REPORTED ADVERSE DRUG REACTIONS FOR SARS CORONAVIRUS 2 TREATMENTS DURING THE PANDEMIC: EVALUATING AND COMPARING DISPROPORTIONALITY ANALYSES OF FAERS DATABASE

by

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Reported Adverse Drug Reactions for SARS Coronavirus 2 Treatments during the Pandemic: Evaluating and Comparing Disproportionality Analyses of FAERS Database

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Abstract

The COVID-19 pandemic is one of the most serious health crises throughout the human history. With countless efforts of drug development and repurposing by the scientific community in a hope of finding safe and efficacious COVID-19 treatment, there is an emerging need for pharmacovigilance for these drugs indicated for COVID-19 treatment. For new drugs, clinical trials can only give limited knowledge about drug safety profiles which are not enough to guide the use of the drugs in large populations. Thus, potential risks of these drugs need to be quickly identified from data sources outside clinical trials. For repurposed drugs, change of indication may lead to unforeseeable risks even for drugs with well-established safety profiles. Thus, adverse events with elevated risks for repurposed drugs also need to be identified. This study set the aim of exploring the power of disproportionality analysis in extracting adverse drug reaction information from spontaneous reporting data to satisfy the pharmacovigilance need. For new drugs, the potential of identifying adverse reactions with limited report data was explored. For repurposed drugs, we focused on whether increase in disproportionality scores can be used to identify adverse drug events with elevated risks during the pandemic. The FDA Adverse Event Reporting System (FAERS) database was utilized, and the performance of two disproportionality scores ─ information component (IC) and reporting odds ratio (ROR) in signal detection and ranking were evaluated and compared. As a result, we found similar and seemingly plausible signal detection by both IC and ROR for a new drug Remdesivir. For repurposed drugs, we found that

increase in IC and fold increase in ROR generally give plausible and comparable performance in signal detection and rankings especially for drug-adverse event combinations with large number of observations. This study explored the potentials of disproportionality analysis on identifying potential health risks for both new and repurposed drugs during the COVID-19 pandemic, which had lasting significance in case of a future public health crisis.

Key words: COVID-19, Pharmacovigilance, Adverse Drug Reactions, Disproportionality Analysis, Food and Drug Administration Adverse Event Reporting System (FAERS)

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Nomenclatures

Here are some nomenclatures used throughout the paper:

IC_{before}: IC (center) value of data during the 6 months before the pandemic outbreak

IC_{after}: IC (center) value of data during the 6 months after the pandemic outbreak

IC_{025}: the 2.5% lower confidence limit of posterior IC distribution

IC_{05}: the 5% lower confidence limit of posterior IC distribution

IC_{95}: the 5% upper confidence limit of posterior IC distribution

ROR_{before}: ROR (center) value of data during the 6 months before the pandemic outbreak

ROR_{after}: ROR (center) value of data during the 6 months after the pandemic outbreak

ROR_{025}: the 2.5% lower confidence limit of ROR

ROR_{05}: the 5% lower confidence limit of ROR

ROR_{95}: the 5% upper confidence limit of ROR

1.0 Introduction

1.1 The COVID-19 Pandemic and Pharmacovigilance Need

The Coronavirus Disease 2019 (COVID-19), caused by the infection of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), is one of the most serious health crises throughout human history. Ever since the first recorded case of SARS CoV-2 infection in Wuhan, China on December 8th, 2019, the virus has shown a high level of transmissibility and severity when local medical facilities are overwhelmed[1]. By March 11, 2020, COVID-19 has been reported in 113 countries and territories on all six continents with permanent human home[2], and COVID-19 was declared by the World Health Organization (WHO) a pandemic[1, 3]. By March 29th, 2022, over two years after the initiation of the COVID-19 pandemic, this pandemic has resulted in over 481 million confirmed cases and over 6 million deaths around the world, with over 79 million confirmed cases and over 969 thousand deaths in the US[4]. As a result of the disruption to the normal pattern of production and life, society has suffered from huge economic and social consequences.

To protect people from SARS CoV-2 infection, there has been an unprecedented commitment of the scientific and medical community to vaccine development and use. As a result, a large population has established immunity against SARS CoV-2. However, vaccines are not enough for protection against COVID-19. As an RNA virus, SARS CoV-2 has a high mutation rate because of its RNA replication process[5]. Since the initial outbreak of the COVID-19 pandemic, twelve major variants of SARS CoV-2 have emerged in different parts of the world[6]. The alteration in the spike proteins enables the variants to evade immunity response, which

combined with a high replication rate puts vaccinated people still at the risk of SARS CoV-2 infection and COVID-19.

Thus, apart from vaccines, drugs for COVID-19 are also needed for patients with severe symptoms after SARS CoV-2 infection. And a major part of the efforts has been focused on drug repurposing since the time and monetary cost of developing new drugs is too high[7]. The drug repurposing aims at utilizing the properties of certain well studied drugs to either inhibit viral entry and replication, or ameliorate the inflammatory response of SARS CoV-2 infection[8, 9]. The drugs most studied for repurposing in COVID-19 treatment include antiviral agents such as oseltamivir and lopinavir/ritonavir, antibiotics such as azithromycin, anti-parasitic drugs such as hydroxychloroquine and ivermectin, and immunomodulators such as steroidal anti-inflammatory drugs and colchicine[8, 10].

However, the increase in the use of new and repurposed drugs for COVID-19 has raised concerns about the safety of these drugs. Drugs approved after the initiation of the COVID-19 pandemic, such as Remdesivir, have limited safety profiles. The clinical trials for these drugs usually do not give enough information on latent and rare adverse drug reactions (ADRs). Also, due to the limited population, patient comorbidities and medical conditions in the clinical trials, the results may not generalize well into the large population in real-world settings[11, 12].

For drugs with off-label or repurposed use, although the focus is usually on efficacy as the drugs already have well-established safety profiles[13], there are also some safety concerns. To treat COVID-19, these drugs may be administered in different doses, dosage forms, and administration frequencies compared to the administration method for their previous indications. For example, ivermectin, an anti-parasitic drug, is normally administered at the dose of 150 microgram/ kilogram of body weight orally to treat filarial nematode infections[14], while several

clinical trials on this drug intended for COVID-19 treatment administer the drug orally at the dose of 400 microgram/ kilogram of body weight[15, 16]. The increased dosage might lead to higher risks of some ADRs of the drug. Also, the body conditions of COVID-19 patients may be significantly different from patients of the previous indications, which may lead to changes in the toxicological and pharmacokinetic profiles of the drugs and an increase in the risk of some ADRs in COVID-19 patients. For example, there were cases of COVID-19 patients administered with dexamethasone developing secondary fungal infections reported[17]. It is suspected that the lack of immunity and the long-term use of ventilators could add up to the immunosuppressive function of dexamethasone in critically ill COVID-19 patients and lead to an increase in the risk for secondary infections.

Thus, there is a highlighted need for pharmacovigilance to identify previously unknown ADRs for newly approved drugs, and ADRs with elevated risks during the pandemic for repurposed drugs.

1.2 Drug Safety Surveillance and Disproportionality Analysis

Pharmacovigilance is the scientific and regulatory framework for detecting, assessing, understanding, and preventing ADRs[12]. Generally, drug safety data is collected and analyzed. Potential drug safety issues are reviewed and validated, and risks are communicated by health authorities to healthcare providers[18].

The information about ADRs generally comes from either drug safety data mandatorily reported during clinical trials or ADRs reported voluntarily by consumers, healthcare providers, and drug manufacturers after the marketing of a drug. The data from clinical trials give an

estimation of the incidence rates of the observed ADRs. However, as mentioned in section 1.1, clinical trials may not identify rare and latent ADRs and lack generalizability. Thus, post-marketing surveillance using spontaneously reported ADRs plays an important role in pharmacovigilance as it provides additional drug safety profiles after drug marketing[19].

There are several spontaneous ADR reporting systems run by different public health authorities, including the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) maintained by FDA, VigiBase maintained by the World Health Organization (WHO), etc.

Using the spontaneous reported ADR data, a step called signal detection can detect potentially highly associated drug-event combinations (DECs), which is usually implemented using the data-driven analysis method called disproportionality analysis[20]. This analysis aims at examining the association between the reporting of a drug and the reporting of an event. If the observed number of reported DEC is higher than expected under that assumption of independence between the reporting of the drug and the event, there would be a positive association.

Table 1 Layout of a 2x2 Contingency Table for a Drug-Event Combination

	Event j	Not Event j	Margin
Drug i	n_{11}	n_{10}	$n_{1.}$
Not Drug i	n_{01}	n_{00}	$n_{0.}$
Margin	$n_{.1}$	$n_{.0}$	n

There have been various scores[20, 21] representing the disproportionality of reporting developed. Some commonly used ones include relative-risk-related proportional reporting ratio (PRR), odds-ratio-related reporting odds ratio (ROR), and observed-to-expected ratio type of score called relative reporting ratio (RRR). Their definitions are as follows:

$$\widehat{PRR} = \frac{P(event\ j|drug\ i)}{P(event\ j|not\ drug\ i)} = \frac{n_{11}n_{0.}}{n_{1.}n_{01}}$$

$$\widehat{ROR} = \frac{odds\ in\ favor\ of\ event\ j\ given\ drug\ i}{odds\ in\ favor\ of\ event\ j\ without\ drug\ i} = \frac{n_{11}n_{00}}{n_{10}n_{01}}$$

$$\widehat{RRR} = \frac{P(event\ j|drug\ i)}{P(event\ j)} = \frac{observed\ DEC}{expected\ DEC} = \frac{n_{11}n}{n_{1.}n_{.1}}$$

These frequentist disproportionality scores are extensively used in practice as they are easily interpretable and generally give a good performance as long as the reporting frequencies of the DECs are not too small. However, for DECs with small frequencies of reporting, the estimations of these scores may become unstable, and the highly inflated scores would result in may unreliable, false-positive signals[22, 23]. This highlights the importance of developing disproportionality scores which become more conservative when reporting frequencies of DECs are small.

$$\underbrace{P(\theta|D)}_{\text{posterior}} = \underbrace{P(D|\theta)}_{\text{likelihood}}\ \underbrace{P(\theta)}_{\text{prior}}\ /\ \underbrace{P(D)}_{\text{evidence}}$$

Figure 1 Schema for Bayes' Theorem
D: variable for data observation; θ: parameter of interest

The aforementioned problem can be properly resolved under a Bayesian paradigm. As shown in Figure 1, the posterior distribution of the parameter of interest θ (a disproportionality score in the context of disproportionality analysis) depends on the distribution of variable for data observation (multinomial distribution for a 2x2 contingency table) and the prior assumption of θ. The evidence P(D) is merely a normalizing constant that ensures the area under the curve of the posterior probability density function is one, which is not of particular interest. Our inference is based on the posterior distribution P(θ|D). When there is high confidence in the data (sample size is large), posterior distribution will be very close to the information given by the likelihood as long

as the prior is not too strong. When there is no high confidence in the data (sample size is small), prior assumptions will dominate the estimation of the posterior distribution. That explains why, given a prior distribution that assumes independence between a drug and an event, the estimated disproportionality under a Bayesian paradigm is usually conservative when the sample size is small.

