Adverse Drug Events in the Prevention and Treatment of COVID-19: A Data Mining Study on FDA Adverse Event Reporting System (FAERS)

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Abstract

Background: In the emergency situation of COVID-19, off-label therapies and newly developed vaccines may bring the patients adverse drug event (ADE) risks. Data mining based on spontaneous reporting systems (SRSs) is a promising and efficient way to detect potential ADEs so as to help health professionals and patients get rid of these risks.

Objective: This pharmacovigilance study aimed to investigate the ADEs of “Hot Drugs” in COVID-19 prevention and treatment based on the data of the US Food and Drug Administration (FDA) adverse event reporting system (FAERS).

Methods: FAERS ADE reports associated with COVID-19 from the 2nd quarter of 2020 to the 2nd quarter of 2021 were retrieved with “Hot Drugs” and frequent ADEs recognized. A combination of support, proportional reporting ratio (PRR) and Chi-square (?2) test was applied to detect significant “Hot Drug” & ADE signals by Python programming language on Jupyter notebook.

Results: 13,178 COVID-19 cases were retrieved with 18 “Hot Drugs” and 312 frequent ADEs on “Preferred Term” (PT) level. 18 ? 312 = 5,616 “Drug & ADE” candidates were formed for further data mining. The algorithm finally produced 219 significant ADE signals associated with 17 “Hot Drugs”and 124 ADEs.Some unexpected ADE signals were observed for chloroquine, ritonavir, tocilizumab, Oxford/AstraZeneca COVID-19 Vaccine and Moderna COVID-19 Vaccine.

Conclusions: Data mining is a promising and efficient way to assist pharmacovigilance work and the result of this paper could help timely recognize ADEs in the prevention and treatment of COVID-19.

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Keywords: COVID-19; data mining; adverse drug events; FAERS

1. Background

Since the outbreak of COVID-19 pandemic around the end of 2019, the world has seen a huge number of infected and death cases (over 218 million infected and 4.53 million death cases when this paper was written) [1]. This is quite a serious infection disease caused by a newly discovered coronavirus (CoV) whose name was given as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) on 11th February 2020 by the International Committee on Taxonomy of Viruses (ICTV) [2]. CoVs are a group of RNA viruses belonging to Coronaviridae family discovered in 1960s. Before COVID-19, we have seen several outbreaks of CoV epidemics such as SARS-CoV in 2003, MERS-CoV in 2012 [3]. Most people infected with SARS-CoV-2 may experience mild to moderate symptoms including fever, fatigue, cough and other respiratory illness and could recover without special treatment. But for some older people and those with underlying health problems like cardiovascular disease, diabetes, respiratory disease and cancer, the risk to develop serious situations becomes higher [4].

In this emergency situation, many therapies (e.g., antiviral chemical drugs, monoclonal antibodies, convalescent plasma transfusion, etc.) and newly developed vaccines have been tried in the treatment and prevention of this deadly virus disease. In order to help timely identify these ADEs, we performed this pharmacovigilance job.

Pharmacovigilance, also known as drug safety surveillance, plays an important role in ADE researches. According to the definition of World Health Organization (WHO), pharmacovigilance is science and activities relating to the detection, assessment, understanding and prevention of drug-related problems. It usually contains two stages: premarketing surveillance (data collected from pre-clinical and phase I - III clinical studies) and post marketing surveillance (data collected after the approval and throughout the market life of a drug). For the former one, there are obviously some inevitable shortcomings such as relatively small sample data, strict enrollment criteria, large time and money consumption, *etc*. Post marketing surveillance, on the other hand, given the rapid development of computer sciences and data mining technologies, may become an even more important and efficient way for pharmacovigilance in the real world [5].

There are some prominent spontaneous reporting systems (SRS) designated for data collection of post marketing surveillance since 1960s, such as the FAERS of US Food and Drug Administration and the VigiBase of World Health Organization (WHO) [6, 7]. Annually

these systems receive a large number of ADE reports and could offer abundant resources for pharmacovigilance research and in this paper, we adopted the reports associated with COVID-19 from the FAERS to perform a data mining of association relationships between one drug and one ADE.

