Adverse drug event risk assessment by the virtual addition of COVID-19 repurposed drugs to Medicare and commercially insured patients' drug regimens: A drug safety simulation study

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Abstract

Drug safety is generally established from clinical trials, by pharmacovigilance programs and during observational phase IV safety studies according to drug intended or approved indications. The objective of this study was to estimate the risk of potential adverse drug events (ADEs) associated with drugs repurposed for coronavirus disease 2019 (COVID-19) treatment in a large-scale population. Drug claims were used to calculate a baseline medication risk score (MRS) indicative of ADE risk level. Fictitious claims of repurposed drugs were added, one at a time, to patients' drug regimens to calculate a new MRS and compute a level of risk. Drug claims data from enrollees with Regence health insurance were used and sub-payer analyses were performed with Medicare and commercial insured groups. Simulated interventions were conducted with hydroxychloroquine and chloroquine, alone or combined with azithromycin, and lopinavir/ritonavir, along with terfenadine and fexofenadine as positive and negative controls for drug-induced Long QT Syndrome (LQTS). There were 527,471 subjects (56.6% women; mean [SD] age, 47 years [21]) were studied. The simulated addition of each repurposed drug caused an increased risk of ADEs (median MRS increased by two-to-seven points, $p < 0.001$). The increase in ADE risk was mainly driven by an increase in CYP450 drug interaction risk score and by drug-induced LQTS risk score. The Medicare group presented a greater risk overall compared to the commercial group. All repurposed drugs were associated with an increased risk of ADEs. Our simulation strategy could be used as a blueprint to preemptively assess safety associated with future repurposed or new drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Although medications provide therapeutic benefits, they also carry a risk for adverse drug events (ADEs). Some repurposed drugs currently being used in patients with coronavirus disease 2019 (COVID-19) have known risk of ADEs.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study conducted a risk assessment for ADEs of five COVID-19 repurposed drug regimens in Medicare and commercially insured patient populations, totaling about 525,000 subjects. A medication risk score analysis was used to predict the risk of ADEs by simulating the addition of the repurposed drugs into existing patient drug regimens.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
In these COVID-19 simulations, an increased risk for ADEs was identified, driven by QT prolongation and CYP450 drug interactions. The combination of hydroxychloroquine or chloroquine with azithromycin, and lopinavir/ritonavir showed the greatest increase in risk. The Medicare population remained at higher risk overall.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
This simulation strategy can be used preemptively with new or repurposed drugs to quantitatively estimate ADE risk in large populations.

INTRODUCTION

On March 11, 2020, coronavirus disease 2019 (COVID-19) was declared a global pandemic. The associated virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly, as no one around the world had immunity against this new strain of coronavirus. In contrast to a seasonal flu, there is currently no US Food and Drug and Administration (FDA) approved vaccine or proven therapeutic medication available to slow or cease the dissemination of this pathogen; therefore, the use of existing medications repurposed for the treatment of COVID-19 is currently being explored.

Even though medications could provide therapeutic benefits, they can also carry a risk for adverse drug events (ADEs). The repurposed drugs currently being used in patients with COVID-19 have been previously administered to different patient populations, and data on their risk of side-effects and ADEs exists. However, a new risk/benefit analysis of these drugs needs to be conducted in the context of COVID-19, especially for patients at the highest risk for infection, including the elderly and those with comorbidities (heart diseases, diabetes, respiratory disease, high blood pressure, cancer, and immunosuppressed patients).[1] Whereas the determination of a new therapeutic agent's effectiveness and safety require clinical studies, prior information can be used to preemptively estimate safety associated with repurposed drugs using simulation studies. We propose that the virtual addition of repurposed drugs to patients' actual drug regimens could be used as a blueprint to assess preemptively safety associated with future repurposed or new drugs.

Chronic underlying medical conditions require multiple medications, and the presence of comorbidities often results in polypharmacy. Polypharmacy is associated with significant consequences (morbidity and mortality), as the more drugs a patient is taking, the higher their risk of ADEs. Based on data from the National Electronic Injury Surveillance System-All Injury Program, it was estimated that ADEs accounted for 2.5% of unintentional injury emergency department visits, with 6.7% of those leading to hospitalization.[2] Further, Gurwitz et al. reported an overall ADE rate of 50.0 per 1000 person-years among Medicare enrolled persons in the ambulatory care setting.[3]

Drug claims data could be a reliable source to attribute risk of ADEs in outpatient populations.[4] A 2019 study showed that 20.7% of Medicare beneficiaries were at high risk for ADEs. The rate of ADEs was 46.3 per 1000 person-years in this population, which also used all hospital services at a significantly higher rate than Medicare beneficiaries who were not at a high risk for ADEs. In agreement with the results of this study, we reported on the usefulness of a proprietary medication risk score based on drug claims to predict ADEs in a frail, elderly population.[5] We recently published a simulation-based strategy using drug claims from 12,383 elderly patients to theoretically identify risk of ADEs when adding COVID-19 repurposed drugs.[6]

Using a large (>525,000) Medicare and Commercially insured beneficiary population, the objective of our study was to assess the risk of ADEs associated with the simulated addition of repurposed drugs for the treatment of COVID-19, including hydroxychloroquine (HCQ) and chloroquine (CQ)—alone or in combination with azithromycin (AZ)—and the clinically used

combination of lopinavir/ritonavir (LPV/r) to their drug regimens. These drugs were selected as they serve to inform on the actual situation and to validate our simulation approach for future repurposed drugs, because data have accumulated specifically for HCQ, CQ, and AZ in patients with COVID-19. A medication risk score (MRS) composed of 5 risk factors and based on drug claims data was used as a predictive tool to simulate the impact of COVID-19 repurposed drugs and to compare the likelihood of ADEs.[7]

