Detecting Drug-Drug Interactions in COVID-19 Patients

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Abstract

COVID-19 patients with multiple comorbid illnesses are more likely to be using polypharmacy to treat their COVID-19 disease and comorbid conditions. Previous literature identified several DDIs in COVID-19 patients; however, various DDIs are unrecognized. This study aims to discover novel DDIs by conducting comprehensive research on the FDA Adverse Event Reporting System (FAERS) data from January 2020 to March 2021. We applied seven algorithms to discover DDIs. In addition, the Liverpool database containing DDI confirmed by clinical trials was used as a gold standard to determine novel DDIs in COVID-19 patients. The seven models detected 2,516 drug-drug pairs having adverse events (AEs), 49 out of which were confirmed by the Liverpool database. The remaining 2,467 drug pairs tested to be significant by the seven models can be candidate DDIs for clinical trial hypotheses. Thus, the FAERS database, along with informatics approaches, provides a novel way to select candidate drug-drug pairs to be examined in COVID-19 patients.

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Introduction

Approximately 25% of COVID-19 patients are reported to have at least one comorbidity [9], and those with one comorbid condition are at increased risk for poor clinical outcomes, including admission to ICU and death[18]. COVID-19 patients with multiple comorbid illnesses are more likely to be using polypharmacy to treat their COVID-19 illness and comorbid conditions. The more medications a patient is taking, the higher the risks of adverse events induced by drug-drug interactions (DDIs)[4]. This situation can lead to an enhanced likelihood of unrecognized adverse DDIs, increasing risks for additional morbidity or even mortality[11].

Research on DDIs in patients with COVID-19 can be broadly classified into three categories. The first category discovers DDIs by conducting a meta-analysis on published articles in PubMed, Medline, Scopus, and Google Scholar[14]. For example, Awortwe et al. identified potential DDIs, particularly between antiretroviral drugs, initially considered for use in the treatment of COVID-19 and other drugs for treating comorbidity[2]. However, there are critical weaknesses of meta-analysis, such as heterogeneity of results and publication bias. Furthermore, reviewing the biomedical literature looking for DDIs is time-consuming by the researchers and professionals, and small differences in search strategies can produce large differences in the set of studies found. The second detects DDIs based on public DDI datasets. For example, Bai et al. trained Bi-Level Graph Neural Networks on public DDI datasets (e.g., Drugbank) for biological DDI prediction[5]. However, despite several resources of DDIs exist to help improve DDI knowledge and have been used as gold standards, detections based on the datasets which were created before the pandemic cannot generalize well to unseen DDIs in patients with COVID-19[3]. The third category focuses on predicting DDIs via analyzing DDIs in clinical trials. For instance, the University of Liverpool evaluated the DDI risk in COVID-19 therapies using results in ClinicalTrials.gov and created a dynamic version of a COVID-19 Drug Interactions Checker (www.covid19-druginteractions.org)[12]. Clinical trials detected/confirmed many DDIs in COVID-19 patients. However, there is a potentiality that they missed many drug-drug paris that have potential interactions. Also, it is challenging for clinical trial studies to select appropriate candidate drug paris to study adverse events from a large number of drug pairs (> 2 million) in COVID-19 patients.

To discover novel DDIs which were not found in previous literature, we applied DDI detection algorithms to the FDA Adverse Event Reporting System (FAERS). The DDI algorithms include logistic regression, the Ω shrinkage measure, additive model, multiplicative model, combination risk ratio model, association rule mining model, and chi-square statistics.

Methods

Study Materials

The FDA adverse event reporting system—The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a database that collects spontaneous adverse events submitted by pharmaceutical companies, clinicians, pharmacists, and patients. FAERS has served as the cornerstone for pharmacovigilance purposes mostly focusing on detecting adverse events of drugs, and has proven to be a useful source of evidence in the safety evaluation process[7; 13; 24]. The FAERS database contains nearly 20 million reports, and more than 28,000 adverse reports are related to COVID-19, which provides an extensive resource to investigate DDIs in COVID-19 patients. It comprises the following information: demographic and administrative information; drug information; adverse events; patient outcomes; report sources; therapy dates; and indications for use.

