURE 2 Potential clinically significant drug-drug interaction (DDI) pairs of hydroxychloroquine involving CYP2C8 inhibitors, substrates and inducer interactions

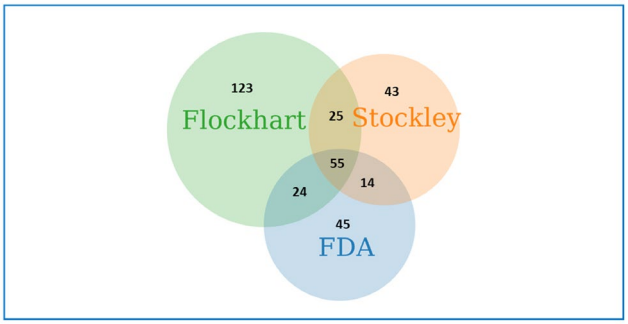

FIGURE 4 All potential clinically significant drug-drug interaction pairs of hydroxychloroquine involving CYP3A4/5, CYP2C8 and CYP2D6 enzymes identified from the FDA, Stockley's and Flockhart lists of CYP inhibitors, substrates and inducer drugs, respectively

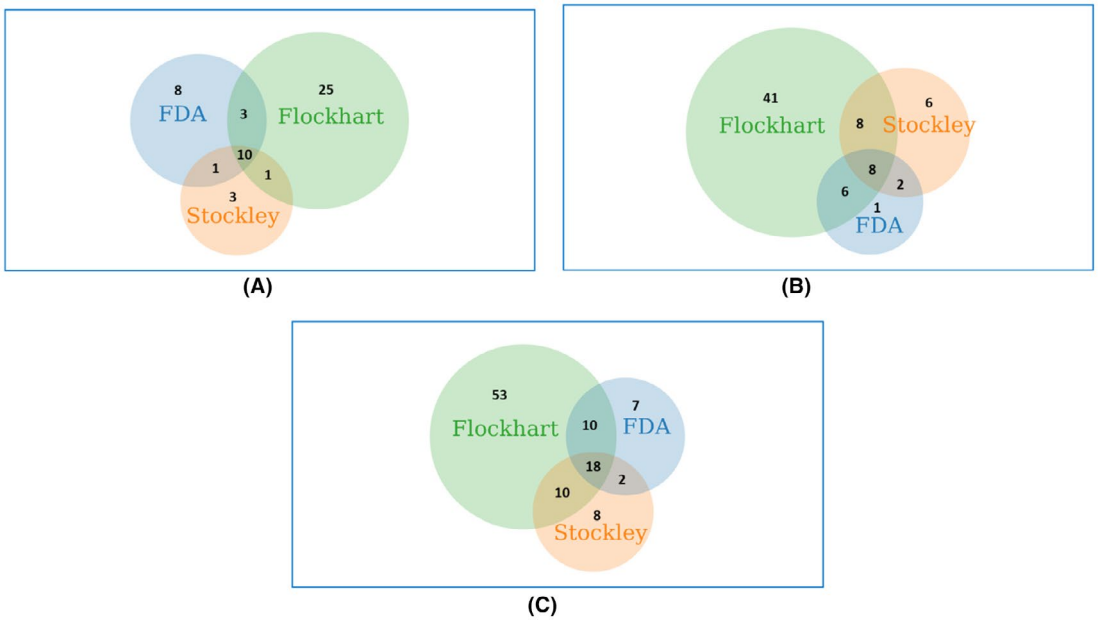

FIGURE 3 Potential clinically significant drug-drug interaction (DDI) pairs of hydroxychloroquine (HCQ) involving CYP2D6 enzyme identified from the FDA, Stockley's and Flockhart lists of CYP2D6 inhibitors, substrates and inducer drugs. A, DDI pairs involving HCQ and CYP2D6 inhibitors interactions. B, DDI pairs involving HCQ and CYP2D6 substrates interactions. C, Cumulative DDI pairs involving HCQ and CYP2D6 inhibitors, substrates or inducer interactions. Since only two inducer drugs were identified, no separate figure was constructed involving CYP2D6 inducer drugs

of HCQ, affecting its safety or efficacy. Of which, 45 (13.7%), 43 (13.1%) and 123 (37.4%) unique (without being duplicated with two/three-way combination) DDI pairs were identified from the FDA, Stockley's and Flockhart lists, respectively. However, 14 (4.3%), 24 (7.3%) and 25 (7.6%) DDI pairs were recognised by both the FDA and Stockley's; FDA and Flockhart; Stockley's and Flockhart lists, respectively. Of interest, 55 (16.7%) DDI pairs were recognised by all three resources. For interest, the list of interacting drugs causing various two or three-way combinations of DDI pairs are shown in Table 1. This showed that at least 55 DDI pairs should be taken into clinical considerations to optimise safety or efficacy of HCQ since these drugs were recognised from all three internationally renowned drug interaction resources.