METHODS

Subjects and study design

This study utilized prescription drug claims from May 1 to October 31, 2019, for Medicare and commercial health plan enrollees (Regence's insurance database) to determine the subjects' baseline drug regimens and to calculate their baseline medication risk scores. Data consist of patients with either a commercial or Medicare Regence health plan on two or more medications. This was class 4 data and consisted of pharmacy and medical claims data. Additional data, including age, medical records, and pharmacy records, were used for this study; data were securely shared using Medwise™ software. Participants with no drug claims data available were excluded from the study. Data elements analyzed were prescribed drugs, dose, age, sex, and health insurance type (commercial or Medicare) for all included drug claims. For data protection, date of birth was represented as a year value, with ages over 90 years old fixed at 89. All individual-level data were anonymized before being made available for analysis in this study.

This research protocol was reviewed and approved by the Biomedical Research Alliance of New York Institutional Review Board (BRANY IRB), an independent review board, prior to study initiation and a waiver of authorization to use protected health information was granted (protocol #20-12-117-427). The study protocol was registered at the US National Institutes of Health website (http://www.clinicaltrials.gov; NCT04378881).

Medication risk score and simulation strategy

A medication risk stratification was used to simulate the impact of different COVID-19 repurposed drugs on the baseline medication risk score. Tabula Rasa HealthCare (TRHC) has developed a proprietary MRS, the MedWise™ Risk Score, that uses algorithms that consider five medication characteristics to compute the risk of ADEs.[5,7] Briefly,

it includes (1) computation of a drug regimen relative odds ratio for ADE using the US FDA pharmacovigilance database (US Food and Drug Administration Adverse Event Reporting System [FAERS]),[8] (2) anticholinergic cognitive burden (ACB),[9] (3) sedative burden (SB),[10,11] (4) drug-induced Long QT Syndrome (LQTS) burden,[12] and (5) CYP450 drug interaction burden risk scores.[13] The total MRS and the individual aggregated risk factors (FAERS, ACB, SB, drug-induced LQTS, and CYP450 drug interaction burden scores) were divided into low-risk, moderate-risk, and high-risk subcategories. The methodology has been recently published and is extensively described in patents #WO2019089725 and #WO2017213825.[6]

To simulate the effects of a repurposed drug (or drug combination) on the MRS, a fictitious claim for the tested repurposed drug (or combination) was added to the database for each subject. If an individual was already taking the added drug, their daily dosage was set to the proposed dose of this drug for treating COVID-19 (or left alone if their original dose was higher). Following the addition of a repurposed drug (or drug combination) a new MRS was derived for each individual.

Five repurposed drugs or drug combinations were tested: comprising HCQ (400 mg twice daily); HCQ with AZ (400 mg twice daily + 500 mg once daily, respectively); CQ (500 mg twice daily); CQ with AZ (500 mg twice daily + 500 mg once daily, respectively); and LPV/r (400 mg twice daily + 100 mg twice daily, respectively). It is known that HCQ, CQ, and AZ can cause QT prolongation and polymorphic ventricular tachycardia (torsade de pointes).[14–18] Because the LQTS risk score is part of the MRS, additional simulations were performed using known negative (fexofenadine) and positive (terfenadine) controls for QT prolongation (fexofenadine 180 mg/day; terfenadine 180 mg/day; and terfenadine 180 mg/day + AZ 500 mg/day).[19]

Data processing and statistical analysis

To perform the medication risk stratification, a webservice interface and customized scripts were used. MRS were generated by processing prescribed drug claims using National Drug Codes (NDC) as drug identifiers. Medication data were extracted from the claims and cleaned of errors and inconsistencies through quality and integrity analyses. Because NDCs can also denote nonmedications (e.g., medical devices), active medication data was further filtered to exclude such NDCs. Active medication data for each subject was filtered based on prescription dates and days of supply, including any possible refills. Finally, enrollees were divided into commercial or Medicare insured groups based on their health insurance plan.

Descriptive population characteristics including MRS and individual risk factors were measured, including means, medians, SDs, range, and proportions as appropriate. For comparing the MRS and composite individual risk factors before and after addition of repurposed drugs into participants' drug regimens, the two-sided Wilcoxon signed-rank test was used. To determine the statistical significance of participants moving to a higher risk stratification category (low-to-moderate, low-to-high, or moderate-to-high), the McNemar test was used. To determine if the MRS or a risk category were more influenced by one drug than by others, we used a Friedman test, followed by paired comparisons with the two-sided Wilcoxon signed-rank test. For all the Wilcoxon signed-rank tests, the ranks of zeros were included in calculating the statistic (implemented as zero method = "zsplit" in SciPy 1.4.0). For the statistical analysis assessing the difference between female and male groups and between insurance types, the two-sided Mann–Whitney U test was used, along with a common language effect size measure denoted f based on the Mann–Whitney U test.[20] The common language effect size f is calculated as follows: the MRS of every patient in the commercial population is compared against the MRS of every patient in the Medicare population. The total number of comparisons is denoted N, the number of comparisons where Medicare has a lower score is denoted N_M, and the number of comparisons where the two are tied is denoted N_T. The effect size f is defined as $f := (N_M + 0.5N_T)/N$. (The numerator is equivalent to the Mann–Whitney U statistic.) An f of 0.5 would mean the two populations were at equal risk, and lower values of f mean the Medicare population tends to be at greater risk (have a higher score) than the commercial population.