The most commonly used Bayesian models for disproportionality scores are Bayesian Confidence Propagation Neural Network (BCPNN)[24] and Gamma-Poisson Shrinker (GPS)[22].

The BCPNN gives an estimation for the information component (IC) which is related to RRR:

$$IC = log_2 RRR = log_2 \frac{P(event\ j|drug\ i)}{P(event\ j)} = log_2 \frac{P(event\ j, drug\ i)}{P(event\ j)P(drug\ i)}$$

The model is based on the multinomial distribution of the report counts n_{11}, n_{10}, n_{01}, and n_{00} in each 2x2 contingency table (Table 1). With the probabilities of a report falling into each of the 4 cells in the contingency table being p_{11}, p_{10}, p_{01}, and p_{00}, the report numbers follow the following distribution: (n_{11}, n_{10}, n_{01}, n_{00}) ~ Multinomial(p_{11}, p_{10}, p_{01}, p_{00}, n). Then, a conjugate Dirichlet prior Dirichlet(α_{11}, α_{10}, α_{01}, α_{00}) is set for (p_{11}, p_{10}, p_{01}, p_{00}), which gives the following posterior distribution for (p_{11}, p_{10}, p_{01}, p_{00}), where $\gamma_{ij} = \alpha_{ij} + n_{ij}$:

$$(p_{11}, p_{10}, p_{01}, p_{00}) \sim Dirichlet(\gamma_{11}, \gamma_{10}, \gamma_{01}, \gamma_{00})$$

Norén and his colleagues proposed an empirical way to estimate α_{ij}, which means that we can directly obtain the posterior distribution of (p_{11}, p_{10}, p_{01}, p_{00}). Thus, Markov Chain Monte Carlo (MCMC) draws of (p_{11}, p_{10}, p_{01}, p_{00}) can be made, and obtain the sample posterior distribution of $RRR = \frac{n_{11}n}{n_{1.}n_{.1}} = \frac{p_{11}}{p_{1.}p_{.1}}$, and thus the posterior distribution of IC[25, 26]. There are also approximations to give point and interval estimation of IC based on the marginal Beta distributions of p_{11}, $p_{1.}$ and $p_{.1}$[20, 27].

The GPS model estimates another disproportionality score called Empirical Bayesian Geometric Mean (EBGM) which is also based on RRR. Although BCPNN and GPS are different models, their performance in estimating RRR and signal detection are similar[21, 23-25].

1.3 Goal of the Study

Due to the need of pharmacovigilance for repurposed drugs and new drugs, efforts in utilizing disproportionality analysis for signal detection in spontaneously reported ADR data are needed.

For newly approved drugs, continuous monitoring of spontaneous ADR reports can provide information on previously unknown ADRs. This can be achieved by the prototypic disproportionality analysis. What is more of interest is whether some useful information can truly be provided by the spontaneous ADR data as early as possible, and the difference in the performance of different disproportionality scores.

For the repurposed drugs, the need to detect ADRs with elevated risks during the pandemic for COVID-19 patients requires the examination of an increase in disproportionality, which is not a common practice in disproportionality analysis. Thankfully, Ståhl et al.(2004)[28] proposed several algorithms using IC to discover different types of drug safety risks, including an algorithm that uses the increase in IC to discover DECs with an increase in reporting. This provides us a framework for comparing the disproportionality in reporting by comparing disproportionality scores. However, there have not been any studies evaluating the performance of the disproportionality analysis using change in disproportionality scores on real or simulated spontaneously reported ADR data, and the performance of this method is unclear.

Thus, in this study, we will focus on evaluating the performance of disproportionality score IC on detecting potential ADRs rising during the ongoing pandemic for both new drugs and repurposed drugs. The performance of IC will also be compared with a commonly used frequentist disproportionality score ROR.

2.0 Methods

2.1 Data Source

2.1.1 Food and Drug Administration Adverse Event Reporting System (FAERS)

This study uses data from the Food and Drug Administration Adverse Event Reporting System (FAERS) database for ADR report data.

FAERS is a spontaneous reporting system aimed at supporting FDA's post-marketing drug safety surveillance program by collecting various events related to drug use including adverse events, medication errors, and product quality defects submitted by healthcare professionals, consumers, and product manufacturers. It is freely accessible and offers quarterly releases of new reports. From 1968 to 2021, this database has seen an exponential increase in the yearly report from 107 cases to more than 2.3 million cases a year[29, 30] as shown in Figure 2. With more than 23 million reports available in total, this database provides extensive adverse event information even for some rare events and is thus one of the most commonly used sources of data for drug safety surveillance.

The FAERS database is publicly available and does not require IRB approval.

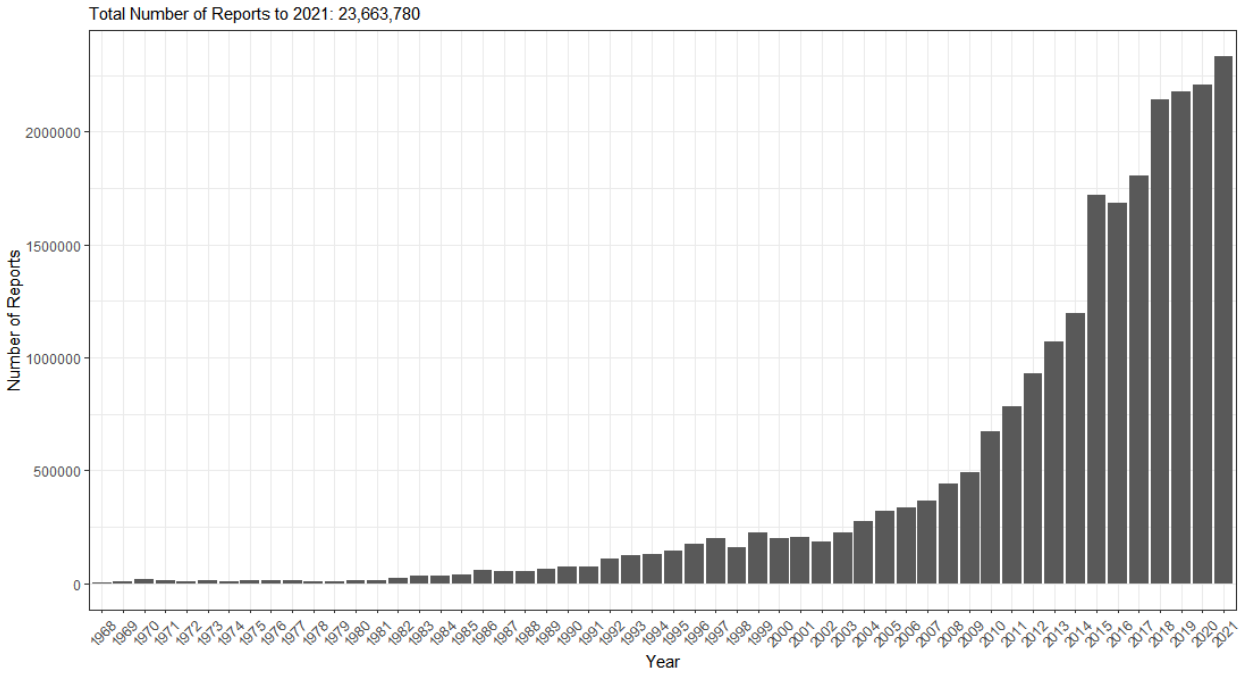


Figure 2 Number of Reports in FAERS Database Each Year

2.1.1.1 Cleaning and Standardization

The data in FAERS is entered by individual consumers, healthcare professionals, or product manufacturers, and is not verified. As a consequence, non-standard terms are common in the raw dataset. For example, drug names may not be correctly entered; events may not be described in appropriate preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) as expected. Also, one case may be reported separately by the consumer, his/her healthcare provider, and the product manufacturer, which would create duplicate reports.

Thankfully, much research has been done to establish practices for dealing with the aforementioned problems[31-33]. Here in our study, the practice of Banda et al[31]. is adopted and is described as follows:

First, raw quarterly data are downloaded from the FAERS website, and other ancillary data for drug and event mapping are downloaded, which include FDA Orange book with new drug application (NDA) number, EU drug name/active ingredient reference table, and Observational Health Data Sciences and Informatics (OHDSI) Common Data Model version 5 (CDM v5) vocabulary tables that include standard terminologies from MedDRA, Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) and RxNorm.

Second, using PostgreSQL, the FAERS data is loaded for the standardization process. During deduplication, the event date and age are updated to the maximum of the same case ID, and duplicated cases are identified using an exact match of demographic information including age, sexuality, report country, and event date.

Third, drug names are mapped to terms in RxNorm, a naming system maintained by the United States National Library of Medicine. RxNorm contains all drugs available on the US market, so it is useful for standardizing drug names under a uniform naming system. This mapping includes exact matching of drug names, mapping from active ingredients, and mapping from NDA numbers. The drug names that fail to be mapped from the previous automotive steps have to be manually mapped using the OHDSI Usagi tool. This tool uses a feature referred to as similarity search, which suggests standard terms similar to the drug name entries. This allows medical professionals to pick the correct term to map the original drug name into. With drug names all standardized, we would be able to work with all the data of the drugs of interest.

For the reactions in MedDRA preferred term, they are first mapped into MedDRA concept IDs and then mapped into concept IDs in SNOMED-CT. This step does not involve manual mapping and would leave some inappropriately entered terms as they are.

With the cleaned FAERS data obtained above, we would be able to perform various analyses and make inferences about potential adverse events of drugs.

2.1.1.2 Data Exclusion Criteria

We used the products' active ingredients as drug names. In FAERS data, one report could contain a primarily suspected drug, a secondarily suspected drug, concomitant drugs, and interacting drugs. Here, we only analyzed the primarily suspected drugs.

We use the MedDRA preferred terms as events in the cleaned FAERS data set for analysis. However, events in the FAERS data set are not all appropriate ADRs. Adverse drug reactions are defined as undesirable clinical manifestations caused by the administration of certain medicine[11, 34]. Thus, events such as medical procedures, medical product issues, etc. should be excluded.

First, we looked at MedDRA system organ class (SOC) terms, a higher level term compared to the preferred term. All events falling into the following four SOC terms are excluded: "investigations", "product issues", "social circumstances", and "surgical and medical procedures".

Then, there are still many preferred terms in other SOC groups needed to be excluded to focus the analysis on ADRs. By reviewing the remaining preferred terms, we identified the following preferred terms to be excluded: "adverse effect absent", "off label uses", "medication errors, product use errors and issues NEC", "product storage errors and issues in the product use system", "product administration errors and issues", "overdoses NEC", "exposures associated with pregnancy, delivery and lactation", "intentional product use issues", "accidental exposures to product", "underdoses NEC", "intentional product misuses", "product dispensing errors and issues", "exposures to agents or circumstances NEC", "product prescribing errors and issues", "product monitoring errors and issues", "non-occupational environmental exposures", "product

preparation errors and issues", "occupational exposures", "pathways and sources of exposure", "product selection errors and issues", "normal newborn status", "normal newborn status", "product transcribing errors and communication issues", and "product confusion errors and issues".

Also, "coronavirus infections" is excluded since we are focusing on drugs to treat COVID-19, and coronavirus infections should not be their ADRs but their indications.