As discussed in the "Method" section and as shown in Table 2, there were 29 (8.8% of total interactions identified) severe DDI pairs were identified from the FDA and Flockhart lists involving strong inhibitors of CYP3A4/5, CYP2C8 and CYP2D6 and were predicted to cause drug toxicity of HCQ. Patients with COVID-19 taking HCQ with any of these 29 drugs need special monitoring as these drugs may increase the blood concentrations of HCQ substantially and may therefore be vulnerable to severe drug toxicity. Since clinicians sometimes become fatigue to DDI alerts functional in some developed countries whereas in many countries computerised DDI alert systems may not exist, hence severe DDI pairs may be useful to them for taking precautions in advance regarding these severe DDIs as shown in Table 2. Because of unprecedented health situations, clinicians may overlook these interactions in patients with COVID-19 because of emergency management of the patients. However, it is predicted that more information of the DDIs of COVID-19 therapies will appear in the literature in the near future if these interactions

TABLE 1 Important clinically significant DDI pairs identified from the FDA, Stockley's and Flockhart lists of CYP3A4/5, CYP2C8 and CYP2D6 substrates, inhibitors and inducers drugs

14 DDI pairs identified from the FDA and Stockley's	24 DDI pairs identified from the FDA and Flockhart	25 DDI pairs identified from Stockley's and Flockhart	55 DDI pairs identified from all three resources (FDA, Stockley's and Flockhart)
Tadalafil, budesonide, darunavir, eletriptan, maraviroc, tipranavir, triazolam, vardenafil, troleandomycin, cilostazol, bosentan, rosiglitazone, tolterodine, trimipramine	Eliglustat, ibrutinib, naloxegol, nisoldipine, boceprevir, ciprofloxacin, fluvoxamine, ranitidine, telaprevir, telithromycin, enzalutamide, modafinil, montelukast, clopidogrel, teriflunomide, tramadol, atomoxetine, encainide, nebivolol, perphenazine, cinacalcet, celecoxib, escitalopram, vemurafenib	Amitriptyline, astemizole, cisapride, dexamethasone, donepezil, fentanyl, hydrocortisone, irinotecan, lercanidipine, lidocaine, methadone, rifabutin, tamoxifen, terfenadine, vincristine, zolpidem, nevirapine, carvedilol, codeine, flecainide, mexiletine, oxycodone, risperidone, thioridazine, diphenhydramine	Buspirone, tacrolimus, alfentanil, alprazolam, aprepitant, atorvastatin, eplerenone, felodipine, indinavir, lovastatin, midazolam, pimozide, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, erythromycin, itraconazole, cimetidine, clarithromycin, cyclosporine, diltiazem, imatinib, ketoconazole, nefazodone, nelfinavir, ritonavir, verapamil, voriconazole, carbamazepine, efavirenz, phenobarbital, phenytoin, rifampin, pioglitazone, repaglinide, gemfibrozil, trimethoprim, desipramine, dextromethorphan, imipramine, metoprolol, nortriptyline, propafenone, propranolol, venlafaxine, bupropion, fluoxetine, paroxetine, quinidine, terbinafine, duloxetine, amiodarone, sertraline

TABLE 2 List of 29 potential clinically significant severe DDI pairs of HCQ as identified from the FDA and Flockhart CYP clinical tables of strong inhibitors involving CYP3A4/5, CYP2C8 and CYP2D6 enzymes

CYP enzyme	Severe DDI pairs
CYP3A4/5	HCQ+Clarithromycin; HCQ+Telithromycin; HCQ+Troleandomycin; HCQ+Itraconazole; HCQ+Ketoconazole; HCQ+Posaconazole; HCQ+Nefazodone; HCQ+Idelalisib; HCQ+Boceprevir; HCQ+Cobicistat; HCQ+Ribociclib; HCQ+Voriconazole; HCQ+Nelfinavir; HCQ+Ritonavir; HCQ+Indinavir; HCQ+Saquinavir; HCQ+Danoprevir; HCQ+Elvitegravir; HCQ+Lopinavir; HCQ+Paritaprevir; HCQ+Telaprevir; HCQ+Tipranavir
CYP2C8	HCQ+Gemfibrozil
CYP2D6	HCQ+Bupropion; HCQ+Fluoxetine; HCQ+Paroxetine; HCQ+Quinidine; HCQ+Terbinafine; HCQ+Cinacalcet

Abbreviations: CYP, cytochrome P450; DDI, drug-drug interaction; FDA, Food and Drug Administration; HCQ, hydroxychloroquine.