For statistical significance, we considered p values below 0.05 to be significant. To adjust for multiple comparisons, the Benjamini/Hochberg adjustment was applied. The p values less than 0.00001 are reported as 0.001. Statistical analysis was performed in Python version 3.7.6 using the pandas (version 1.0.0), SciPy (version 1.4.0), statsmodels (version 0.01.0), Matplotlib (version 3.0.3), and seaborn (version 0.00.0) packages and in R (version 1.2.5019) with the dplyr, data.table, sqldf, scales, and ggplot2 packages. Microsoft SQL Server (version 15) was used to manipulate and analyze large datasets.

RESULTS

Participant characteristics

In our study, 1,588,645 prescribed drug claims from 527,471 participants were analyzed; demographic and clinical characteristics at baseline are described in Table 1. Approximately 95% of participants are categorized as low MRS risk, with the remaining 3% as moderate risk, and 2% as high risk. Results are also presented by payers in Table 1. Medicare patients tended to be older (mean age of 75 years), take more drugs (mean of 4.7 per day), and be at a higher risk of ADEs (mean MRS of 7.0 ± 6.2 with only 87.5% at low risk, 7.4% at moderate risk, and 5.2% at high risk) compared to the commercial insured group (mean MRS of 3.7 ± 4.4 with 96.4% at low risk, 2.3% at moderate risk, and only 1.3% at high risk).

Concomitant drugs were explored that can potentially interact with CYP450 pathway: HCQ (30% by CYP2C8, and to a lesser extent via CYP3A4 [15%] and CYP2D6 [15%]); CQ (35% by CYP2C8 and 15% by CYP2D6); and LPV (90% by CYP3A4) and ritonavir (competitive inhibitor of CYP3A4).[21–24] Prior to the addition of repurposed drugs, frequencies of individuals receiving potential interacting drugs metabolized by CYP2C8, CYP3A4, and/or CYP2D6 are listed in Table 1. The percentage of individuals taking potential CYP450-interacting drugs was 2–5 times higher in the Medicare group, with the exception of CYP2C8 inhibitors or competitive substrates, which was similar between both groups. The most common prescribed CYP2C8 interacting drugs found in both studied populations were ibuprofen, trimethoprim, pioglitazone, primidone, and gemfibrozil. An exhaustive list of the commonly prescribed medications and the CYP2C8 potential interacting drugs are presented in Tables S1 and S2, respectively.

Simulated effects of repurposed drugs for COVID-19 on MRS

In Figure 1, violin plots, which illustrate the distribution and probability density of the MRS, are shown for the commercial and Medicare groups at baseline and after the virtual addition of each repurposed drug or drug combination. The addition of all repurposed drugs increased the MRS for both groups (median increased by 2 to 7 points; $p < 0.001$). The addition of AZ to HCQ or CQ resulted in a greater increase of MRS than that of HCQ or CQ alone (Figure 1). The addition of LPV/r was associated with the highest MRS rise, with the median MRS increasing by six and seven points for the commercial and Medicare groups, respectively.

The frequency distributions of individuals classified in the low, moderate, and high MRS are presented in Figure 2. The virtual addition of repurposed drugs caused a significant increase of individuals in the moderate and high MRS categories for both the commercial and Medicare groups. The number of patients at moderate risk enhanced by ~ 60% to 420% compared to baseline for the commercial insured group ($n = 10,028$,

TABLE 1 Demographic characteristics of the total studied population and stratified by health insurance plans (i.e., commercial and Medicare insured groups)

Characteristics at baseline	Total	Commercial insured group	Medicare insured group
Total number of patients, n	527,471	435,035	92,436
Age (years); mean $\pm$ SD (range)	47 $\pm$ 21 (0–89)	41 $\pm$ 18 (0–89)	75 $\pm$ 9 (20–89)
Sex; male, N (%)	228,942 (43.4%)	189,548 (43.6%)	39,394 (42.6%)
Sex; female, N (%)	298,529 (56.6%)	245,487 (56.4%)	53,042 (57.4%)
Number of drugs/day; $N \pm$ SD (range)	3.0 $\pm$ 2.4 (1–27)	2.7 $\pm$ 2.1 (1–27)	4.7 $\pm$ 3.1 (1–26)
MRS			
Total MRS; mean $\pm$ SD (range)	4.3 $\pm$ 5.0 (0–40)	3.7 $\pm$ 4.4 (0–40)	7.1 $\pm$ 6.2 (0–40)
Low-risk group[a]; N (%)	500,269 (94.8%)	419,374 (96.4%)	80,895 (87.5%)
Moderate-risk group[a]; N (%)	16,754 (3.2%)	10,028 (2.3%)	6726 (7.3%)
High-risk group[a]; N (%)	10,448 (2.0%)	5633 (1.3%)	4815 (5.2%)
Medication: patients currently receiving			
HCQ, N (%)	2695 (0.51%)	1932 (0.44%)	763 (0.83%)
CQ, N (%)	8 (0.0015%)	6 (0.0014%)	2 (0.0022%)
AZ, N (%)	8404 (1.6%)	7605 (1.7%)	799 (0.86%)
LPV/r, N (%)	133 (0.025%)	101 (0.023%)	32 (0.035%)
Potential CYP450 drug-drug interactions, patients currently receiving			
CYP2C8 inhibitors or competitive substrates[b]; N (%)	18,999 (3.6%)	16,117 (3.7%)	2882 (3.1%)
CYP2C8 inducers, N (%)	659 (0.12%)	310 (0.07%)	349 (0.38%)
CYP3A4 inhibitors or competitive substrates[b]; N (%)	150,655 (28.6%)	99,184 (22.8%)	51,471 (55.7%)
CYP2D6 inhibitors or competitive substrates[b]; N (%)	105,559 (20%)	74,701 (17.2%)	30,858 (33.4%)
Combination of CYP3A4 + CYP2D6 inhibitors or competitive substrates[b]; N (%)	50,554 (9.6%)	29,109 (6.7%)	21,445 (23.2%)
Combination of CYP2C8 + CYP3A4 + CYP2D6 inhibitors or competitive substrates[b]; N (%)	2169 (0.41%)	1248 (0.29%)	921 (1%)