2. Methods

2.1 Data source

The FAERS is a publicly available computerized relational database for spontaneous reporting of adverse events and medication errors held by the US Food and Drug Administration (FDA) for monitoring post-marketing safety of drugs and therapeutic biologic products. The data structure complies with the international safety reporting guidance issued by International Conference on Harmonization (ICH) and the adverse events and therapy indications are all coded on “Preferred Term” (PT) level of the Medical Dictionary for Regulatory Activities (MedDRA). This database is a descendant of the former Adverse Event Reporting System (also known as Legacy AERS, which was decommissioned in the year of 2012). The FDA issues FAERS data packages to the public quarterly and provides two formats (ASCII/XML) which could be downloaded from its website [8]. In this study, we used the ASCII format and reports submitted between the 2nd quarter of 2020 and 2nd quarter of 2021 were retrieved.

In each ASCII format data package, there are 7 data sets: patient demographic and administrative information (“DEMO”), drug/biologic information (“DRUG”), adverse events (“REAC”), outcomes for the event (“OUTC”), report sources (“RPSR”), drug therapy start dates and end dates (“THER”) and diagnoses (“INDI”). We imported the “DEMO”, “DRUG”, “REAC” and “INDI” data sets into a SQL server to create a local database for this study.

2.2 Data Preprocessing

The FAERS database is a Case/Version system in which a new case will be given a “CASEID” (e.g., “17462593”) and a “CASEVERSION” (1 for the first report) and if any follow-up reports of this case available afterward, new “CASEVERSION”s will also be given in a sequentially incremented way (for example, 2, 3, 4, etc.). According to the FDA’s recommendations for adopting the most recent case version for deduplication, we wrote a program to extract only the most updated reports (i.e., having the max “CASEVERSION” for a certain case) in which the most complete data was included.

The attribute “PRIMARYID” is a concatenated key of a “CASEID” and a “CASEVERSION” which uniquely identifies an FAERS report and through this key, we linked the imported data sets together and created a “Sum Table” in which each report consisted of demographic, drug, ADE and diagnosis data. In order to get rid of possible confusions between a cause and a bystander, only drugs labeled as primary suspect or secondary suspect were included.

As our aim was to explore the “Hot Drug” & ADE signals in COVID-19 prevention and treatment, we extracted all reports whose diagnosis matched up with the regular expression “%COVID-19%” or “%SARS-COV-2%” in the “Sum Table” to form a “COVID-19 Case Table”. A program was written to calculate the frequency (i.e., the count) of drugs and ADEs in this “COVID-19 Case Table”. When the frequency was over 80 for a drug or over 20 for an ADE, the drug or the ADE would be marked as frequent.

Since the FAERS permits arbitrary registrations of drugs and this would surely lead to dilutions of some important ADE signals, these frequent drugs we got were all transformed into their generic names in the “COVID-19 Case Table”. Then we selected “Hot Drugs” and ADEs from those marked as frequent to create a list of “Hot Drug” & ADE candidates.

Meanwhile, all the drugs and ADEs of each report in “COVID-19 case Table” were combined into a transaction so as to form a transaction set *T*.

After this step, the preparation of the data we needed for further analysis had been completed.

2.3 Association Rule Mining (ARM)

In this study, we adopted a combination of support, Proportional Reporting Ratio (PRR) and Chi-square (χ^2) test for recognition of interesting signals.

Support is the frequency of transactions in the *T* set containing a certain Drug & ADE. Proportional Reporting Ratio (PRR) is the risk ratio of a certain ADE between exposed and comparison groups proposed by *S.J.W. Evans (2001)* for ADE analyses and has been adopted by regularity agencies (e.g., Eudravigilance - EMEA) in daily routinely pharmacovigilance work [5, 9]. To facilitate the discussion of PRR, a 2 x 2 contingency table was created as shown in Table_1. Here, “$Drug_i$” and “ADR_j” respectively refer to a specific drug and ADE and “$!Drug_i$” and “$!ADR_j$” represent those other than “$Drug_i$” and “ADR_j”. So PRR could be calculated as follows:

$$PRR = \frac{a/(a+b)}{c/(c+d)},$$

in which “a”, in fact, is the support of $Drug_i$” & “ADR_j. As we could see, the higher the PRR, the more significant the signal is.