Liverpool Database—We used the Liverpool database as a gold standard to discover novel DDIs in patients with COVID-19. The Liverpool database is created based on Covid19-druginteraction.org[12], the COVID-19 Drug Interactions website created by the University of Liverpool based on the drug-drug interaction risk of experimental COVID-19 therapies. The Liverpool database provides information on whether the combination of medications for COVID-19 and comorbidity treatment is safe or not. It is updated regularly as new treatment regimens for COVID-19 emerge, and the last update was performed on 19 April 2021. The Liverpool database contains 28 and 552 drugs for COVID-19 and comorbidity treatments, respectively. DDIs were graded into four levels: "no clinically significant interaction expected"; "potential weak interaction"; "potential interaction that may require close monitoring"; and "do not be co-administered." We considered drug-drug pairs which were not in the "no clinically significant interaction expected" group as positives (DDIs). Among 15,456 drug-drug interactions, 2,049 drug-drug pairs had at least potential weak interactions.

COVID-19 Cohort creation

Our study extracted all adverse events in the FAERS database from January 2020 to March 2021. Adverse events in the FAERS database were coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. However, since the FDA did not curate drug names, the drug name normalization step was essential. Therefore, we used the Adverse Event Open Learning through Universal Standardization (AEOLUS) ETL process to remove FAERS data deduplication and map drug names to RxNorm concepts[6].

We created a COVID-19 cohort in which each patient had at least one adverse event between January 2020 to March 2021, and the medication indication was for COVID-19 treatment.

A 4 by 2 contingency table creation

We created two groups of drugs: i) drugs used to treat COVID-19 (Drug 1 group), and ii) drugs used to treat illnesses other than COVID-19 (Drug 2 group). "Drug 2" group may include the drugs in the "Drug 1 group" since the drugs in the "Drug 1" group could be used for the treatment of diseases other than COVID-19 in pre- or intra-COVID-19 pandemic.

We extracted all possible Drug 1-Drug 2 combinations from the COVID-19 cohort and created the 4 by 2 contingency table for drug-drug-AE combinations (Table 1). Reports are assigned to one of the contingency table cells according to the status of Drug 1, Drug 2, and AE. For example, a denotes the number of reports that contain neither Drug 1 and Drug 2 but contained the targeted AE, and b denotes the number of reports that contain neither Drug 1 and Drug 2 and didn't contain the targeted AE. To maintain adequate candidate drug-drug-AE combinations, we excluded the drug-drug-AE combinations occurring in less than ten counts (g < 10).

DDI detection algorithms

Logistic regression model—The logistic regression model for DDI detection was first proposed by van Puijenbroek et al [21]. The following logistic regression model was used to estimate the individual drug and DDI effect.

$$\log(\text{odds}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{gender} + \beta_3 D_1 + \beta_4 D_2 + \beta_5 D_1 D_2 \tag{1}$$

where D_1= drug D1 exposure status, D_2= drug D2 exposure status, $D_1 D_2$ = the concomitant use of a drug D_1 and drug D_2. A statistically significant value of the coefficient β_5 indicates an additional effect of concomitant use of drug1 and drug 2. p-values of 0.05 or less and odds ratio of the statistical interaction term of the combined use of both drugs bigger than 1 were considered statistically significant

Ω shrinkage measure model—The Ω shrinkage measure model developed by Norén et al.[17] is based on a measure calculated as the observed reporting ratio of AE caused by concomitant use of 2 drugs (Drug 1 and Drug 2) and its expected value.

$$\Omega = log_2 \frac{g + 0.5}{E_g + 0.5} \tag{2}$$

$$\Omega_{025} = \frac{\phi(0.975)}{log(2)\sqrt{g}} \tag{3}$$

E_g is the expected value of adverse events targeted by the Drug 1-Drug2 combination. Ω025 > 0 is used as a threshold for detecting the DDI signals.

Additive model—The additive model assumes that there is the potential DDI if the risk associated with Drug 1 without Drug 2 is lower than the risk associated with Drug 1 and Drug 2 together[20].

$$f_{11} - f_{00} = (f_{10} - f_{00}) + (f_{01} - f_{00}) \tag{4}$$

When $f_{11} - f_{10} - f_{01} + f_{00} > 0$, the DDI signal of the additive model is detected.

Multiplicative model—The multiplicative model assumes that there is a positive DDI if the proportion of an AE associated with the concomitant use of Drug 1 and Drug 2 is bigger

than the product of proportional risks of individual drugs in the absence of either Drug 1 or Drug 2[20].

$$\frac{f_{11}}{f_{00}} = \frac{f_{10}}{f_{00}} \times \frac{f_{01}}{f_{00}} \qquad (5)$$

When $\frac{f_{11} \times f_{00}}{f_{10} \times f_{01}} > 1$ the DDI signal of the multiplicative model is detected.