Abbreviations: AZ, azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; LPV, lopinavir; LVP/r, lopinavir + ritonavir; MRS, medication risk score.

[a]MRS risk groups are defined as follows: MRS values <15 are classified in the low-risk group, MRS values ≥15 to <20 in the moderate-risk group, and MRS values ≥20 in the high-risk group.

[b]Competitive substrates are drugs exhibiting a high affinity for a respective isoform. Concomitant administration of these drugs with the weak affinity substrates HCQ and CQ is associated with potentially significant drug interactions. LPV is also a weak substrate of CYP3A4 but since its administration was always with ritonavir, a strong inhibitor of CYP3A4, no additional inhibition and interaction was considered for LPV. However, ritonavir, when virtually added to a patient regimen, was considered as a perpetrator drug.

2.3%) and by ~ 30% to 200% for the Medicare group ($n = 6726$, 7.3%). The number of subjects classified in the high MRS group increased by ~ 90% to 570% and by 70% to 310% for the commercial ($n = 5633$, 1.3%) and Medicare ($n = 4815$, 5.2%) groups, respectively (Figure 2).

The Medicare group appeared at higher risk of ADEs than the commercial group. This effect size f was calculated by comparing commercial insured patients' MRS to every Medicare insured patients' MRS (f value < 0.5 indicates that the Medicare group tends to be at greater risk—represented by a higher MRS—than the commercial insured group; Table 2). However, it is notable that the addition of drugs caused a greater increase in risk for

the commercial population than for the Medicare group (although the Medicare group remains at greater risk overall), as can be seen by examining the effect size f in Table 2.