2.1.2 National COVID Cohort Collaborative (N3C)

Richard Boyce, Ph.D., Matthew Gray, PharmD, and their colleagues identified 20 drugs most prescribed for COVID-19 patients as shown in Table 2 using data from the National COVID Cohort Collaborative (N3C).

Table 2 List of 20 Drugs Most Prescribed For COVID-19 Treatment

Drug Names			
Methotrexate	Apixaban	Azathioprine	Azithromycin
Clozapine	Colchicine	Cyclosporine	Dexamethasone
Hydrocortisone	Hydroxychloroquine	Ivermectin	Lopinavir/Ritonavir
Methylprednisolone	Mycophenolic Acid	Mycophenolate Mofetil	Oseltamivir
Prednisone	Remdesivir	Tacrolimus	Tocilizumab

N3C is a collaborative project that collects COVID-19 clinical data from over 100 participating medical institutions to provide large-scale data for COVID-19 studies[35].

With N3C, data on prescriptions for COVID-19 patients in the participating institutions can be obtained[36, 37]. Among these drugs, those not intended for COVID-19 treatment are

excluded and 20 drugs with the highest prescription frequencies are selected. Among these drugs, Remdesivir is newly approved after the initial pandemic outbreak, and all the other 19 drugs are under repurposed use or off-label use.

2.1.3 Description of the Data Analyzed

In the analysis, we take March 11, 2020, as the start of the COVID-19 pandemic, and look at cases reported to the FDA 6 months before and 6 months after the initial outbreak of the pandemic, which is from September 11, 2019 to September 11, 2020. There are 167707 cases reported to FDA during the six months before the pandemic outbreak, and 160018 cases during the pandemic.

The report numbers before and after the pandemic outbreak as well as the number and percentage of change in the report numbers for the 20 drugs of interest are shown below in Table 3. Most drugs of interest in this list have increased report numbers after the outbreak of the pandemic, which is expected as it is likely that more attention has been paid to these drugs since the start of the pandemic. There are eight drugs with decreased number of reports (apixaban, colchicine, hydrocortisone, ivermectin, mycophenolate mofetil, methylprednisolone, mycophenolic acid, and oseltamivir). However, a decrease in the report of a drug does not mean a decrease in the report of all its ADRs as well as a change in its association with the reporting of its ADRs. That means we would still apply disproportionality analysis to the drugs with a decrease in report numbers.

Another thing to notice is that Remdesivir does not have any report before the outbreak of the pandemic, which makes sense because this drug got the emergency use authorization (EUA) on May 1, 2020 and there might only be very limited use of the drug before this date.

Table 3 Change in Report Numbers of Drugs of Interest

Drug Name	Report Number before Pandemic	Report Number after Pandemic	Change in Report Number	Percentage Change in Report Number
Apixaban	7842	7444	-398	-5.08
Azathioprine	258	319	61	23.64
Azithromycin	49	77	28	57.14
Clozapine	2706	2986	280	10.35
Colchicine	111	74	-37	-33.33
Cyclosporine	419	538	119	28.4
Dexamethasone	1655	1826	171	10.33
Hydrocortisone	178	175	-3	-1.69
Hydroxychloroquine	335	913	578	172.54
Ivermectin	112	42	-70	-62.5
Lopinavir\Ritonavir	35	375	340	971.43
Methotrexate	5056	6782	1726	34.14
Methylprednisolone	763	753	-10	-1.31
Mycophenolate Mofetil	478	326	-152	-31.8
Mycophenolic Acid	227	153	-74	-32.6
Oseltamivir	97	87	-10	-10.31
Prednisone	1752	2007	255	14.55
Tacrolimus	1740	2101	361	20.75
Tocilizumab	2488	3794	1306	52.49
Remdesivir	0	1546	1546	Inf

2.2 Disproportionality Analysis

2.2.1 Signal Detection Algorithms

In this study, we follow the algorithm suggested by Ståhl et al.[28] to detect drug-event combinations with rapid increases in reports. This means that we are focusing on increase or fold increase in certain disproportionality scores to detect DECs with potential increase in disproportionality in reporting. The disproportionality scores we will consider here are information component (IC), and reporting odds ratio (ROR).

The estimation of the centers and confidence limits of ICs uses Markov Chain Monte Carlo (MCMC) simulation as it gives more accuracy compared to approximations especially when observed and expected frequencies are small[25]. Here, we use 10000 runs for each simulation and the implementation is fulfilled by the PVM package in R[26].

For ROR, the point estimator is given in section 1.2. Its $\sigma \times 100^{\text{th}}$ lower/ upper confidence limit is given as $\widehat{ROR} \cdot e^{\pm z_\sigma \cdot \sqrt{\frac{1}{n_{11}}+\frac{1}{n_{01}}+\frac{1}{n_{10}}+\frac{1}{n_{00}}}}$ [20], where z_σ is the $\sigma \times 100^{\text{th}}$ percentile of the standard normal distribution.

For the 19 repurposed drugs, both IC_{before} and IC_{after} can be estimated for their DECs, and their changes in IC values from the two time periods can be calculated to represent changes in the strengths of associations of the reporting of the DECs. The same goes for ROR, as ROR_{before}, ROR_{after} and the fold increases in ROR are calculated. An increase of 1 in IC equals a fold increase of 1 in shrunk RRR. Thus, we set the fold increase of 1 in ROR as a criterion to be comparable. Also, the drug and event should be positively associated at least during the six months after the pandemic outbreak since DECs not positively associated would not be of interest.

The signal detection criteria using IC are summarized as follows:

1) $IC_{after} - IC_{before} > 1$
2) $IC_{after} > 0$

The signal detection criteria using ROR are summarized as follows:

1) $\frac{ROR_{after}}{ROR_{before}} - 1 > 1$
2) $ROR_{after} > 1$

The signals detected by the two disproportionality scores will be compared. Signals will also be ranked by the magnitude of change in IC or ROR to identify DECs with potentially the largest increase in disproportionality of reporting.

For Remdesivir, which does not have any reports before the COVID-19 outbreak, no disproportionality scores can be appropriately estimated for this time period. Thus, for this drug, we would only examine the values of IC_{after} and ROR_{after}. Indeed, we will only need to ensure that the lower confidence limit IC_{025} or ROR_{025} is positive to ensure a positive IC_{after} or ROR_{after} with statistical significance. The criterion is as follows: $IC_{025,after} > 0$ or $ROR_{025,after} > 1$

The signals detected by the two disproportionality scores will be compared and also be ranked by the magnitude of IC or ROR to identify DECs with potentially the strongest association between the reporting of the drugs and events.

2.2.2 Sample Size and Statistical Significance

Disproportionality analyses generally have high sensitivities but low specificities, and DECs with small sample sizes (numbers of observed reports) can easily generate a large number of false-positive signals[38, 39]. Thus, we would examine whether more restrictions on sample size and statistical significance can help to obtain signals with higher confidence.

First, the signal detecting algorithms will be implemented for DECs with both the sample sizes before and during the pandemic larger than one.

Then, only DECs with both the sample sizes before and during the pandemic larger than three will be analyzed as a previous study showed that IC and ROR generally give a comparable performance for data with sample size of four or more[38].Statistical significance will also be

reached by ensuring the confidence intervals/ credible intervals of a disproportionality score before and during the pandemic do not overlap. This is expressed as follows:

$$IC_{95,before} < IC_{05,after} \text{ or } ROR_{95,before} < ROR_{05,after}$$

2.2.3 Bias and Causal Relationship

As spontaneous reporting data, FAERS data contains a high level of bias[40, 41], a large part of which may be due to unprofessional reporting of drugs and adverse events that lack a causality assessment. Thus, analysis of data only reported by healthcare professionals may help to reduce the bias in the data, and obtain signals that are more likely to have a causal relationship.

Thus, we will compare the signals derived by the main disproportionality analysis using the whole data and the results of the analysis using data reported by healthcare professionals as part of a sensitivity analysis. The information of reporters is in the column "occp_cod" of the FAERS data. We choose data reported by physicians (MD), pharmacists (PH), and other health-professionals (OT). Data reported by lawyers (LW) and consumers (CN) will be excluded in this subsection.

2.3 Sensitivity Analysis

Although Ståhl et al.[28] have put forward the logic of taking IC as a representation of the strength of association between the reporting of a drug and an event and look at the DECs with the highest increase in IC as they are most likely to have a rapid increase in reporting, there is a lack of studies on the change of IC values under different parameters such as number of reports, the

probability of having an adverse event j when taking drug i P(ADR j|drug i), and the probability of having an adverse event j when other drugs but not drug i is taken P(ADR j| not drug i) in the two time periods. The same goes for the other disproportionality score ─ ROR. Thus, we carry out a sensitivity analysis using some simply simulated data to see how sensitive the change in IC and the fold change in ROR are under the change of the parameters of interest.

Our simulated data is created based on the real data for analysis. In our FAERS data to be analyzed, there are 167707 reports during the half-year before the pandemic outbreak and 160018 reports during the six months after the pandemic outbreak initiation. Before the pandemic outbreak, the number of reports for the DECs ranges from 0 to 2273 with a median of 1 and a third quartile of 5. The changes in the number of reports for DECs before and after the pandemic outbreak range from -236 to 1130, with positive changes ranging from 1 to 1130 with a median of 2 and third quartile 5.

Thus, in our simulated data, the total number of reports before and after the pandemic outbreak is set to be 167707 and 160018 respectively. For the number of reports of a DEC, five levels are considered: 1, 10, 100, 1000, and 2000. The probability P(ADR j|drug i) before the pandemic outbreak is set on two levels: 0.01, and 0.1; the probability P(ADR|not drug i) before the pandemic outbreak is set on two levels: 0.0001, and 0.001. The above settings make sure that we are looking at the DECs of our interest: ADR is positively associated with a certain drug over other drugs.

There are generally three situations to consider:

(1) A drug gets more reported because of more use and attention, while P(ADR j|drug i) does not change. In such a situation, a rarely reported DEC might get enough reporting

and be identified as a signal. For simplicity, we assume no change in P(ADR j|not drug i). The investigated increase in the number of reports ranges from 1 to 1000.

(2) For repurposed drugs with a different administration dose, dosage forms, or administration intervals, there could be an increase in P(ADR j|drug i). Under such circumstances, P(ADR j|not drug i) is assumed to be the same as before the pandemic outbreak. Here, we look at five levels of fold increase in P(ADR j|drug i): 0.5, 1, 1.5, 2, and 3.

(3) COVID-19 patients might be more likely to report some adverse events due to COVID-19 and its complications, or the body conditions of these patients, which could lead to an increase in both P(ADR j|drug i) and P(ADR j|not drug i). For simplicity, we investigate the case where P(ADR j|drug) and P(ADR j|not drug) increase by the same folds (and the number of reports increases by 100).

3.0 Results

3.1 Disproportionality Analysis for Repurposed Drugs

For the 19 repurposed drugs of interest, there are 3163 DECs with at least 2 reports both before and during the COVID-19 pandemic. The algorithm using IC detected 87 DECs as signals, and the algorithm using ROR detected 102 DECs as signals. There are 84 signals detected by both algorithms.