Table_1 2 × 2 Contingency Table for Computation of PRR

	Counts of ADR_j	Counts of !ADR_j	Sum
$Drug_i$	a	b	a + b
!$Drug_i$	c	d	c + d
Sum	a + c	b + d	a + b + c + d

Chi-square (χ^2) test is an often-used measure to assess the correlations between two nominal attributes. Suppose A has c distinct values, namely a_1, a_2, ... a_c, B has r distinct values, namely b_1, b_2, ... b_r, the data tuples described by A and B could be shown in a contingency table (shown in Table_2), in which c values of A making up the columns and r values of B making up the rows. Let the tuple (A_i, B_j) denotes the joint event ($A = a_i$, $B = b_j$) so as to each possible (A_i, B_j) has its own cell in the table. So χ^2 could be computed as follows:

$$\chi^2 = \sum_{i=1}^{c}\sum_{j=1}^{r}\frac{(o_{ij} - e_{ij})^2}{e_{ij}},$$

where o_{ij} refers to the observed count of (A_i, B_j) and e_{ij} refers to the expected count of (A_i, B_j) which could be got by equation:

$$e_{ij} = \frac{count(A = a_i) \times count(B = b_j)}{n},$$

where n is the sum of counts of all the tuples, count($A = a_i$) is the number of tuples having value a_i for A and count($B = b_j$) is the number of tuples having value b_j for B. Chi-square test rejects the null hypothesis that A and B are independent from each other based on a significance level σ with (r - 1) × (c- 1) degrees of freedom. Hence, in our study, according to Table_2 the χ^2 could be calculated as follows:

$$\chi^2 = \frac{[\frac{a+c}{a+b+c+d}\times(a+b) - a]^2}{\frac{a+c}{a+b+c+d}\times(a+b)} + \frac{[\frac{b+d}{a+b+c+d}\times(a+b) - b]^2}{\frac{b+d}{a+b+c+d}\times(a+b)} + \frac{[\frac{a+c}{a+b+c+d}\times(c+d) - c]^2}{\frac{a+c}{a+b+c+d}\times(c+d)} + \frac{[\frac{b+d}{a+b+c+d}\times(c+d) - d]^2}{\frac{b+d}{a+b+c+d}\times(c+d)}$$

. The degrees of

freedom were (2 - 1) × (2 - 1) = 1 and we set σ= 0.001 [10].

Table_2 r × c Contingency Table for Computation of Chi-square (χ^2) Test

A / B	a_1	a_2	...	a_i	...	a_c
b_1	(a_1, b_1)	(a_2, b_1)	...	(a_i, b_1)	...	(a_c, b_1)
b_2	(a_1, b_2)	(a_2, b_2)	...	(a_i, b_2)	...	(a_c, b_2)
...	...	...	...	...	...	...
b_j	(a_1, b_j)	(a_2, b_j)	...	(a_i, b_j)	...	(a_c, b_j)
...			...	...	...	
b_r	(a_1, b_r)	(a_2, b_r)	...	(a_i, b_r)	...	(a_c, b_r)

Let the transaction set $T = \{t_1, t_2, ... t_m\}$ be an itemset. We wrote a program to scan *T* to calculate the frequencies of transactions in *T* that contain each specific “Hot Drug”, ADE and the both so as to get “a + b”, “a + c” and “a” mentioned in Table_2. As “a + b + c + d” equals to the total number of transactions of *T,* all the parameters “a”, “b”, “c” and “d” we needed for support, PRR and χ^2 were ready.

2.4 Screening for Significant “Hot Drug” & ADE Signals

As we could imagine, the frequencies (i.e., a + b) of “Hot Drugs” in “COVID-19 Case Table” would be significantly different from each other. In order to improve the performance of our algorithm, we set different thresholds “THR” for the support (i.e., a) of each Drug & ADE candidate and according to the researches before, in this paper, a significant signal was recognized when its support ≥ THR, PRR ≥ 2.00 and χ^2 ≥ 10.828 [5, 9].

2.5 Experiment environment

MySQL (Version 5.6.32.0) was used to create a local database from the FAERS quarterly ASCII packages while Navicat for MySQL (Version 11.1.13) as a graphic user interface (GUI) tool to process database operations. The proposed data-preprocessing, mining algorithm and graphs were implemented by Python (Version 3.8.0) programming language on Jupyter Notebook (Version 6.3.0). We stored the “COVID_19 Case Table”, significant signals and the other results in Microsoft Office Excel 2017 files.