The effect of repurposed drugs on individual aggregated risk factors comprised in the total MRS is presented in Table 2 and Figure S1. FAERS and CYP450 drug interaction burden were both significantly augmented after the virtual addition of repurposed drugs, as indicated by an increase of median value and shift in the probability density (violin plots), after the addition of repurposed drugs ($p < 0.001$; Figure S1a and Table 2). Of particular note is LPV/r: the mean CYP450 score increased by 3.5-fold and 5.5-fold in the Medicare and commercial insured groups,
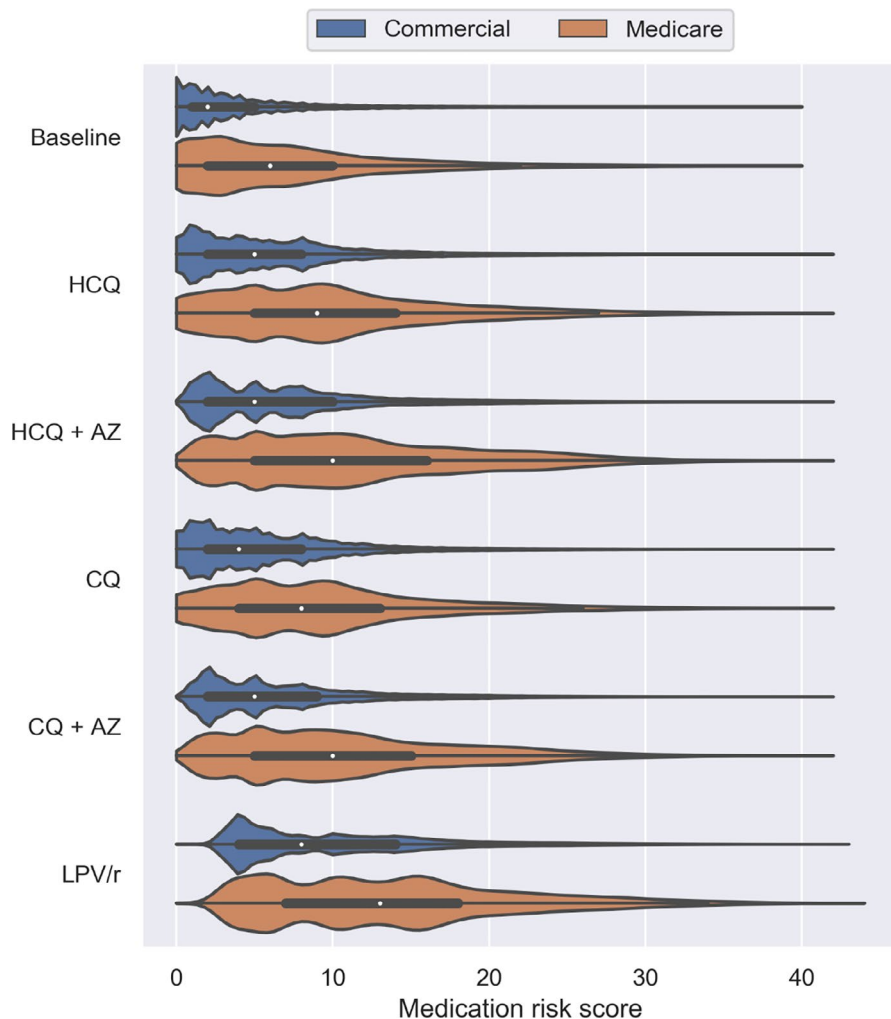
FIGURE 1 Medication risk score (MRS) distribution of commercial and Medicare populations before and after virtual addition of repurposed drugs. Violin plots of the MRS at baseline and after the virtual addition of repurposed drugs into subjects' drug regimens from commercial and Medicare insured groups (blue and orange, respectively). The white dots are the medians, and the colored areas are probability density estimates. The $p < 0.001$ compared to the baseline for all repurposed drugs. AZ, azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; LPV/r, lopinavir + ritonavir
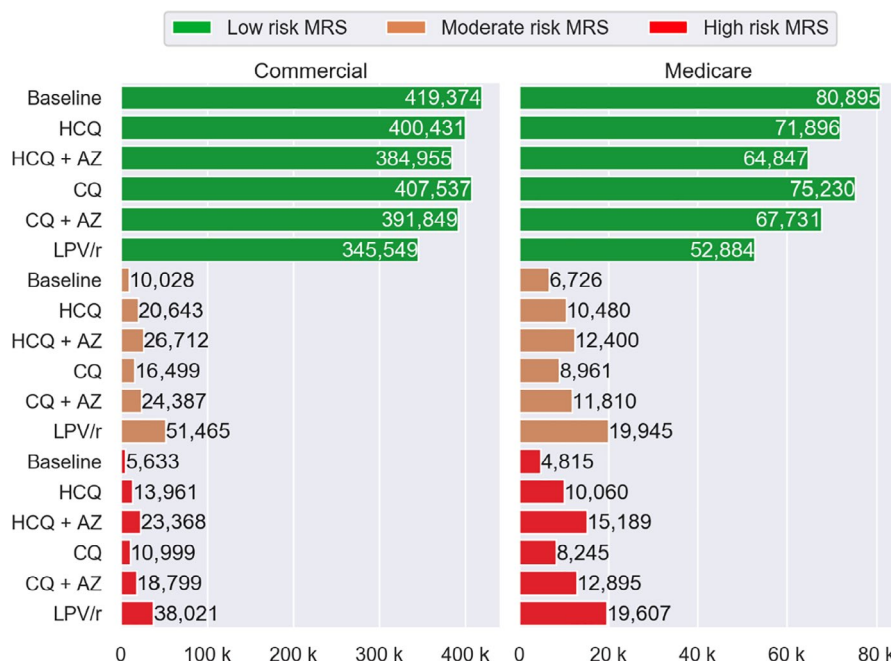

FIGURE 2 Medication risk score (MRS) risk category distributions of both populations before and after virtual addition of repurposed drugs. Histogram showing frequency of individuals in low, moderate, and high MRS categories by drug compared to the baseline. Data are shown for commercial (left) and Medicare (right) insured groups. The green, orange, and red represent the low-risk (MRS < 15), moderate-risk (MRS ≥ 15 to <20), and high-risk (MRS ≥ 20) group categories, respectively. AZ, azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; LPV/r, lopinavir + ritonavir

respectively. The anticholinergic burden score and sedative burden score were both unaffected by the addition of repurposed drugs. The effect size was also assessed for each aggregated risk factor: the Medicare group was at higher risk for both FAERS and CYP450 drug interaction burden scores compared to the commercial group (Table 2).

TABLE 2 The medication risk factor scores for commercial insured group and Medicare insured group at baseline and following the addition of COVID-19 repurposed drugs