Figure 3 shows the rankings of the 84 signals by an increase in IC and a fold increase in ROR. For the given FAERS data, IC and ROR give similar rankings for most signals with a correlation coefficient of 0.877, which shows a strong positive correlation. The signals with large differences in rankings (difference in rankings > 20) are listed in Table 4. Among the 8 signals, 7 have sample sizes before the pandemic outbreak smaller than 4.

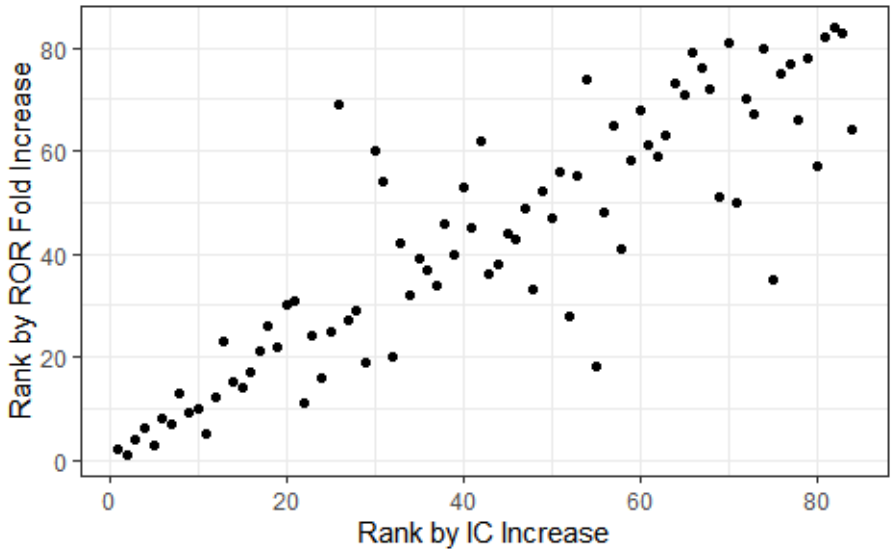


Figure 3 Alignment of Signal Rankings by IC Increase and ROR Fold Increase

Table 4 Signals with Varying Ranks by IC Increase and ROR Fold Increase

Drug Name	Adverse Event	N_{before}	N_{during}	E_{before}	E_{during}	IC Increase [Rank]	ROR Fold Increase [Rank]
Cyclosporine	Transplantation complications	2	11	0.81	2.00	1.53[26]	1.33[69]
Cyclosporine	Epstein-Barr viral infections	2	10	1.02	2.17	1.49[30]	1.44[60]
Cyclosporine	Nephropathies and tubular disorders NEC	2	9	1.22	2.26	1.46[31]	1.50[54]
Apixaban	Dementia (excl Alzheimer's type)	48	142	26.04	32.35	1.26[52]	2.18[28]
Methotrexate	Molluscum contagiosum viral infections	2	6	1.70	2.28	1.25[55]	2.79[18]
Prednisone	Muscle infections and inflammations	3	4	3.15	1.73	1.15[71]	1.58[50]
Mycophenolate Mofetil	Bile duct infections and inflammations	2	3	0.98	0.52	1.11[75]	1.90[35]
Apixaban	Tricuspid valvular disorders	2	4	1.47	1.39	1.08[80]	1.46[57]

(N_{before}: number of observed reports before pandemic outbreak; N_{during}: number of observed reports during pandemic; E_{before}: number of expected reports during pandemic outbreak; E_{during}: number of expected reports during the pandemic.)

The ranking behaviors of IC and ROR are shown in Figure 4. In this figure, the rankings of the 84 signals by IC and ROR are overlaid on one figure against the increase in the observed-to-expected ratio[21], which is calculated as $O/E = \frac{observed\ count}{expected\ count} = \frac{n_{11}}{n_{1.}n_{.1}/n} = \frac{n_{11}n}{n_{1.}n_{.1}}$. This figure clearly shows a hyperbolic trend between the rank number and the increase in the observed-to-expected ratio for both IC and ROR (the higher the rank number, the lower the DEC is ranked). This means that as the observed-to-expected ratio of a DEC gets larger, the DEC is likely to have an increase in both IC and ROR.

The outliers of the hyperbolic trend are generally DECs with both small observed numbers and expected numbers of reports as shown in Figure 4 and Appendix Figure 2, and the outliers also generally have relatively small increases in observed-to-expected ratios.

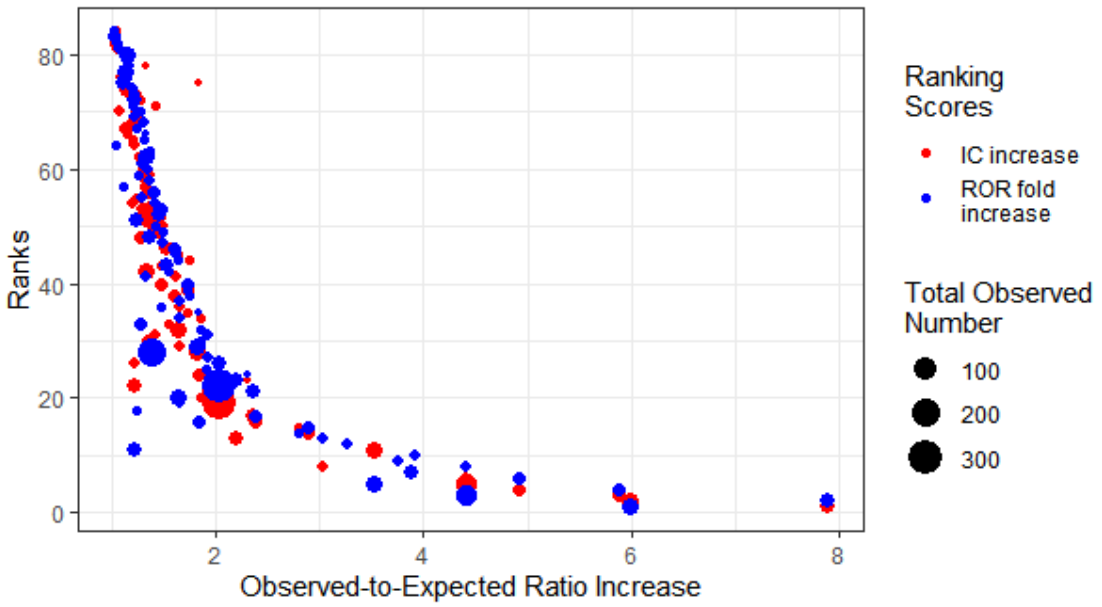


Figure 4 Relationship of Signal Ranking and Observed-to-expected Ratio Increase
Rankings by IC increase, and ROR fold increase are overlaid on one plot. Dot sizes reflect the total numbers of observed reports of the signals over one year (from September 11, 2019 to September 11, 2020).

The signals detected by either IC or ROR but not both are shown in Appendix Table 1. There are only 3 signals detected by IC but not ROR, while there are 18 signals detected by ROR but not IC. We can see that IC is generally more conservative than ROR and detects fewer suspicious signals even when comparing the disproportionalities of the two time periods.

When the candidate DECs are restricted to DECs with numbers of reports larger than 3 both before and during the pandemic, there are 2131 DECs for the 19 drugs of interest. After applying the statistical significance restriction that the 5% upper confidence limit of a disproportionality score before the pandemic must be lower than the 5% lower confidence limit of that score during the pandemic, IC algorithm detected 17 signals and ROR also detected 17 signals. The two algorithms detected 15 signals in common as shown in Appendix Table 3. By setting more restrictions on sample size and statistical significance, the signals detected by both algorithms generally have higher confidence and show more concordance in ranking by both IC increase and

ROR fold increase. As shown in Figure 5, the difference in the rankings of IC and ROR of these 15 signals is no greater than 4, and the two rankings have a correlation coefficient of 0.886. In such a case, inference by IC and ROR would be largely equivalent.

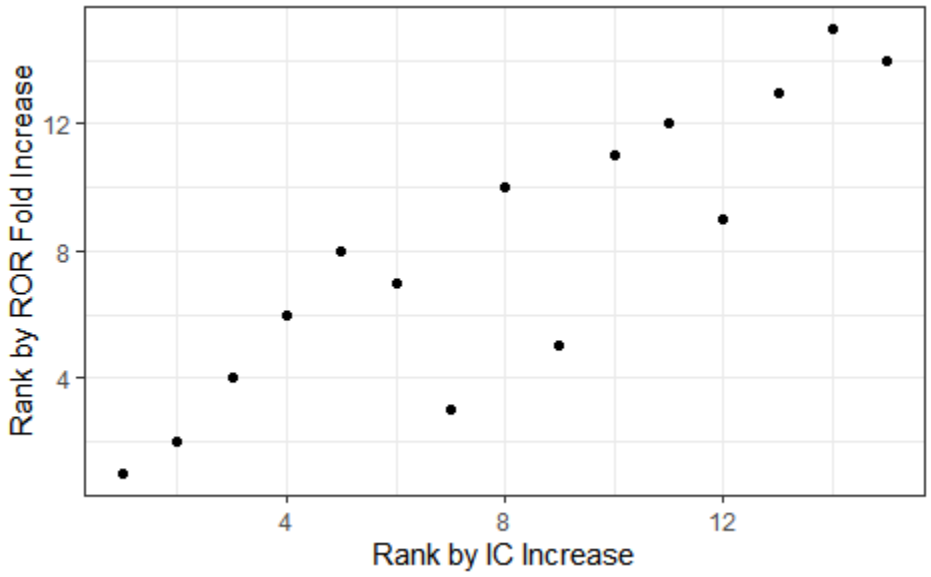


Figure 5 Alignment of Signal Rankings by IC Increase and ROR Fold Increase with High Confidence

When working with FAERS data reported only by healthcare professionals, with a sample size restriction of at least 4 both before and during the pandemic and statistical significance requirement as mentioned above, the two algorithms have 10 signals in common (Appendix Table 5). These signals consist of 9 different drugs: clozapine, methylprednisolone, prednisone, methotrexate, apixaban, hydroxychloroquine, cyclosporine, tacrolimus, and dexamethasone. Among the 10 signals, 5 are overlapping with the 15 signals detected with the whole data set (Appendix Table 3). They are “clozapine-substance related and addictive disorders”, “methylprednisolone-leukocytoses NEC”, “methotrexate-protein metabolism disorders NEC”, “tacrolimus-hepatitis virus infections”, and “dexamethasone- Bone disorders NEC”.

These signals are backed by some evidence and shows plausibility to some extent. For example, glucocorticoids including methylprednisolone are known to have the side effect of leukocytosis through the down regulation of neutrophil L-selectin and macrophage antigen 1 (Mac-1) and the up regulation of granulocyte-colony stimulating factor[42]. Meanwhile, severe COVID-19 infections are reported to trigger strong immune reactions including leukocytosis in patients[43], which would put COVID-19 patients on methylprednisolone with elevated risks of developing leukocytosis. This is shown in the disproportionality analysis with an over 3-fold increase in the reporting odds ratio along with an increase of 1.95 in IC for the DEC "methylprednisolone-leukocytoses NEC" during the pandemic for COVID-19 patients.