3. Results

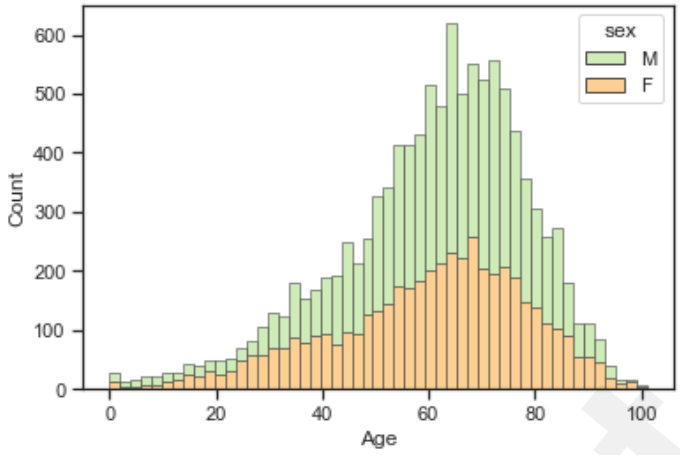
From 2020Q2 to 2021Q2, the FAERS received 1,359,467 reports in which 25,631 were associated with COVID-19. After deduplication the number was reduced to 13,178 with 43 frequent drugs and 312 frequent ADEs recognized.

The mean and median age of the patients were 70.96 and 63.00 years old. Males (50.60%) accounted for a larger proportion than females (41.29%). The most reports were from the US (63.40%). The demographic data of COVID-19 cases was shown in Table_3 and Figure_1.

Table_3 Demographic Data of COVID-19 Cases

Items	Events	
2020Q2	2,404	
2020Q3	4,328	
2020Q4	4,967	
2021Q1	6,600	
2021Q2	7,331	
Duplicated	12,452	
Total	13,178	
Sex	**Events**	**Percentage**
Male	6,668	50.60%
Female	5,441	41.29%
unknown	1,069	8.11%
Age (Year)		
0-9	103	0.78%
10-19	193	1.46%
20-29	363	2.75%
30-39	754	5.72%
40-49	1,108	8.41%
50-59	1,941	14.73%
60-69	2,693	20.44%
70-79	2,408	18.27%
80-89	1,138	8.64%
90-99	272	2.06%
>100	8	0.06%
unknown	2,197	16.60%
Top 3 Reported Countries		
US	8,365	63.40%
Spain	796	6.00%
Italy	740	5.60%

Figure_1 Age and Sex Distribution of COVID-19 Patients



Among the 43 frequent drugs, 18 “Hot” drugs were selected to form 18 × 312 = 5,616 “Drug & ADE” candidates. After scanning the transaction set *T* with these candidates, support, PRR and χ^2 *of* each of these candidates were calculated. According to the counts of frequent drugs (shown in Figure_2), we set different “THR”s (from 1% to 5% of the count of each drug) for the 18 “Hot” drugs (shown in Table_4). Our mining algorithm finally produced 219 significant signals encompassing 17 “Hot” drugs and 124 ADEs.

A flow chart was also drawn to show the whole data mining process (Figure_3).

Table_4 THRs for “Hot Drugs”

Drug	Count	Propertion	THR	Category
remdesivir	2,881	1.00%	29	Hot Drug
hydroxychloroquine	2,650	1.00%	27	Hot Drug
bamlanivimab	2,117	1.00%	22	Hot Drug
azithromycin	1,740	2.00%	35	Hot Drug
tocilizumab	1,107	2.00%	23	Hot Drug
lopinavir\ritonavir	929	2.00%	19	Hot Drug
tozinameran	414	3.00%	13	Hot Drug
casirivimab\imdevimab	255	3.00%	8	Hot Drug
etesevimab	215	3.00%	7	Hot Drug
cx-024414	160	4.00%	7	Hot Drug
sarilumab	149	4.00%	6	Hot Drug
azd-1222	98	5.00%	5	Hot Drug
baricitinib	97	5.00%	5	Hot Drug
chloroquine	96	5.00%	5	Hot Drug
favipiravir	95	5.00%	5	Hot Drug
ritonavir	88	5.00%	5	Hot Drug
bamlanivimab\etesevimab	87	5.00%	5	Hot Drug
casirivimab	80	5.00%	4	Hot Drug