were not taken seriously for clinical manifestations. For example, it was found the most severe DDIs of HCQ with azithromycin in patients with COVID-19 in which these drug pairs increasing the risk of life-threatening Q and T wave (QT) prolongation. This in turn leads to cardiac arrhythmias and sudden cardiac deaths of many COVID-19 patients as evidenced in recent two studies.[19,20]

Altogether, 185 interacting drugs were identified from the Liverpool COVID-19 interaction resource predicted to cause clinically significant DDIs with HCQ. After combining this Liverpool COVID-19 interacting drugs of HCQ with the FDA, Stockley's and Flockhart lists of interacting drugs and removing duplicates, it was found that in a total of 423 DDI pairs of HCQ were identified in this analysis predicted to cause clinically significant DDIs. Of these, 238 (56.3%) and 94 (22.2%) unique (without being duplicated with two/three-way combination) DDI pairs were identified from all three resources (FDA, Stockley's and Flockhart lists) and Liverpool DDI lists, respectively. Of interest, only three (0.7%) DDI pairs were recognised by both the three international resources and Liverpool DDI lists of HCQ.

Since chloroquine (CQ) has comparable PK properties with HCQ and is also metabolised by CYP2C8, CYP3A4/5 and CYP2D6 enzymes,[6] therefore the potential clinically significant DDIs identified for HCQ may also generally be applicable to CQ.

In summary, at least 29 DDI pairs should be taken into clinical considerations to optimise safety of HCQ since these drugs were predicted to cause clinically significant severe DDIs.

4 | DISCUSSION

As HCQ is using in many countries for combating COVID-19, it is inevitably important to aware clinicians regarding the potential ADRs

associated with the therapies provided to the COVID-19 patients. Since it has been replicated in numerous studies that these patients had multiple comorbidities[7,8] and are vulnerable to polypharmacy, therefore it is reasonably assumed that polypharmacy driven DDIs and ADRs are feasible in these patients. However, no study has been conducted yet to compile a list of drugs that could potentially interact with HCQ and may cause DDIs. Hence, the results of this current study may be considered as novel in this regard and had provided lists of drugs that may need clinical considerations when prescribing with HCQ.

Since DDI alert fatigue is highly prevalent in developed countries[21-23] and sometimes clinicians become fed-up with the alert warnings without being considerations of clinically significant DDIs especially in this emergency circumstances. Disagreement for enlisting interacting drugs as identified in this study indicated that if clinicians rely on only Liverpool COVID-19 interactions resource, large number of interacting drugs (ie, 238 out of 423 total interactions) potentially causing clinically significant DDIs with HCQ may out of clinical considerations and vice versa. This may increase the chances of developing safety or efficacy concerns of HCQ in many COVID-19 patients. The findings of this study, therefore, suggest taking careful considerations of all DDI pairs identified in this analysis. However, because of considering alert fatigue, this study further emphasised for considering at least 91 DDI pairs that were recognised from all international resources. At the very least, the findings of this study suggest taking serious concerns for at least 29 DDI pairs predicted to cause severe DDIs in patients with COVID-19.

Although it was not possible to measure the clinical effects of the potential clinically significant DDI pairs identified in this study, however, some insights can be obtained from the studies that had already assessed some of the clinical effects of HCQ taking with other interacting drugs in patients with COVID-19.

Serious life-threatening ADRs, for example cardiac arrhythmias because of QT prolongation for concomitant use of HCQ and azithromycin had been reported in recent studies,[19,20] although some authors indicated that this combination could result in numerically superior viral clearance compared with HCQ monotherapy.[5,9] However, the current study identified five antibiotics, for example telithromycin, troleandomycin, clarithromycin, ciprofloxacin and erythromycin that may potentially interact with HCQ and may cause clinically significant DDIs. Since antibiotics are being prescribed as second-line therapy after antivirals in patients with COVID-19,[24-26] therefore, it is highly suggested to take extra precautions and close clinical monitoring for prescribing any of these five antibiotics with HCQ in patients with COVID-19.