3.2 Disproportionality Analysis for Remdesivir

For Remdesivir, there are 165 DECs with at least 2 reports both before and during the COVID-19 pandemic. IC_{025} detected 23 DECs as signals, while ROR_{025} detected 35 DECs as signals. All the 23 signals detected by IC_{025} are also detected by ROR_{025} as signals. The 12 signals only detected by ROR_{025} are listed in Appendix Table 2, among which half have sample sizes smaller than 4 before the pandemic outbreak.

Figure 6 shows how the rankings of IC and ROR for the 23 signals detected by both IC_{025} and ROR_{025} align. Similar to the situation in section 3.1, IC and ROR rank most signals similarly with a correlation coefficient of 0.910 between the two rankings, although in this case we are looking at one time period rather than two.

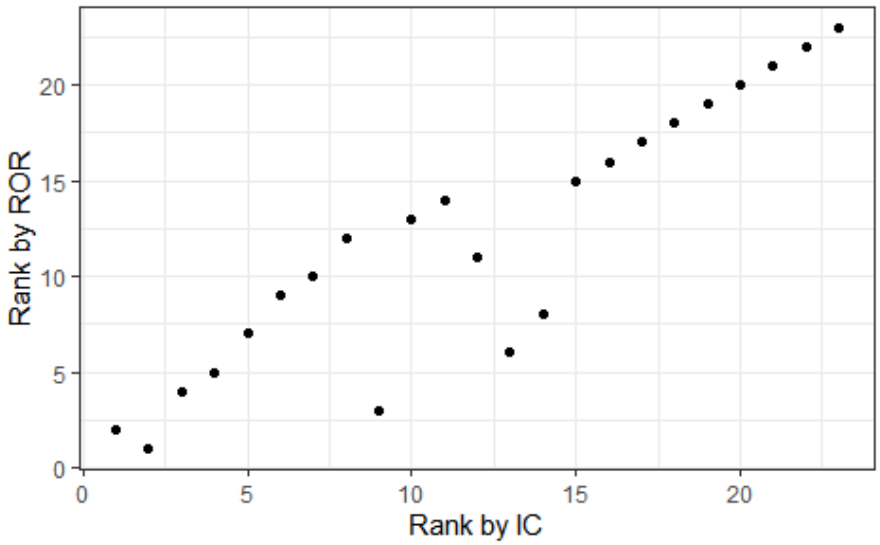


Figure 6 Alignment of Signal Rankings by IC and ROR

Three signals have a large difference in rankings by IC and ROR (difference in rankings > 5) are shown in Table 5. The numbers of observations of the three DECs are small (4, 3, and 3 respectively), and their expected number of observations are also very small (less than 1). Because of the small sample sizes, reports of these 3 DECs do not have much certainty. And it seems that IC tends to suppress the estimates of the association, and rank these signals with high uncertainties behind DECs with higher certainties (with higher rank numbers).

Table 5 Signals with Varying Ranks by IC and ROR

Drug Name	Adverse Event	N	E	IC [Rank]	ROR [Rank]
Remdesivir	Right ventricular failures	4	0.26	2.42[9]	21.67[3]
Remdesivir	Renal failure complications	3	0.28	1.97[13]	13.30[6]
Remdesivir	Phosphorus metabolism disorders	3	0.34	1.87[14]	10.45[8]

(N: number of observed reports during the pandemic; E: number of expected reports during the pandemic)

As shown in Figure 7, IC and ROR show similar preference in ranking signals. Signals are ranked higher when their observed-to-expected ratios are larger, and there seems to be an approximately hyperbolic trend between the rank and the observed-to-expected ratio. For the 23 signals detected, their IC ranks perfectly follow the hyperbolic trend, while the ROR ranks of some

signals with small observed and expected number of reports divert from this trend (Figure 7, Appendix Figure 3).

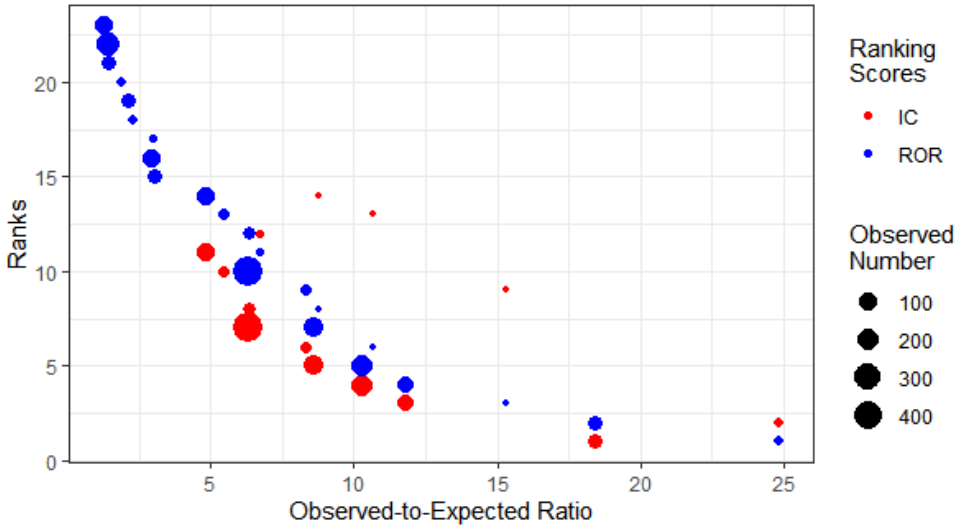


Figure 7 Relationship of Signal Ranking and Observed-to-expected Ratio
Rankings by IC, and ROR are overlaid on one plot. Dot sizes reflect the total numbers of observed reports of the signals over one year (from September 11, 2019 to September 11, 2020).

When looking at adverse events of Remdesivir with numbers of reports larger than three both before and during the pandemic, the number of candidate DECs is reduced to 106. Among the 106 DECs, 22 were detected by IC_{025} as a signal, and 26 were detected by ROR_{025} as signals. Again, all the 22 signals detected by IC_{025} are also detected by ROR_{025} (Appendix Table 4). But the number of signals only detected by ROR_{025} is reduced to 5.

As shown in Figure 8, the rankings by IC and ROR for the 22 signals perfectly align with a correlation coefficient of 0.967. This indicates that, by restricting the sample sizes, we have obtained generally satisfactory levels of confidence in estimating the disproportionality either by IC or ROR. Since IC and ROR rank the signals in high concordance, we expect the estimation of the strength of these signals by IC and ROR to be highly comparable.

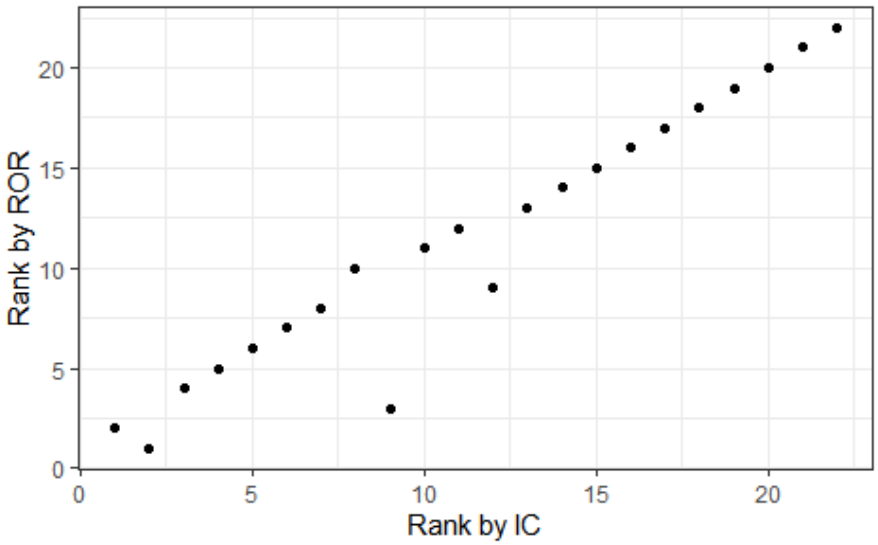


Figure 8 Alignment of Signal Rankings by IC and ROR with High Confidence

Using FAERS data reported only by healthcare professionals, with a sample size restriction of at least 4 both before and during the pandemic, the IC_{025} and ROR_{025} had 17 signals in common (Appendix Table 6), all of which are detected using the whole data as shown in Appendix Table 4. The high alignment of signals detected using the whole data and signals detected using healthcare professional-reported data may result from the high proportion of healthcare professional reported data among Remdesivir ADR reports. As a new drug to treat COVID-19, the patients taking this drug may be closely monitored by healthcare professionals and their ADRs may consist of a high proportion of the existing reports of Remdesivir.

The 17 ADRs of Remdesivir detected by both IC_{025} and ROR_{025} using data reported by healthcare professionals (Appendix Table 6) mainly focus on cardiovascular system, respiratory systems, renal tract, and metabolism disorders. For ADRs related to the respiratory system, "conditions associated with abnormal gas exchange", "respiratory failures", "Pulmonary oedemas", and "breathing abnormalities". Since SARS CoV-2 infections mainly target the lung[10], these adverse reactions could be a result of COVID-19 rather than Remdesivir, and need further judgement by medical professionals. Meanwhile, renal tract related ADRs such as "renal

failure and impairment" is also identified as a potential side effect of Remdesivir by other studies including studies using analysis of the WHO VigiBase[44], medical reports of COVID-19 patients with compassionate use of Remdesivir[45] and medical reports of Remdesivir randomized clinical trials[46]. In our analysis, the DEC "remdesivir-renal failure and impairment" has a reporting odds ratio as high as 5.79, which means that the odds of developing renal failure and impairment for COVID-19 patients taking remdesivir is 5.79 times the odds of developing this adverse event for patients not taking remdesivir. Thus, this signal is considered reliable and deserve further studies.

3.3 Sensitivity Analysis

3.3.1 Situation 1

When there is simply an increase in the reporting of a DEC without any change in P(ADR|drug i) and P(ADR|not drug i), DECs generally would not have an increase in IC but rather a decreasing trend.

The universal decreasing trend of IC especially when an increase in report numbers are large should be partially related to the increase in P(ADR) which decreases the ratio $\frac{P(ADR\ j|drug\ i)}{P(ADR\ j)}$.

However, there is a special case with DECs with an initial number of reporting as small as 1, where they would have an increase in IC when the increase in reporting is smaller than 100. This might be because small frequencies cause the estimate of IC unstable. This is especially obvious when P(ADR j|drug i) is large (0.1 rather than 0.01), where even DECs with 10 reports before the pandemic could also have an increase in IC larger than 1.

Meanwhile, ROR does not have a fold increase larger than 1 for all cases in the simulated data (Appendix Figure 4).