Drug name	Commercial insured group			Medicare insured group			Commercial vs. Medicare	
	Mean (SD)	Median	p value[a]	Mean (SD)	Median	p value[a]	p value[b]	Effect size f[c]
Total MRS								
Baseline	3.7 (4.4)	2	N/A	7.1 (6.2)	6	N/A	0.001	0.312
HCQ	6.0 (5.5)	5	0.001	9.9 (7.0)	9	0.001	0.001	0.324
HCQ + AZ	7.1 (5.9)	5	0.001	11.4 (7.5)	10	0.001	0.001	0.320
CQ	5.7 (5.1)	4	0.001	9.3 (6.6)	8	0.001	0.001	0.322
CQ + AZ	6.8 (5.6)	5	0.001	10.8 (7.1)	10	0.001	0.001	0.317
LPV/r	9.8 (6.4)	8	0.001	13.7 (7.7)	13	0.001	0.001	0.340
FAERS score								
Baseline	1.1 (1.1)	1	N/A	2.0 (1.2)	2	N/A	0.001	0.306
HCQ	1.7 (0.9)	2	0.001	2.3 (1.0)	2	0.001	0.001	0.308
HCQ + AZ	2.2 (0.7)	2	0.001	2.7 (0.8)	3	0.001	0.001	0.322
CQ	1.8 (0.9)	2	0.001	2.4 (1.0)	3	0.001	0.001	0.315
CQ + AZ	2.2 (0.6)	2	0.001	2.7 (0.8)	3	0.001	0.001	0.322
LPV/r	2.3 (0.7)	2	0.001	2.8 (0.8)	3	0.001	0.001	0.321
CYP450 drug interaction burden score								
Baseline	1.0 (1.9)	0	N/A	2.1 (2.8)	2	N/A	0.001	0.370
HCQ	2.6 (2.9)	2	0.001	4.1 (3.3)	4	0.001	0.001	0.360
HCQ + AZ	2.6 (2.9)	2	0.001	4.1 (3.3)	4	0.001	0.001	0.360
CQ	2.1 (2.5)	2	0.001	3.5 (2.9)	3	0.001	0.001	0.359
CQ + AZ	2.1 (2.5)	2	0.001	3.5 (2.9)	3	0.001	0.001	0.359
LPV/r	5.5 (3.9)	5	0.001	7.4 (4.3)	8	0.001	0.001	0.364
Anticholinergic burden score								
Baseline	0.4 (1.0)	0	N/A	0.8 (1.2)	0	N/A	0.001	0.393
HCQ	0.4 (1.0)	0	1.0	0.8 (1.2)	0	1.0	0.001	0.393
HCQ + AZ	0.4 (1.0)	0	1.0	0.8 (1.2)	0	1.0	0.001	0.393
CQ	0.4 (1.0)	0	1.0	0.8 (1.2)	0	1.0	0.001	0.393
CQ + AZ	0.4 (1.0)	0	1.0	0.8 (1.2)	0	1.0	0.001	0.393
LPV/r	0.4 (1.0)	0	1.0	0.8 (1.2)	0	1.0	0.001	0.393
Sedative burden score								
Baseline	1.0 (1.0)	1	N/A	1.6 (1.1)	2	N/A	0.001	0.344
HCQ	1.0 (1.0)	1	1.0	1.6 (1.1)	2	1.0	0.001	0.344
HCQ + AZ	1.0 (1.0)	1	1.0	1.6 (1.1)	2	1.0	0.001	0.344
CQ	1.0 (1.0)	1	1.0	1.6 (1.1)	2	1.0	0.001	0.344
CQ + AZ	1.0 (1.0)	1	1.0	1.6 (1.1)	2	1.0	0.001	0.344
LPV/r	1.0 (1.0)	1	1.0	1.6 (1.1)	2	1.0	0.001	0.344
LQTS score								
Baseline	0.1 (0.7)	0	N/A	0.5 (1.4)	0	N/A	0.001	0.448
HCQ	0.3 (1.2)	0	0.001	1.0 (2.0)	0	0.001	0.001	0.419
HCQ + AZ	0.9 (1.9)	0	0.001	2.1 (2.7)	2	0.001	0.001	0.359
CQ	0.3 (1.2)	0	0.001	1.0 (2.0)	0	0.001	0.001	0.418

(Continues)

TABLE 2 (Continued)

Drug name	Commercial insured group			Medicare insured group			Commercial vs. Medicare	
	Mean (SD)	Median	*p* value[a]	Mean (SD)	Median	*p* value[a]	*p* value[b]	Effect size f[c]
CQ + AZ	0.9 (1.9)	0	0.001	2.2 (2.7)	2	0.001	0.001	0.359
LPV/r	0.5 (1.5)	0	0.001	1.1 (2.1)	0	0.001	0.001	0.425
Fexofenadine	0.1 (0.7)	0	1.0	0.5 (1.4)	0	1.0	0.001	0.448
Terfenadine	0.6 (1.6)	0	0.001	1.2 (2.2)	0	0.001	0.001	0.420
Terfenadine + AZ	1.0 (2.0)	0	0.001	2.3 (2.8)	2	0.001	0.001	0.358

Abbreviations: AZ, azithromycin; CQ, chloroquine; FAERS, US Food and Drug Administration Adverse Event Reporting System; HCQ, hydroxychloroquine; LPV/r, lopinavir boosted with ritonavir; LQTS, Long QT Syndrome; MRS, medication risk score; N/A, not available; SD, standard deviation.

[a]The *p* values were calculated using the Wilcoxon signed-rank test against baseline.

[b]The *p* values Medicare vs. commercial using the Mann–Whitney *U* test.

[c]The lower *f*, the greater risk is the Medicare group compared to the commercial group.

Simulated effects of COVID-19 repurposed drugs on the LQTS risk score

The addition of all repurposed drugs and terfenadine caused an increase of the drug-induced LQTS score for both studied populations (Figure S2 and Table 2). As anticipated, fexofenadine did not affect the LQTS score for any subject (negative control). When HCQ and CQ were virtually added into the drug regimens, the extent of the change in the drug-induced LQTS score was similar to what was observed with terfenadine alone. The magnitude of changes with HCQ or CQ combined with AZ was also comparable to the one observed with terfenadine plus AZ. The effect size analysis indicated that, at baseline, the Medicare group was slightly at an increased risk for the drug-induced LQTS versus the commercial insured group (*f* = 0.448; Table 2). The HCQ or CQ combined with AZ was associated with a greater risk of LQTS for the Medicare group compared to the commercial group (*f* baseline of 0.448 to 0.359 in presence of AZ + HCQ or AZ + CQ). Figure 3 shows the number of patients allocated to the low-risk, moderate-risk, and high-risk LQTS scores. No change was observed in the frequency distribution with fexofenadine.