Combination risk ratio model—The combination risk ratio model assumes that there is the DDI signal if the ratio between the PRR of concomitant use and the maximum PRR among PRRs obtained separately for both drugs exceeded 2[19].

$$Combination\ risk\ ratio;\ = \frac{PRR_{Drug\ 1\ \cap\ Drug\ 2}}{max\left(PRR_{Drug\ 1}, PRR_{Drug\ 2}\right)} \qquad (6)$$

When g ≥ 3, $PRR_{Drug\ 1\ \cap\ Drug\ 2} > 2$, $\chi^2_{Drug\ 1\ \cap\ Drug\ 2} > 4$, Combination risk ratio > 2, the DDI signal of the combination risk ratio model is detected.

Association rule mining—The association rule mining is a data mining technique that discovers patterns hidden in large databases [1]. Many recent studies have been applied this model for the identification of patterns of high-order interactions [10; 16]. In this study, the association rule "$Drug2 \rightarrow Drug1 \cap AE$" was used to check the degree of the influence on Drug1-AE combination by the addition of Drug2. Two measurements were calculated to detect DDIs: lift, and conviction. Lift is the ratio of the observed frequency of co-occurrence $Drug1 \cap AE$ and $Drug2$ the expected frequency. The lift of rule $Drug2 \rightarrow Drug1 \cap AE$ is defined as:

$$lift(Drug2 \rightarrow Drug1 \cap AE) = \frac{\frac{g}{(g + h + e + f)}}{\frac{g \times c}{N}} \qquad (7)$$

When the lift value is larger than one, it indicates that the occurrence of $Drug2$ has a positive effect on the occurrence of $Drug1 \cap AE$ The larger the lift value, the more significant the association.

Conviction compares the probability that $Drug2$ appears without $Drug1 \cap AE$ if they were dependent with the actual frequency of the appearance of $Drug2$ without $Drug1 \cap AE$.

$$conviction(Drug2 \rightarrow Drug1 \cap AE) = \frac{1 - \frac{g \times c}{N}}{1 - \frac{g}{(g + h + e + f)}} \qquad (8)$$

Similar to lift, if $Drug1 \cap AE$ and $Drug2$ are independent, the conviction is 1. If the conviction value is greater than 1, it means that incorrect predictions $Drug2 \rightarrow Drug1 \cap AE$ occur less often than if $Drug1 \cap AE$ and $Drug2$ were independent. We used the lift and conviction as the detection criteria, and when lift > 1 and conviction > 1 were used as a threshold for detecting signals.

Chi-square statistics model—For the chi-square statistics model, χ_0 is used to estimate the discrepancy between the observed and expected numbers of AEs with drug combinations[8].

$$\chi = \frac{g - E_g - 0.5}{\sqrt{E_g}} \tag{6}$$

When $\chi > 2$, the DDI signal of the chi-square statistics model is detected.

Random permutation model—To test that the DDIs detected by the seven algorithms are not random, we generated a random permutation of 100 times. We generated random drug-drug pairs based on the FAERS database by shuffling between drugs in the "Drug 1" group and drugs in the "Drug 2" group for each random permutation. We counted the number of DDIs confirmed in the Liverpool database in each random permutation. The p-value was calculated as the fraction of the runs where the number of permutations whose number of DDIs confirmed by the Liverpool database was greater than or equal to the minimum number of DDIs detected by the seven models and confirmed by the Liverpool database.

Results

Sample characteristics

Table 2 summarizes the characteristics of the study population. 28,912 reports met our defined criteria for COVID-19. Among the adverse event reports from patients in COVID-19, the female: male ratio was 37.4:62.6, and the number of reports was highest in persons aged 60–79 (53.6%). The most frequent drug which was used for the treatment of COVID-19 was "Aspirin"(36.3%) and followed by "Xarelto" (22.4%).

Potential drug-drug interactions

In the COVID-19 cohort, 1,135 and 2,504 drugs were assigned to the "Drug 1" and "Drug 2" groups, respectively. We noted that the total number of AEs in MedDRA was 4,048. Therefore, the number of drug-drug combinations and drug-drug–AE combinations were 2,842,040 and 11,504,577,920, respectively. After filtering out DDI-AEs whose counts were smaller than 10, we extracted 6,512 drug-drug pairs (53,486 drug-drug–AE combinations).