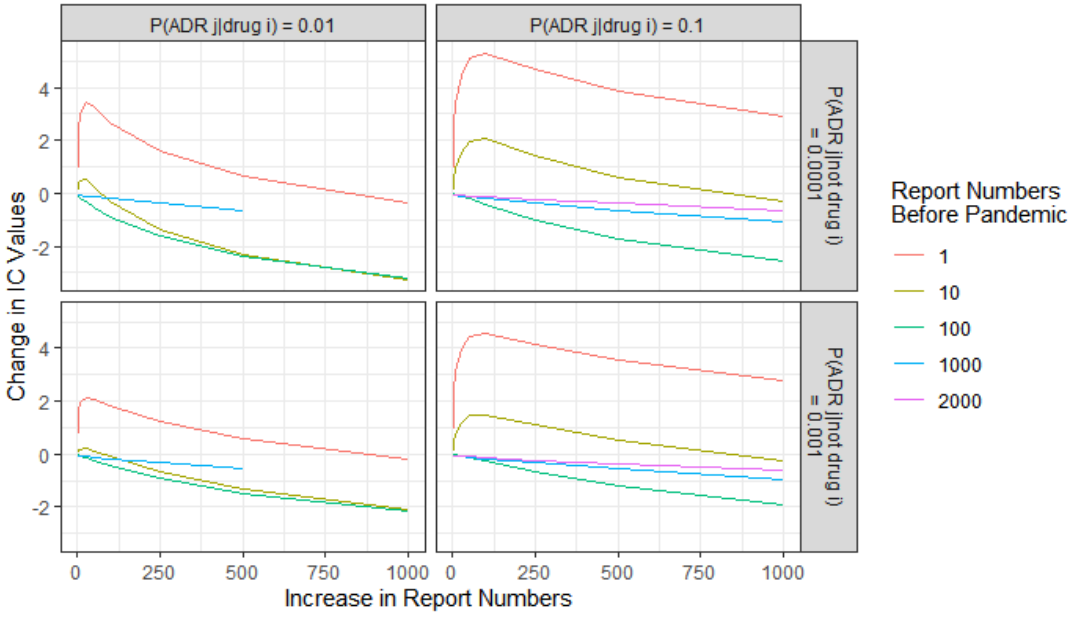


Figure 9 Change in IC with Increase in Report Numbers

3.3.2 Situation 2

With a 100-case increase in report number, there is generally an obvious increase in IC. The increase in IC gets larger when P(ADR j|drug i) increases by a higher fold. DECs with numbers of reports as small as 1 or 10 are more sensitive to the increase in P(ADR j|drug i). For DECs with one of report before the pandemic, a fold change in P(ADR j|drug i) as small as 0.5 would be enough to generate an increase in IC larger than 1. This is also true for DECs with 10 reports before the pandemic when P(ADR j|drug i) is as large as 0.1 before the outbreak of the pandemic. In contrast, the pattern of increase in IC for DECs with 100 or more reports before the pandemic is rather stable against different levels in P(ADR j|drug i) and P(ADR j|not drug i) and generally need a two-fold increase in P(ADR j|drug i) to generate a signal (IC increase > 1).

Meanwhile, as shown in Appendix Figure 5, the increasing pattern of ROR is quite stable for all cases. There seems to be a more rapid increase in ROR when the starting P(ADR j|drug i) is large (0.1 compared to 0.01). When P(ADR j|drug i) is 0.01, there needs to be a one-fold increase in P(ADR j|drug i) to have a one-fold increase in ROR. When P(ADR j|drug i) is 0.1, there only needs to be less than one-fold increase in P(ADR j|drug i) to have a one-fold increase in ROR.

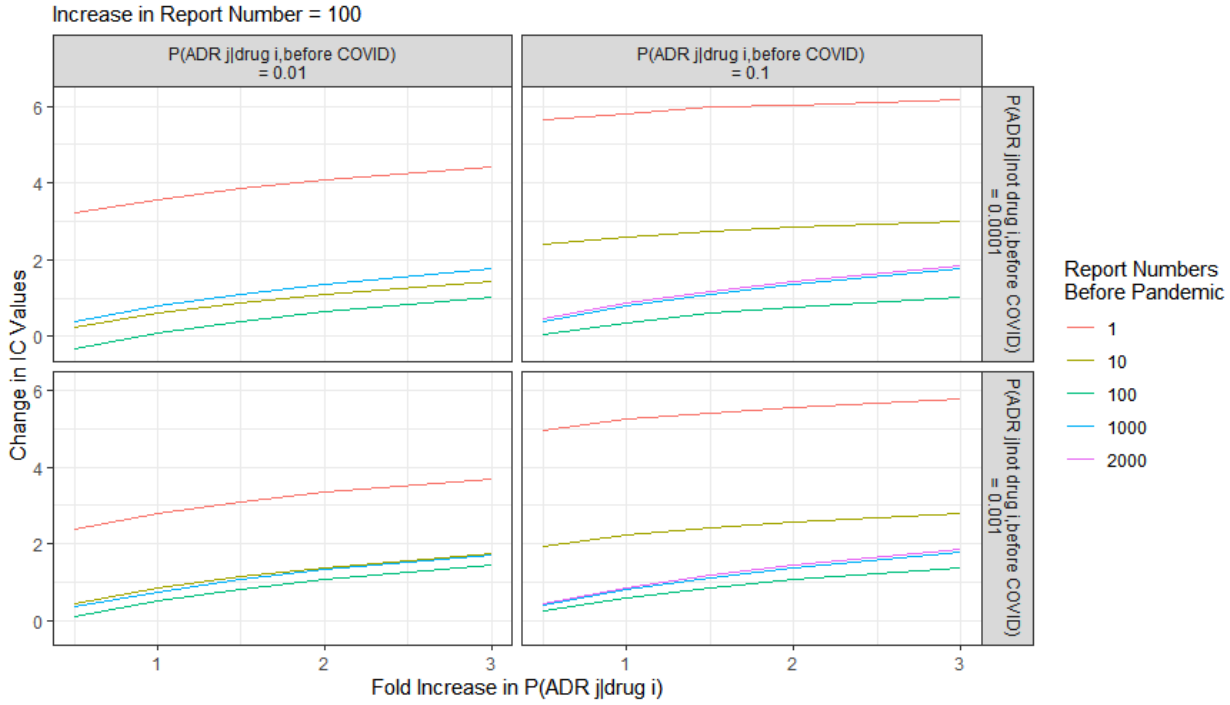


Figure 10 Change in IC with Increase in P(ADR j|drug i)

3.3.3 Situation 3

Similar to situation 2, when there is a same fold increase in both P(ADR j|drug i) and P(ADR j|not drug i), DECs could still have an increase in IC, which is especially true for DECs with numbers of reports as small as 1. Such an increase in IC may be because P(ADR|not drug i) is too small to lead to a fold increase in P(ADR) as large as that in P(ADR|drug i).

However, as shown in Appendix Figure 6, the fold increase in ROR would be suppressed with an increase in P(ADR j|not drug i) and generally would be difficult to reach one in our settings. But still, we have only considered the case of same fold increase in both P(ADR j|drug i) and P(ADR j|not drug i) in this situation. Compared with results in situation 2, we would expect higher fold increase in ROR (thus more signals detected) when the fold increase in P(ADR j|not drug i) is smaller than the fold increase in P(ADR j|drug i).

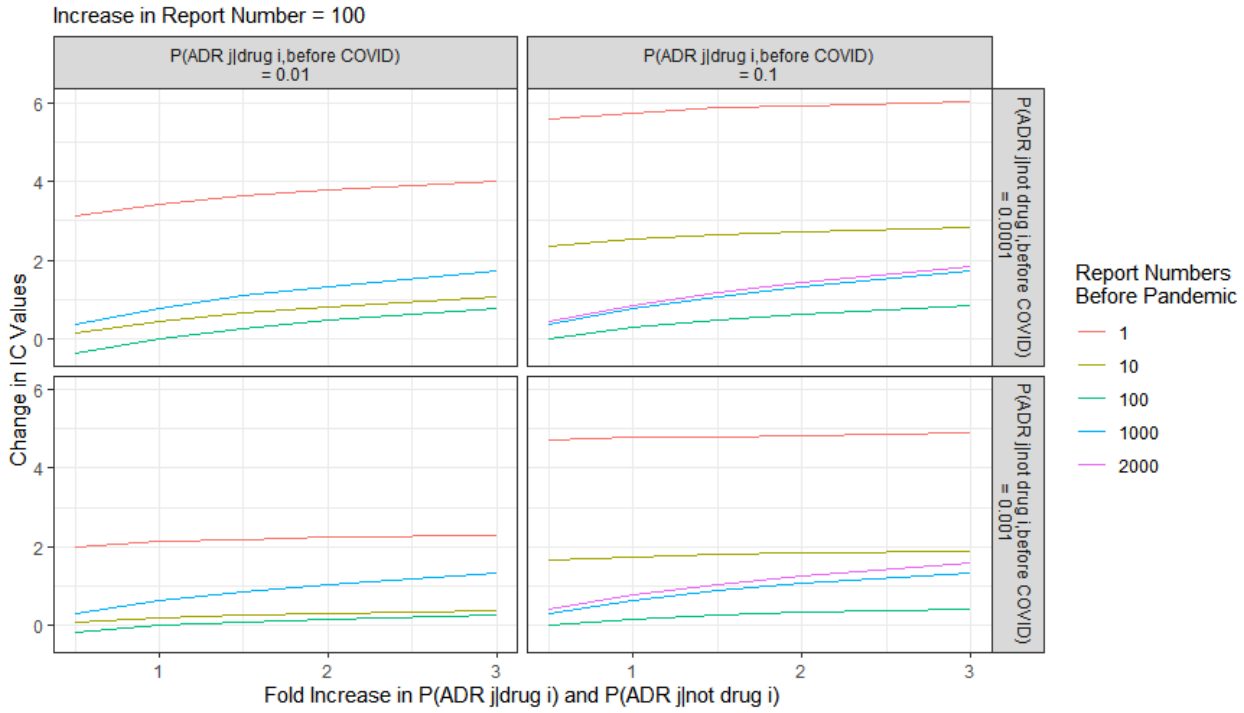


Figure 11 Change in IC with Increase in P(ADR j|drug i) and P(ADR j|not drug i)

3.3.4 Summary for Sensitivity Analysis

From the sensitivity analysis shown above, both IC and ROR would generally have an increase when there is an increase in P(ADR j|drug i). The increase in IC is generally higher when the starting value of P(ADR j|drug i) is larger compared to P(ADR j|not drug i). For ADRs that are not that common, that is when P(ADR j|drug i) is not as high as 0.1, a DEC with a moderate report

number such as 10 would need a fold increase in P(ADR j|drug i) higher than the fold increase in P(ADR j|drug i) to be detected as a signal (increase in IC > 1). The increase in ROR is generally higher when there is small or even no fold increase in P(ADR j|not drug i) compared to P(ADR j|drug i). Thus, we would expect the majority of signals detected by both increase in IC and increase in ROR to be DECs with relatively high fold increase in P(ADR j|drug i), which is the same as our major interest of discovering ADRs with elevated risks during the pandemic for repurposed drugs.

The aforementioned claim is backed up by the result of main analysis (Appendix Table 3). Among the 15 signals detected by both IC and ROR, 7 have fewer than 10 reports before the pandemic, while all reports have more than one-fold increase in report number after the pandemic outbreak. As shown in Table 6, these signals detected by our algorithms all have more than one-fold increase in P(ADR j|drug i) and very small or even no increase in P(ADR j|not drug i).