Figure_2 Counts of Frequent Drugs in COVID-19

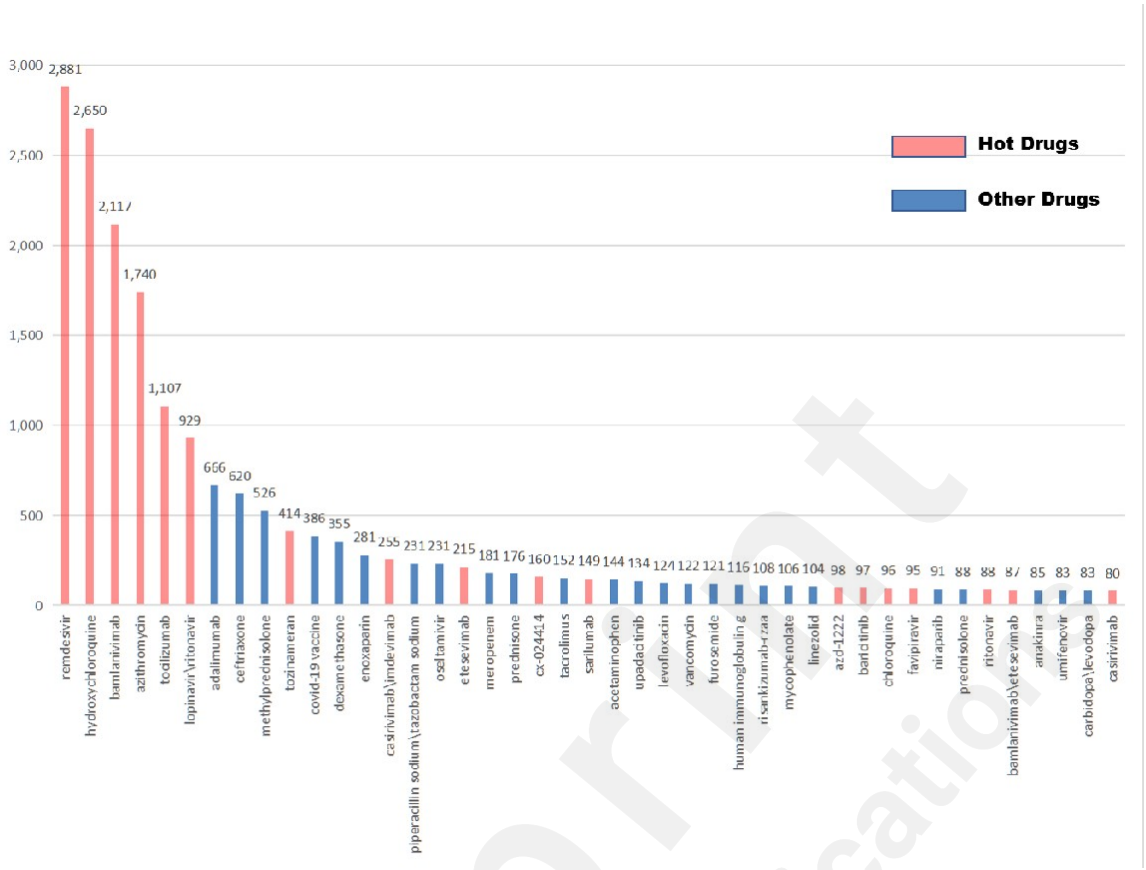
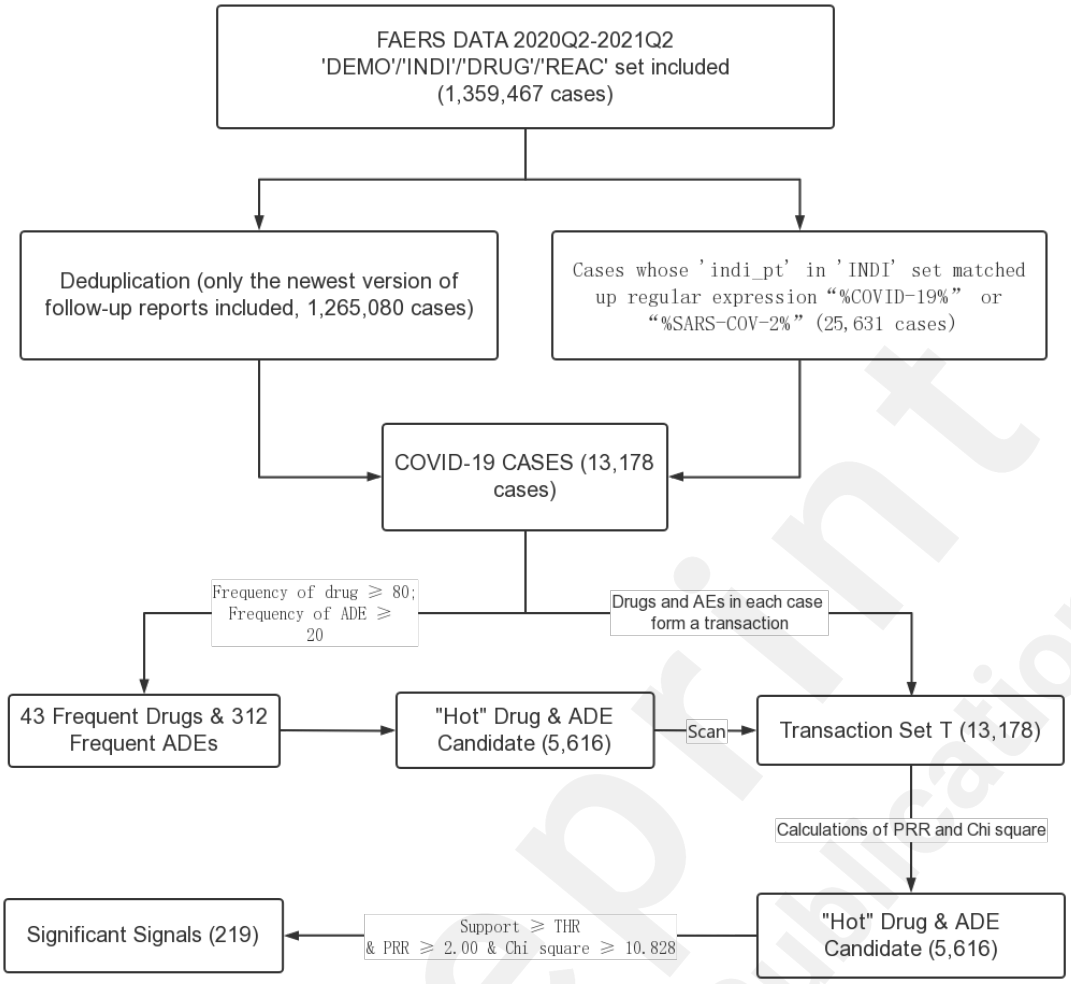