Since there was an urgent need for COVID-19 treatment; the repurposing of available drugs was a quick and cheap option, HCQ being the most prescribed drug in this context. In late March, US President Donald Trump repeatedly proclaimed that HCQ could prevent or effectively treat COVID-19 and within days, the number of prescriptions for the drug was skyrocketed. On 15 June 2020, FDA definitively revoked the Emergency Use Authorization (EUA) for emergency use of HCQ to treat COVID-19. However, because of its widespread off-label use for the treatment of COVID-19 on the basis of low-quality evidence, the use of HCQ has attained the status of one of the most disputed drugs. Clinical evidence suggests a lack of benefit from HCQ use in hospitalised patients with COVID-19 because HCQ appears to be associated with an increased adverse risk of QT interval prolongation and potentially lethal ventricular arrhythmias. Therefore, on July 4, 2020, World Health Organization (WHO) discontinued the HCQ treatment arm for hospitalised patients with COVID-19.[27,28]

Recent experience of antimalarial drug repositioning in the era of COVID-19 showed that even in pandemic times, the use of repurposed drugs should be cautiously investigated only in randomised controlled trials, mainly to avoid drug-related toxicity and potentially life-threatening adverse events. Although HCQ use may represent an effective prophylactic strategy against COVID-19 infected hospitalised patients,[28] however, in total, more than four hundred interacting drugs were identified from the evidenced-based international resources predicted to cause clinically significant DDIs of HCQ which suggested that such interactions should carefully be investigated in the real-world treatment scenarios where patients may expose to polypharmacy.

Although over 60 years, HCQ is being used in the treatment of malaria, amoebic liver abscess, and several rheumatological conditions, however, there is a good rationale for HCQ use, at least within a compassionate approach, for COVID-19 treatment, but possibly not to severe stage of the disease. The risk/benefit ratio of HCQ use alone or in combination with other drugs such as Azithromycin has yet to be established with the available level of evidence, thus clear information regarding the risk/benefit ratio of HCQ prescription needs to be shared among health professionals and extended to patients and the population.[29-31]

Aside from the considerations of potential DDIs, patients treated with HCQ and had liver and kidney failure should also give an important clinical consideration. Unlikely, HCQ is a very slow-acting drug and has a prolonged half-life for blood clearance. Patients with kidney failure will not able to clear the HCQ from the blood at the rate as it is desired and eventually decreased clearance rate may increase the bioavailability of this drug and may cause drug toxicity.[6] As known, ~40 of HCQ is metabolised in the liver and subsequently excreted from the body.[6] Patients with liver dysfunction may therefore prone be to accumulate blood concentrations of HCQ and which may in turn cause drug toxicity.

Although different ways, for example computerised DDI alerts, web-based drug DDI checkers, etc, can be used to identify potential clinically significant DDIs, however, there are lots of limitations of these checking systems including alert fatigue, lack of robust evidence of the interactions, etc The findings of the present study may therefore serve as considerably best DDI lists for checking the potential clinically significant interactions of HCQ in COVID-19 patients since the interactions were identified from the internationally well-recognised evidenced-based resources.

5 | FUTURE IMPLICATIONS OF POTENTIAL DDI PAIRS

Since the DDI pairs were identified from the FDA, Stockley's and Flockhart lists were comprehensive lists involving CYP3A4/5, CYP2C8 and CYP2D6 substrates, inhibitors and inducers drugs, therefore these lists may have wide applicability in checking DDIs for the drugs metabolised by CYP3A4/5, CYP2C8 or CYP2D6. The DDI pairs as identified in this study may also be applicable to investigate potential clinically significant DDIs of HCQ in other disease conditions, for example malaria, rheumatoid arthritis, systemic lupus erythematosus, etc, where HCQ is clinically indicated.

6 | LIMITATIONS

This study has some limitations. First of all, it is a predictive study therefore the possibilities of the DDIs as predicted in this study may not actually observed in the real-world treatments of COVID-19 patients. Secondly, while some of the ADRs had observed because of DDIs of HCQ as evidenced in the published literature, however, data are extremely limited for assessing observed ADRs in patients with COVID-19 whether these observed ADRs were because of DDIs of HCQ or because of other clinical factors, therefore, we could not assess these.

In spite of these limitations, it is expected that the findings of this study will facilitate clinicians for taking decisions regarding rational therapies for COVID-19 patients. Further, considerations of the severe DDI pairs as identified in this study may substantially reduce the drug toxicity of HCQ.

7 | CONCLUSIONS

The clinician should consideration all resources for checking DDIs of HCQ since there was disagreement for enlisting interacting drugs. Although, using HCQ has clinical debate whether it should or should not continue in COVID-19 patients because of safety or efficacy concerns, however, potential clinically significant DDI identified in this study may optimise safety or efficacy of HCQ in considerable proportion of patients. At least, 29 severe DDI pairs as identified in this study should be given serious clinical considerations for the safety concerns of HCQ in patients with COVID-19. The suggestions recommended in this study if considered cautiously by the clinicians may be expected to reduce the toxicity of HCQ in considerable proportion of patients. In cooperation with effective infection control policies functional in different countries, reviewing DDIs of HCQ may reduce morbidity and mortality from COVID-19.

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DISCLOSURES

No conflict of interest to declare.

AUTHORS CONTRIBUTIONS

The lead author contributed 90% of this manuscript while the second author contributed 10%.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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