Table 6 Fold Increase in Marginal Probabilities for the 15 Signals

Drug Name	Adverse Event	Fold Increase in P(ADR j|drug i)	Fold Increase in P(ADR j|not drug i)
Clozapine	Substance related and addictive disorders	7.84	0.25
Apixaban	Alzheimer's disease (incl subtypes)	5.88	0.01
Methylprednisolone	Leukocytoses NEC	3.28	0.06
Apixaban	Cortical dysfunction NEC	2.27	-0.09
Azathioprine	Hepatic fibrosis and cirrhosis	2.72	0.15
Apixaban	Hearing losses	3.07	0.17
Tacrolimus	Acquired immunodeficiency syndromes	3.01	-0.25
Apixaban	Parkinson's disease and parkinsonism	1.95	-0.03
Methotrexate	Protein metabolism disorders NEC	4.30	0.43
Tacrolimus	Hepatitis virus infections	1.16	-0.21
Methylprednisolone	Aspergillus infections	1.57	0.0004
Apixaban	Dementia (excl Alzheimer's type)	2.10	-0.02
Prednisone	Atypical mycobacterial infections	1.24	-0.13
Dexamethasone	Bone disorders NEC	1.43	0.11
Apixaban	Retinal structural change, deposit and degeneration	1.54	0.13

Although it is likely for some DECs with a very small number of reports before the pandemic to have an increase in IC even though they do not have an elevated risk for the ADR, most of these signals would be excluded when we apply the restrictions on sample size and statistical significance. But this still gives us a notice that when looking at signals with small sample sizes, we should be aware that this DEC may not have an increase in P(ADR j|drug i). Whether these signals are the ones with an elevated risk will need further judgement by medical professionals.

4.0 Discussion

4.1 Results and Discussion

In this study, we explored the practice of disproportionality analyses using IC and ROR on the FAERS database in the context of resolving rising pharmacovigilance concerns during the COVID-19 pandemic. For Remdesivir, a new drug, we found that IC_{025} and ROR_{025} give generally comparable performance in signal detection and ranking especially among DECs with more than three observations. Most signals detected are also selected by the data reported by healthcare professionals, and seem to be reliable based on preliminary research. ROR_{025} tends to identify more signals than IC_{025} with most discrepancies having small sample sizes. Also, we have discovered a hyperbolic trend between the rankings by IC or ROR, and the observed-to-expected ratios (O/E ratios). For the 19 repurposed drugs, we found that the algorithms using increase in IC larger than one or fold increase in ROR larger than one generally give comparable performance in signal detection and rankings especially among DECs with more than three observations both before and after the pandemic outbreak. One third of the signals are also detected by the data reported by healthcare professionals, and seem to be reliable based on preliminary research. Also, a hyperbolic trend between the rankings by increase in IC or fold increase in ROR is observed. Finally, the sensitivity analysis showed the change of increase in IC and ROR under different parameter settings, and confirmed that both increase in IC and fold increase in ROR favor DECs with high fold increase in P(ADR j|drug i).

Introduced in the early 1990s, the reporting odds ratio (ROR) is the first score used in disproportionality analysis[47, 48], and has a relatively long and common use in the

pharmacovigilance field compared to other disproportionality scores. It is easy to understand and program, but cannot give point and/or interval estimations when there are zeros inside the corresponding 2x2 contingency tables. Also, as its frequentist counterparts PRR and RRR, previous studies claimed ROR to be unstable when sample sizes are small[38], giving rise to a large number of false-positive signals. Meanwhile, under the Bayesian paradigm, the information component (IC) and its counterpart, empirical Bayesian geometric mean (EBGM), can give point and interval estimations even with the presence of zeros in the 2x2 contingency table[24, 38]. More importantly, with the conservative prior assuming the independence between the drug and the adverse event, IC and EBGM are claimed to be relatively stable and conservative, which could give improved performance in signal detection by reducing false-positive signals for DECs with small sample sizes and having enough sensitivity for DECs with large sample sizes[22, 24, 25].

By comparing the signal detection performance between IC and ROR using FAERS data in the context of the COVID-19 pandemic, our study collected evidence of the comparison between frequentist and Bayesian disproportionality scores that can be compared to the previous studies. First, the claim of conservatism of Bayesian scores for the classical type of disproportionality analysis on a single time period agreed with the performance of IC_{025} and ROR_{025} for Remdesivir. Without strict sample size restrictions, ROR_{025} detected 12 more signals than IC_{025}, which consists of 34% of the signals detected by ROR_{025}. And, most of the 12 signals only detected by ROR_{025} had small sample sizes (less than 4). This provided new evidence for the claim of conservatism, but with new data ─ Remdesivir ADR data during the pandemic. Then, the analysis was extended to comparing the disproportionality scores before and during the pandemic for repurposed drugs, and the results showed that the conservatism of Bayesian scores still exist. Without sample size restrictions, the algorithm based on increase in IC detected 87 signals, 15% less than the algorithm

based on fold increase in ROR. This extends the comparison between IC and ROR into the seldom discussed but meaningful type of disproportionality analysis that compares the disproportionalities of two time periods.

Also importantly, we identified a hyperbolic trend between signal rankings and the observed-to-expected ratios (O/E ratios) which has not been mentioned by previous studies up to out knowledge. In our study, we found that, with a small number of discrepancies on DECs with small sample sizes, IC and ROR rankings generally followed the same trend line for Remdesivir. When it came to the repurposed drugs, rankings by increase in IC and fold increase in ROR also aligned pretty well on a hyperbolic trend line. In fact, this concordance in rankings has its mathematical logics. Disproportionality scores for pairwise associations such as IC, RRR where IC is based upon, and ROR can all be classified into the broad concept of O/E ratios[21]. In $RRR = \frac{n_{11}}{n_{1.}n_{.1}/n}$, the expected count is calculated with the assumption of equality between P(ADR j|drug i) and P(ADR j). In $ROR = \frac{n_{11}}{n_{10}n_{01}/n_{00}}$, the expected count is calculated assuming the equality between the odds of ADR j given drug i and the odds of ADR j without drug i. And $IC = log_2 RRR$ is a shrunk version of RRR in a Bayesian paradigm that can be approximated by the equation in the form of O/E ratio: $IC \approx log_2 \frac{Observed+1/2}{Expected+1/2}$ in a frequentist paradigm[21, 24]. Thus, these scores are all based on O/E ratio, and this explains their similarity in ranking signals with regard to the strength of associations. And as sample size increases, these different O/E ratios would give increasing concordance in estimating the strength of association, which explains the observed concordance in ranking behavior between IC and ROR in our data. The significance of the finding is that if the rankings by two scores are similar, we may have enough confidence that the two scores are behaving similarly for the signals we are looking at. Thus, using the alignment of

rankings in future studies as a sign of concordance between two disproportionality scores is a disproportionality score comparison method worth further exploration.

Another point deserving a further discussion is the interpretability of the disproportionality scores. In contrast to ROR which can be interpreted as odds ratio, the Bayesian score IC has more complex mathematical construction and is difficult to interpret. In fact, previous studies using IC as a disproportionality measure merely looked at the signals detected without interpreting the values of IC[24, 49]. In an effort to better understand this score, we refer to the definition of IC: $IC = log_2 RRR$ [20, 24], which is a shrunk version of RRR on the log2 scale based on a prior belief of independence between drug i and ADR j. Plus, RRR is actually the classic form of O/E ratio[21]. Thus, for a signal with an IC of n, we may interpret it as a DEC with the shrunk O/E ratio of 2^n. And an increase of n in IC may be viewed as a $(2^n - 1)$-fold increase in the shrunk O/E ratio RRR. Furthermore, since frequentist O/E ratio is better interpretable, and IC converge to $\log_2$RRR for large sample sizes, we may switch to RRR (or O/E ratio) for interpretation of signals with large sample sizes. Or we may even use ROR for interpretation since we have shown that IC and ROR have similar performance in signal detection and ranking.

4.2 Limitations

There are several limitations for this study.

First, the time frame of the FAERS data we use is short. Each disproportionality score only estimates the disproportionality of a DEC over half a year, while previous studies using disproportionality analysis to identify signals from FAERS data could a time frame of several years or even more than 10 years[50-52]. Within a short time, there may not be large numbers of reports

for many DECs. This could result in lack of reports for rare DECs, and thus some rare and unknown signals with particular interest for disproportionality analysis may not be detected. The lack of reports is also not ideal for methodological study that compares the performance between IC and ROR. Previous study[22] comparing the performance of disproportionality scores EBGM, and RRR used FAERS data with a total number 4864480 reports. The large number of reports generated thousands of signals. With the large number of signals, the difference in the two disproportionality scores were clearly highlighted. For example, a signal ranked 40 by EBGM and 224 by RRR would surely indicate a striking difference in ranking. However, with a small amount of data and signals, it would hard to decide whether the difference in ranking is high or not. Thus, further studies would need to include more FAERS data in order to detect more signals and better compare the performance of IC and ROR.

Second, the evaluation and comparison of the signal detection performance of IC and ROR needs improvement. An important part for the evaluation of a signal detection procedure is looking at whether the procedure can detect enough true signals without generating too much false-positive signals. This is usually reflected in indices such as sensitivity, specificity, positive predictive value and negative predictive value[38, 49]. However, the estimation of these indices requires the knowledge of DECs with true causal relationship. Thus, such methodological studies for disproportionality scores usually depend on simulated data where the causal relationship can be manually set[26], or real world data where true signals have been identified by medical professionals[49]. To better evaluate and compare the performance of IC and ROR, we would need to either create a simulated data set or seek help from medical professionals to identify true signals for new drug ADRs or ADRs with elevated risks during the pandemic for repurposed drugs before using the FAERS data for methodological research.

Third, the drawbacks of spontaneous reporting data should be recognized. The bias in reporting drugs and adverse events may cause underreporting and overreporting[40]. Also, duplicate reports are common because a single case may be reported separately by the consumer, a healthcare provider of that person, and the drug manufacturer[41], and it is difficult to remove all the duplicate reports simply by an exact match of demographical data as there would be missing values. Also, records of drug prescription without adverse events are not included, thus incidence rate of ADRs cannot be estimated[20]. All these biases may make the estimated association far from the truth. Thus, an effort for removing biases from the spontaneous reporting data is needed. In this study, we tried to remove reporting bias by relying on the data reported by healthcare professionals. This would help in identifying true associations. However, excluding other reporters will reduce approximately 50% of the whole number of reports, which would make it more difficult to detect rare DECs. Thus, we do not suggest simply relying on this reduced data especially when sample size is small. Also, the highly biased nature of the data implies that we still have to view the detected signals critically. These signals have to be further reviewed by medical professionals, and verified by more rigorous experiments and testing procedures such as sequential ratio tests[20].

4.3 Conclusion

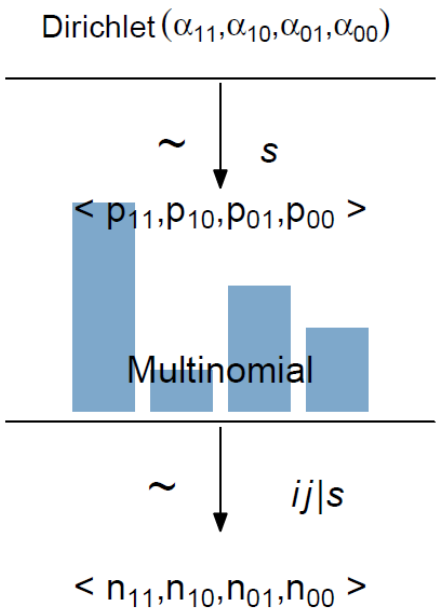
Overall, this study used disproportionality analysis on FAERS data and sensitivity analysis to provide evidence for the viability of using disproportionality scores IC and ROR for discovering unestablished ADRs of new drugs and discovering ADRs with elevated risks during the pandemic. We found that the signal detection and signal ranking performance of IC is generally comparable

to ROR for both new drugs and repurposed drugs in the FAERS data in the context of the COVID-19 pandemic.