In our studied populations, the most common prescribed drugs contributing to the drug-induced LQTS score are listed in Table S3. In the Medicare group, more than 9.8% of the Medicare insured individuals were receiving one of these drugs, whereas 8.7% of the commercial insured group were also prescribed such drugs.

The covariable of sex was examined during the drug-induced LQTS simulation analysis. The violin plots of the distribution of the drug-induced LQTS scores and probability density estimation stratified by sex for the commercial and Medicare groups can be found in Figure S3. Sex analysis demonstrated that the virtual addition of repurposed drugs or terfenadine had a greater effect on women than on men (*p* < 0.001), except for fexofenadine.

DISCUSSION

Data on the frequency and type of ADEs with studied repurposed drugs are available from previous clinical experience; however, a quantitative risk for ADEs in the context of COVID-19 is unknown. Furthermore, in the context of COVID-19, little is known about the likelihood of ADEs in large-scale outpatient populations, such as Medicare and commercially insured populations. Results from our study indicate that a simulation strategy based on a medication risk score could be used as a blueprint to estimate ADE risk with current and future repurposed drugs.

Our results demonstrated that the virtual addition of all repurposed drugs increased the number of patients within the high-risk category for the MRS. A recent study assessed this current MRS as a predictive medication risk tool for ADEs and medical outcomes in a cohort of older adults with polypharmacy.[5] Each unit of the MRS was associated with an increase of ADEs (risk increased by 8.6% per point increase), additional emergency visits (+ 3 visits/100 patients/year) and additional medical expenditure (extra of $1,037/MRS unit).[5] Polypharmacy was seen in our studied cohort: 20% of subjects were taking 5 drugs or more (44% in the Medicare group vs. 15% in the commercial group). Following the addition of repurposed drugs into the subjects' drug regimens, the median of the MRS was increased by two to seven points in the entire population. This finding suggests that in both groups, some individuals could become at increased risk of ADEs if exposed to repurposed drugs. Among the individual aggregated risk factors to derive the total MRS, the impact on the MRS when adding the repurposed drugs was mainly

FIGURE 3 LQTS risk category distributions of both populations before and after virtual addition of drugs. Histogram showing frequency of individuals in low, moderate, and high LQTS risk categories by drug compared to the baseline. Data are shown for commercial (left) and Medicare (right) insured groups. The inset shows the high-risk categories. The green, orange, and red represent the low-risk, moderate-risk, and high-risk, respectively. AZ, azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; LPV/r, lopinavir + ritonavir; LQTS, Long QT Syndrome
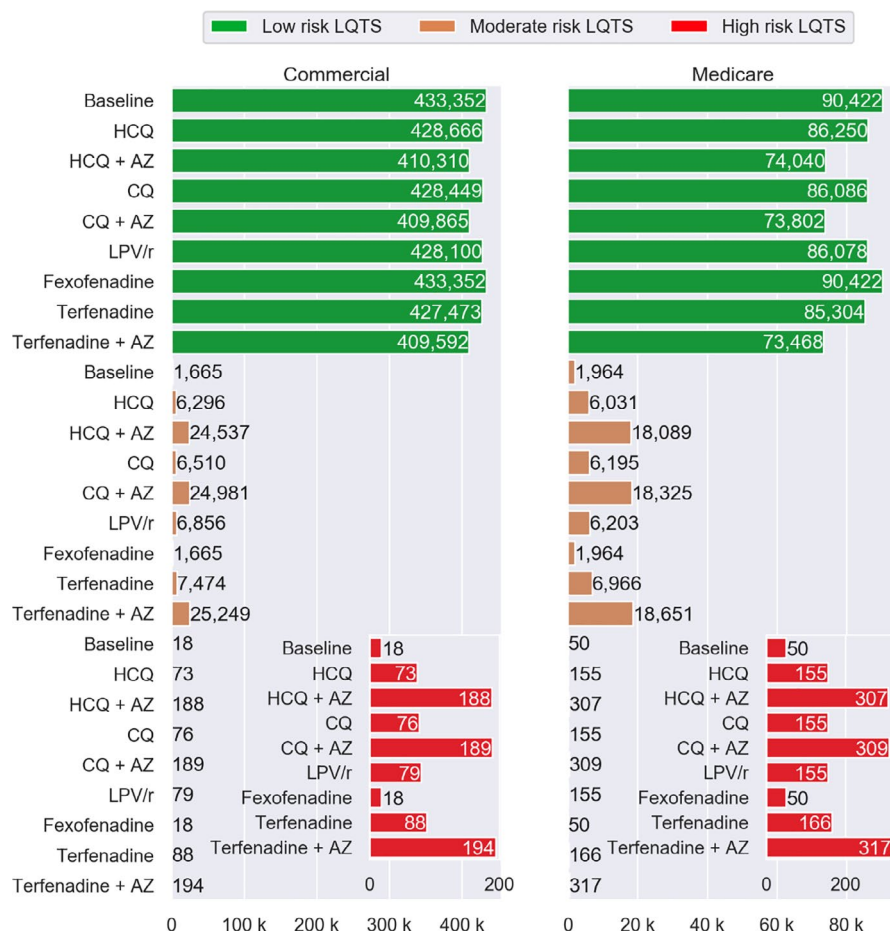
related to drug-induced LQTS and CYP450 drug interaction burden scores.