Figure_3 Flow Chart of the Data Mining Algorithm



4. Discussions

Data mining is an emerging field in pharmacovigilance with its obvious merits such as high efficiency, much low cost and has been adopted in routinely pharmacovigilance work by some regularity agencies. During the past year, over 13,000 ADE cases associated with the treatment of COVID-19 had been reported to the FAERS and as far as we knew, there was no systematic data mining work about these cases. Hence our purpose was set to figure out some kind of associations between "Hot Drugs" & ADEs in the treatment and prevention of COVID-19 on the basis of the data the FAERS had accumulated.

Our study finally produced 219 ADE signals associated with chemical drugs, Janus kinase (JAK) inhibitors, monoclonal antibodies and vaccines. Although many of these ADEs may be regarded as possible complications of COVID-19 *per se,* the signals with relatively high PRRs should still be paid attention to as they may give additional support or clues for further researches (top signals were shown in Table_5).

Table_5 Top Signals of “Hot Drug” & ADE

Category	Drug	ADE	a	a + b	c	c + d	PRR	χ2
Antiviral Chemical Drugs	azithromycin	long qt syndrome	41	1643	26	11535	11.07	146.51
		hypertransaminasaemia	40	1643	36	11535	7.8	112.99
		electrocardiogram qt prolonged	138	1643	180	11535	5.38	285.63
	chloroquine	brain oedema	7	111	13	13067	63.39	279.81
		pulmonary oedema	7	111	40	13067	20.6	111.5
		encephalopathy	7	111	42	13067	19.62	106.42
	hydroxychloroquine	premature baby	27	2650	12	10528	8.94	58.75
		premature delivery	27	2650	18	10528	5.96	44.72
	lopinavir\ritonavir	hypertriglyceridaemia	27	929	6	12249	59.33	282.24
		hyperbilirubinaemia	24	929	15	12249	21.1	177.23
		rash maculo-papular	21	929	18	12249	15.38	130.73
	remdesivir	glomerular filtration rate decreased	62	2881	2	10297	110.8	211.84
		liver function test increased	206	2881	23	10297	32.01	632.58
		pulseless electrical activity	31	2881	6	10297	18.47	83.28
	ritonavir	acute generalised exanthematous	10	88	15	13090	99.17	584.17
		liver injury	23	88	56	13090	61.09	969.53
		delirium	5	88	31	13090	23.99	95.13
Janus Kinase (JAK) Inhibitor	baricitinib	leukocytosis	6	97	29	13081	27.9	129.29
		infection	5	97	47	13081	14.35	56.33
		respiratory distress	6	97	79	13081	10.24	46.81
Monoclonal Antibody	sarilumab (IL-6) inhibitor	hepatocellular injury	19	149	43	13029	38.64	485.41
		enterococcal infection	6	149	18	13029	29.15	122.54
		pneumonia bacterial	15	149	56	13029	23.42	255.33
	tocilizumab (IL-6) inhibitor	hypofibrinogenaemia	30	1107	0	12071	∞	327.87
		septic shock	45	1107	117	12071	4.19	80.04
		death	114	1107	404	12071	3.08	129.75
	bamlanivimab	infusion related reaction	174	2117	113	11061	8.05	432.08
		body temperature increased	33	2117	23	11061	7.5	76.63
		chills	214	2117	168	11061	6.66	465.79
	bamlanivimab\etesevimab	fibrin d dimer increased	5	87	50	13091	15.05	59.86
		chest discomfort	7	87	104	13091	10.13	54.41
		infusion related reaction	17	87	270	13091	9.47	123.92
	etesevimab	chest discomfort	9	215	102	12963	5.32	29.26
		acute respiratory failure	10	215	124	12963	4.86	28.68
		hyperhidrosis	8	215	123	12963	3.92	16.51
	casirivimab	urticaria	6	80	95	13098	10.34	47.98
		infusion related reaction	12	80	275	13098	7.14	62.11
		erythema	4	80	97	13098	6.75	18.97
	casirivimab\imdevimab	throat irritation	8	255	30	12923	13.51	73.4
		anaphylactic reaction	9	255	43	12923	10.61	65.01
		infusion related reaction	36	255	251	12923	7.27	174
Vaccines	azd-1222	influenza like illness	5	98	30	13080	22.24	87.19
		ischaemic stroke	5	98	31	13080	21.53	84.51
		thrombocytopenia	10	98	88	13080	15.17	119.72
	cx-024414	rheumatoid arthritis	8	160	50	13018	13.02	76.85
		vaccination complication	7	160	51	13018	11.17	57.23
		injection site pain	8	160	63	13018	10.33	60.15
	tozinameran	pain in extremity	35	414	177	12764	6.1	126.54
		malaise	27	414	195	12764	4.27	60.38
		arthralgia	28	414	210	12764	4.11	59.23

4.1 Antiviral Chemical Drugs

For the antiviral chemical drugs, a number of expected ADE signals were observed such as “glomerular filtration rate decreased”, “liver function test increased” and “pulseless electrical activity” of remdesivir, “torsade de pointes” and “electrocardiogram qt prolonged” of hydroxychloroquine [11]. These signals were also consistent to other researches before [12, 13].

Possible unexpected ADEs were “premature baby” (PRR = 8.94) and “premature

delivery" (PRR = 5.96) of hydroxychloroquine, "brain oedema" (PRR = 63.39) and"pulmonary oedema" (PRR = 20.60) of chloroquine and "acute generalised exanthematous pustulosis" (PRR = 99.17) of ritonavir.

Hydroxychloroquine is a recommended antirheumatic medication during pregnancy by the American College of Rheumatology and American College of Obstetrics and Gynecology [14]. Because "premature baby" and "premature delivery" are ADEs only associated with females, we made a combination of these 2 signals to "premature delivery" and recalculated its support, PRR and χ^2 of which only female patients were included and the new support, PRR and χ^2 were 35, 10.25 and 95.96. So in our study, hydroxychloroquine was still associated with "premature delivery".

The signals of chloroquine here were against the results of former animal researches that chloroquine may attenuate brain or pulmonary oedema [15, 16]. So further researches may be necessary to confirm this signal. For ritonavir, Enrico Pezzarossa et al., reported 12 acute generalised exanthematous pustulosis cases in the treatment of COVID-19 and in these cases ritonavir was involved in the therapies [17]. Our study gave an additional support for this possibility.

4.2 Janus Kinase (JAK) Inhibitors

The most commonly reported adverse events associated with Janus kinase (JAK) inhibitors are generally not serious and have included upper respiratory infections, urinary tract infections, and nasopharyngitis, as well as nausea, headache, and occasional diarrhea. The signals "leukocytosis", "infection" and "respiratory distress" observed in our study were consistent to the ADEs above [18].