The logistic regression, additive, multiplicative, combination risk score, association rule mining, Ω shrinkage measure, and chi-square statistics models detected 3,705 drug-drug pairs (16,451 DDI-AEs), 5,869 (46,054), 5,321 (36,836), 2,806 (16,467), 6,404 (52,860), 6,047 (45,831), and 4,847 (36,562), respectively (Table 2). After implementing the random permutation procedure, the p-value was 0/100 < 0.0001 (Table 3).

There were 2,516 drug-drug pairs which all seven models detected. Out of 2,516 pairs, 49 were confirmed to be in the Liverpool database (Figure 1).

Discussion

This study investigated potential DDIs in patients with COVID-19 by using seven DDI detection models and employed the Liverpool database as our gold standard to discover potential DDIs which were unrecognized.

Among the seven models, most DDI signals were detected by the association rule mining model with 6,404 drug-drug pairs (98.3% of the total 6,512 pairs), followed by the additive model (6,047 pairs). In contrast, the logistic regression showed the most conservative DDI detection tendency (3,705 drug-drug pairs), but still had the highest number of drug-drug pairs confirmed by the Liverpool database. Unlike other models, the logistic regression model included confounding factors: age and gender, suggesting that it may be the most reliable model detecting novel DDIs.

Based on the results of random permutation, the 2,516 DDIs detected by the seven models are likely not occurring by chance. Thus, there is a high potentiality to generate clinical trial hypotheses based on the DDIs detected by the several models but not found in the Liver pool database.

There are known limitations in this study. First, the FAERS database doesn't include patient characteristics, his/her medical history, and dosage information which are important risk factors of DDIs. Second, the FAERS database is recognized to be underreported of AEs, and AEs reported by it need to be further validated. Third, we did not examine the underlying pharmacology mechanism of detected DDIs.

Conclusions

This study showed the potentiality of using seven models to detect potential DDIs from a spontaneous adverse event reports dataset. The detected DDIs by the seven models are not likely to occur in chance.

Acknowledgments

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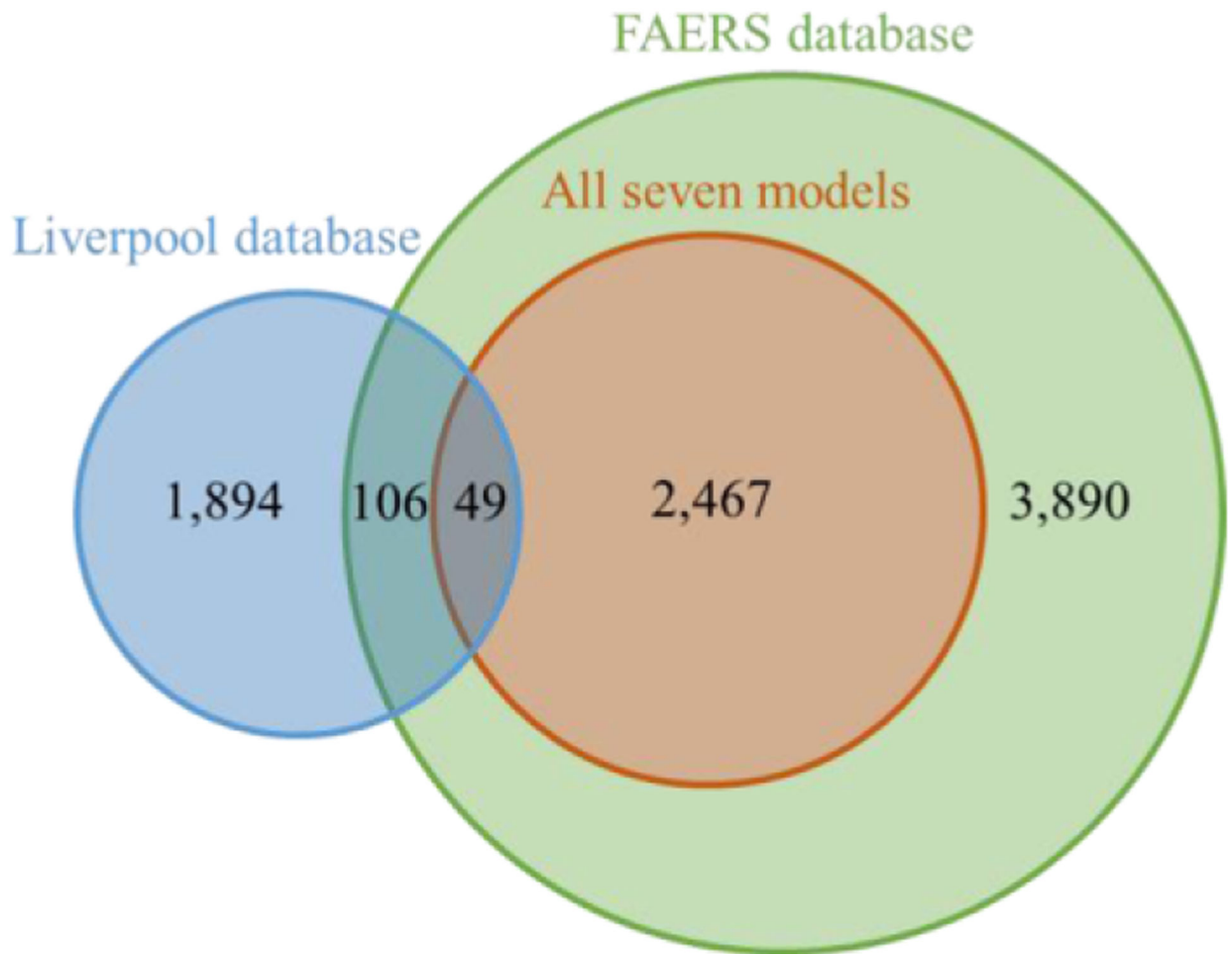
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FAERS database