Repurposing drugs may require deviations from the approved dosing regimens and from prescribing practice for which they were intended. Such deviations can raise complex issues, especially those associated with the safety profile and toxicity. The side effects that raised particular safety concerns with regard to HCQ and CQ are cardiac toxicity related to QT prolongation and risk of torsade de pointes.[25] Such ADEs were reported in patients treated for malaria or for lupus erythematosus.[18,26,27] Recently, results from a multinational, retrospective study published by Lane et al. reported on the risk of ADEs associated with the acute and long-term administration of HCQ with or without AZ compared to sulfasalazine in a new user population of patients (>1 million) treated with these drugs for rheumatoid arthritis.[28] No excess risk of ADEs was identified when acute (30-day) HCQ or sulfasalazine use were compared. However, long-term use of HCQ exhibited an increase in cardiovascular mortality risk (calibrated hazard ratio of 1.65) and concomitant treatment with AZ appeared to increase even further the level of risk for cardiovascular mortality (calibrated hazard ratio of 2.19).[28] These results are consistent with our observations from the simulation approach used in our study. Furthermore, it highlights that a simulation approach could be very timely (once claims data from large populations are cleaned and available, it could be done in days/weeks) and can be very flexible allowing testing and comparison for multiple drugs being repurposed. Additionally, safety concerns were raised as cases of significant QT prolongation were observed in patients receiving HCQ or CQ ± AZ to treat COVID-19 infection; these data are consistent with the use of our simulation strategy to assess risk of drug-related ADEs and our prediction of a prolonged QT interval.[29–32] Importantly, our simulation results demonstrated that women were at increased risk of drug-induced LQTS as indicated with higher LQTS risk score compared to men. However, underlying comorbidities can influence drug effects, specifically efficacy and toxicity. In that sense, our approach may underestimate the risk for ADEs associated with repurposed drugs included in our study. At the same time, risk scoring approaches looking only at disease state and comorbidities, without considering drug combinations, are missing the most relevant information as ADEs are drug-specific.

Studies discussed previously reveal some of the strengths and weaknesses of observational versus simulation studies. On one hand, observational studies offer a clear picture of drug efficacy and safety in real-world situations but often require long observation periods in large populations to

detect small signals and dissect the impact of covariables and establish a causal effect. Furthermore, they are based on real people cases experiencing either a lack of efficacy or suffering from ADEs. On the other hand, simulation studies can rapidly detect and quantify risk of ADEs in large populations or in subpopulations with predefined characteristics but are often limited to safety assessment (except in the case of prodrugs where drug-drug interactions inhibiting activation of the prodrug may suggest lack of efficacy) and could be semiquantitative depending on the quality and completeness of data in the database.

The virtual addition of drugs to a patient's drug regimen is also a powerful approach to discern the risk of ADEs associated with a particular medication as, with this approach, each patient is its own control. This is a perfect match for each patient for disease state, other medications in the drug regimen, and other covariables. There is no need to perform statistical analyses adjusting for confounding factors. This approach also allows us to use positive and negative controls, such as terfenadine and fexofenadine for drug-induced LQTS, as demonstrated in this study. Hence, the number of patients at risk of drug-induced LQTS when exposed to fexofenadine was exactly the same as the number of patients at baseline, although this number increased to 317 when exposed to terfenadine (Medicare subpopulation). We also demonstrated that the risk was greater in women than in men (Figure S3).

Polypharmacy carries an increased risk for ADEs with potential COVID-19 therapies. Older adults taking multiple drugs are often ineligible for COVID-19 therapeutic trials. As reported by Harvard Medical School researchers, older adults were routinely excluded from important clinical trials for COVID-19.[33] Results from our previous study conducted in 12,383 participants of the National Program of All-Inclusive Care for the Elderly demonstrated an increased risk of ADEs following the virtual addition of COVID-19 repurposed drugs; major risk factors were also observed for CYP450 drug interactions and risk of drug-induced LQTS.[6] A simulation strategy similar to the one conducted in this study was performed in the COVID-SAFER study: a treatment with HCQ (5 days at a minimum dose of HCQ 600 mg daily) was theoretically added to hospitalized older adults.[34] From 1001 patients, 59% of these were receiving one or more medications that could potentially interact with HCQ.

Our study has some limitations associated with a simulation approach based on drug claims. It was assumed that patients were taking their prescribed medications and it did not consider over-the-counter medicine. Additionally, using medical claims (International Classification of Disease [ICD] codes) in a large study population can also represent limitations in this study, as coding can be variable from one provider to the next and there may also be a delay in entering these codes into the system.

In conclusion, our simulation strategy using drug claims data allows the estimation of ADE risk in individuals from various populations, including Medicare and commercial insured populations. The virtual addition of drugs to a patient's drug regimen is a powerful approach to discern the risk of ADEs associated with a particular medication. Our results demonstrate that a medication risk score could be used to assess drug safety before exposing patients to repurposed drugs. The proposed strategy, which virtually adds drugs to the patients' actual drug regimen, could be used as a blueprint to assess preemptively safety associated with future repurposed or new drugs.

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CONFLICTS OF INTEREST

M.K.S., R.B., S.B.R., M.D., P.D., J.T., and V.M. are all employees and shareholders of Tabula Rasa HealthCare. J.T. and V.M. are listed as inventors on two pending patents. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.K.S., P.D., J.T., and V.M. wrote the manuscript. M.H., J.T., and V.M. designed the research. M.K.S., R.B., M.D., S.B.A.R., M.H., P.D., J.T., and V.M. performed the research. M.K.S., R.B., and V.M. analyzed the data. M.K.S. and R.B. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.