4.3 Monoclonal Antibodies

The WHO recently made a strong recommendation to use IL-6 receptor blockers (tocilizumab and sarilumab) in patients with severe or critical COVID-19 [19].

Common ADEs of IL-6 receptor inhibitors include nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. Infections are the most frequent serious adverse events reported. Gastrointestinal perforation can occur in adults. Laboratory abnormalities include neutropenia, thrombocytopenia, dyslipidemia, and elevated liver enzymes [20]. In our study, a strong unexpected signal "hypofibrinogenaemia" (a = 30, c = 0, PRR = ∞) was observed for

tocilizumab which meant in all the cases where “hypofibrinogenaemia” was reported, tocilizumab always got involved. So, we thought additional attention should be paid to this signal. As tocilizumab is often used in severe or critical patients, the “death” signal (PRR = 3.08, relatively low) was thought to be associated COVID-19 per se.

Other monoclonal antibodies our study covered were bamlanivimab, etesevimab, casirivimab, imdevimab and some of them are usually administered together. These are all recombinant neutralizing human IgG1 monoclonal antibodies. Hypersensitivity reactions including anaphylaxis and infusion related reaction, have been reported with bamlanivimab and etesevimab [21, 22]. The results of our study were also consistent to those reports.

4.5 Vaccines

Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for containing the pandemic and are being vigorously pursued. By the end of 2020, several vaccines had become available for use in different parts of the world.

In the COVID-19 cases the FAERS received, we actually got four frequent vaccine candidates in which, however, the “covid-19 vaccine” candidate lacked the information of manufacturers. So we explored ADE signals of the other three vaccines: azd-1222 (Oxford/ AstraZeneca COVID-19 Vaccine), cx-024414 (Moderna COVID-19 Vaccine) and tozinameran (PFIZER-BIONTECH COVID-19 Vaccine) [23-25].

Azd-1222 is adenovirus vector based vaccine developed by University of Oxford, AstraZeneca and the Serum Institute of India. Its common ADEs are fatigue, headache, fever, etc. This vaccine is recently associated with an extremely small risk of unusual types of thrombotic events associated with thrombocytopenia [26]. In our study, “ischaemic stroke” (PRR = 21.53) and “thrombocytopenia” (PRR = 15.17) were also observed for azd-1222.

For cx-024414, a messenger RNA (mRNA) vaccine, an unexpected ADE “rheumatoid arthritis” (PRR = 13.02) was observed. There was a case report in which a 23-year-old woman suffered an acute reactive arthritis on her left knee joint after COVID-19 vaccination [27]. Another case reported a septic arthritis of shoulder after tozinameran vaccination [28].

For tozinameran, also a mRNA vaccine, apart from common vaccination complications, no unexpected signals were observed in our study.

5. Conclusions

COVID-19 has become a pandemic causing large loss of lives and property since the end

of 2019 and even though many efforts have been made to contain this pandemic, the world still has to see more and more new infection and death cases daily. What even worse is the appearance of SARS-COV-2 variants – Alpha (first found in United Kingdom, Sep-2020), Beta (first found in South Africa, May-2020), Gamma (first found in Brazil, Nov-2020) and Delta (first found in India, Oct-2020) [29]. It was predicted, without effective measures taken, COVID-19 might affect 90% of the world population and kill over 40 million people [30].

Fortunately, many vaccines have been developed or under development for prevention of COVID-19. Enough vaccination may be a game-changing weapon for this disease. According to the WHO, as of 31 August 2021, over 5 billion doses have been administered around the world [1].

Our study gave a brief on the potential ADE risks in the prevention and treatment of COVID-19 based on the data of FAERS in order to help health professionals timely recognize ADEs and adjust their therapies. But what we had to emphasize was that data mining could only reflect some kind of associations among “items” and does not provide enough evidence on causality. The result we offered here was just an assistance for pharmacovigilance and possible clues for more well-organized clinical researches in the future.

Author contributions

Qiang Guo, Shaojun Duan, Yaxi Liu and Yinxia Yuan conceived this study. Qiang Guo wrote the manuscript and computer programs. Yaxi Liu made contributions to the creation of the SQL database and data extractions. Shaojun Duan and Yinxia Yuan together proposed the algorithms on data analysis.

Conflict of interest

The authors declared they have no conflict of interest.

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Supplementary Files

Multimedia Appendixes

The whole 219 significant signals.
URL: http://asset.jmir.pub/assets/ab0545422cdbcfec914adf241305b246.xlsx