All seven models

Liverpool database

1,894 106 49 2,467 3,890

Figure 1.
A Venn diagram depicting the DDIs. There were 2,089 DDIs confirmed in the Liverpool database, while there were 6,512 DDIs in the FAERS database. All seven models detected 2,516 DDIs. Out of all total pairs examined, 49 pairs were significant in both the Liverpool database and seven models. There were 106 pairs found in both the Liverpool database and FAERS, but not detected by the seven models.

Table 1.

Four-by-two contingency table for evaluating Drug 1-Drug 2–AE combinations.

	Target AE	All other AEs	
Neither Drug 1 and Drug 2	a	b	$f_{00}=a/(a+b)$
Only Drug 1	c	d	$f_{10}=c/(c+d)$
Only Drug 2	e	f	$f_{01}=e/(e+f)$
Both Drug 1 and Drug 2	g	h	$f_{11}=g/(g+h)$

Table 2.

A summary of the characteristics of the study population.

	Adverse event reports from patients with COVID-19 (n=28,912)		
	Female n (%)	**Male n (%)**	**Total n (%)**
Age			
0–19	381 (1.32)	549 (1.9)	930 (3.22)
20–39	813 (2.81)	828 (2.86)	1,641 (5.68)
40–59	2,291 (7.92)	4,094 (14.2)	6,385 (22.1)
60–79	5,411 (18.7)	10,094 (34.9)	15,505 (53.6)
80	1,915 (6.62)	2,536 (8.77)	4,451 (15.4)
Total	10,811 (37.4)	18,101 (62.6)	28,912 (100)
Top 5 COVID-19 treatments			
Aspirin	3,555 (12.3)	6,948 (24)	10,503 (36.3)
Xarelto	2,170 (7.51)	4,302 (14.9)	6,472 (22.4)
Remdesivir	2,172 (7.51)	3,359 (11.6)	5,531 (19.1)
Hydroxychloroquine	1,615 (5.59)	2,919 (10.1)	4,534 (15.7)
Azithromycin anhydrous	1,271 (4.4)	2,448 (8.47)	3,719 (12.9)

Table 3.

The number of DDIs detected by our models.

Model	# of drug-drug-AE	# of drug-drug pairs	# of drug-drug pairs confirmed by the Liverpool database
Logistic regression	16,451	3,705	75
Additive	46,054	5,869	74
Multiplicative	36,836	5,321	74
Combination risk ratio	16,467	2,806	50
Association rule mining	52,860	6,404	49
Ω shrinkage measure	45,831	6,047	74
Chi-square statistics	36,562	4,847	50
Random permutation (best result)	-	6,512	0