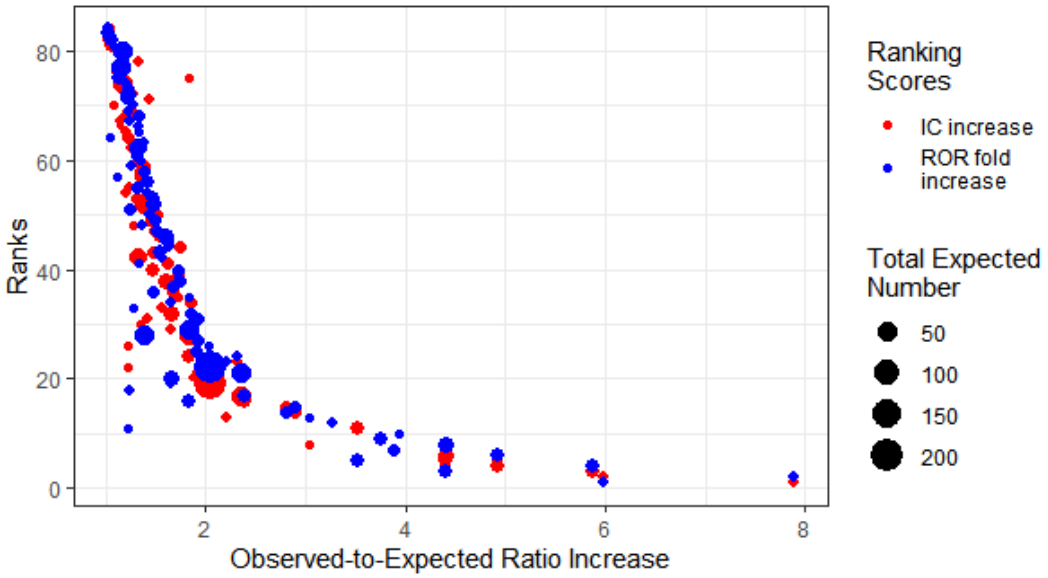
One strength of this study is the focus on pharmacovigilance needs during the COVID-19 pandemic. Both the need for discovering unknown ADRs for new drugs and the need for discovering ADRs with elevated risks during the pandemic for repurposed drugs were considered. With FAERS data analysis and sensitivity analysis, we provided evidence for the viability of using disproportionality analysis to satisfy the aforementioned pharmacovigilance needs. Based on the observation of a similarity in signal detection and signal ranking, the conservatism of IC scores compared to ROR, as well as the difference in interpretability, a disproportionality analysis framework can be suggested where we use IC for signal detection and refer to ROR for signal ranking and interpretation if ROR values are available. This framework has importance and practicality for pharmacovigilance during the COVID-19 pandemic as well as future public health crisis.

Also, this study made an effort to extend the application of disproportionality scores to the comparison of two disproportionalities. The idea of comparing associations by comparing disproportionality scores has been mentioned in previous publications[21, 28, 53], but has not been well justified. Based on the concordance of increase in IC and fold increase in ROR in signal detection and their ranking preference for high fold increase in O/E ratios as well as the result of the sensitivity analysis showing the importance of a high fold increase in P(ADR j|drug i) for an increase in IC or ROR, this study provided evidence that the increase in IC and fold increase in ROR are generally good representations of change in disproportionality reporting. This evidence we provided would benefit future methodological research and practical applications of this type of disproportionality analysis.

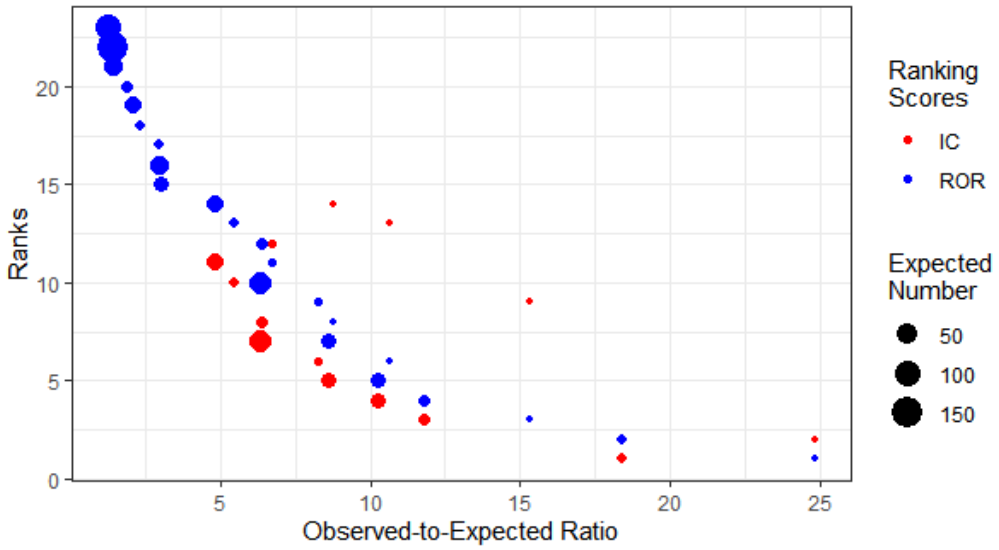
Appendix A Supplementary Figures



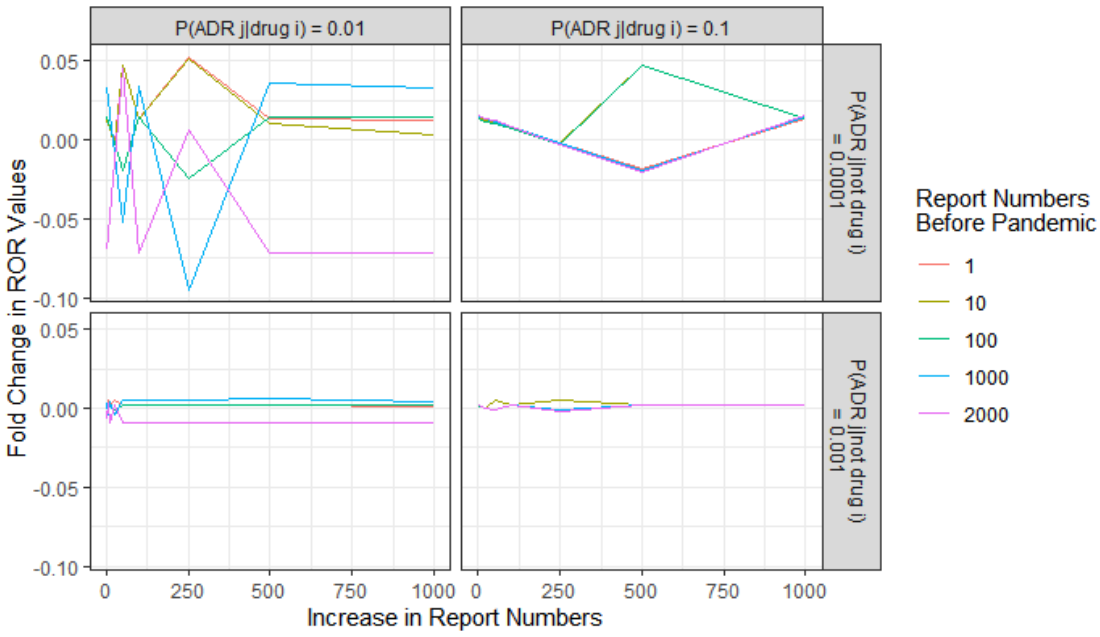
Appendix Figure 1 Schema for the Bayesian Hierarchical Model BCPNN



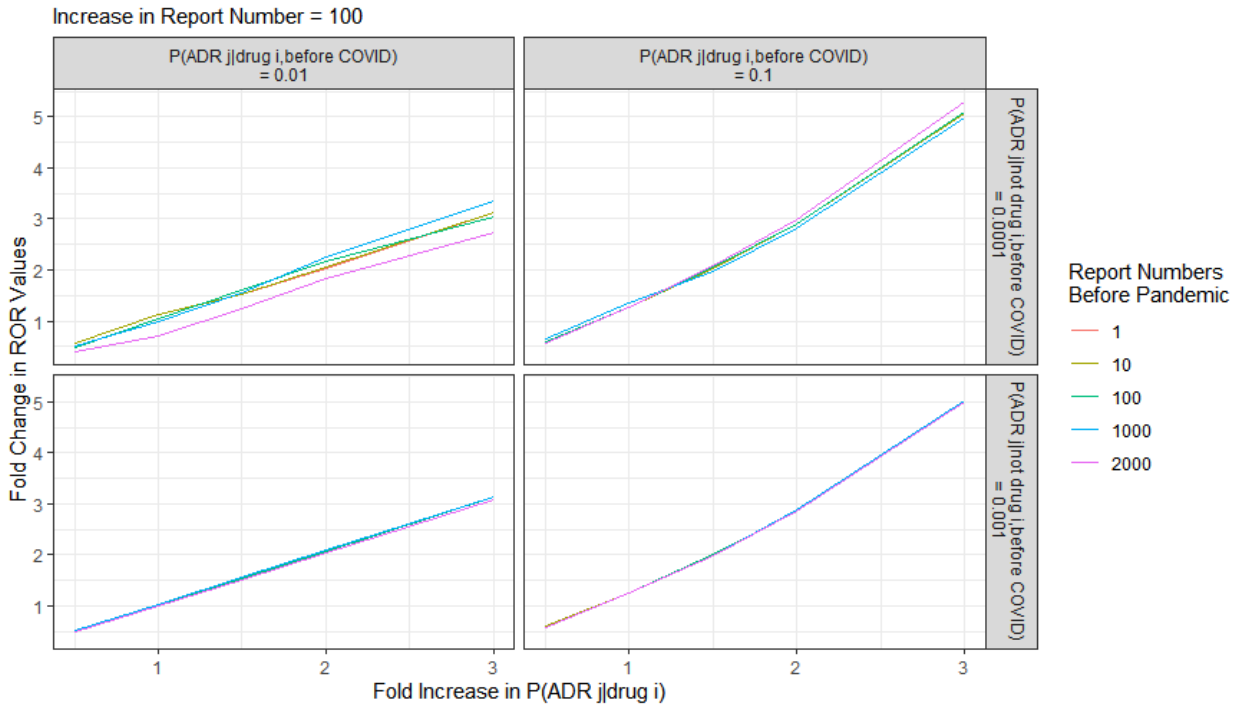
Appendix Figure 2 Relationship of Signal Ranking and Observed-to-expected Ratio Increase
Rankings by IC increase, and ROR fold increase are overlaid on one plot. Dot sizes reflect the total numbers of expected reports of the signals over one year (from September 11, 2019 to September 11, 2020).



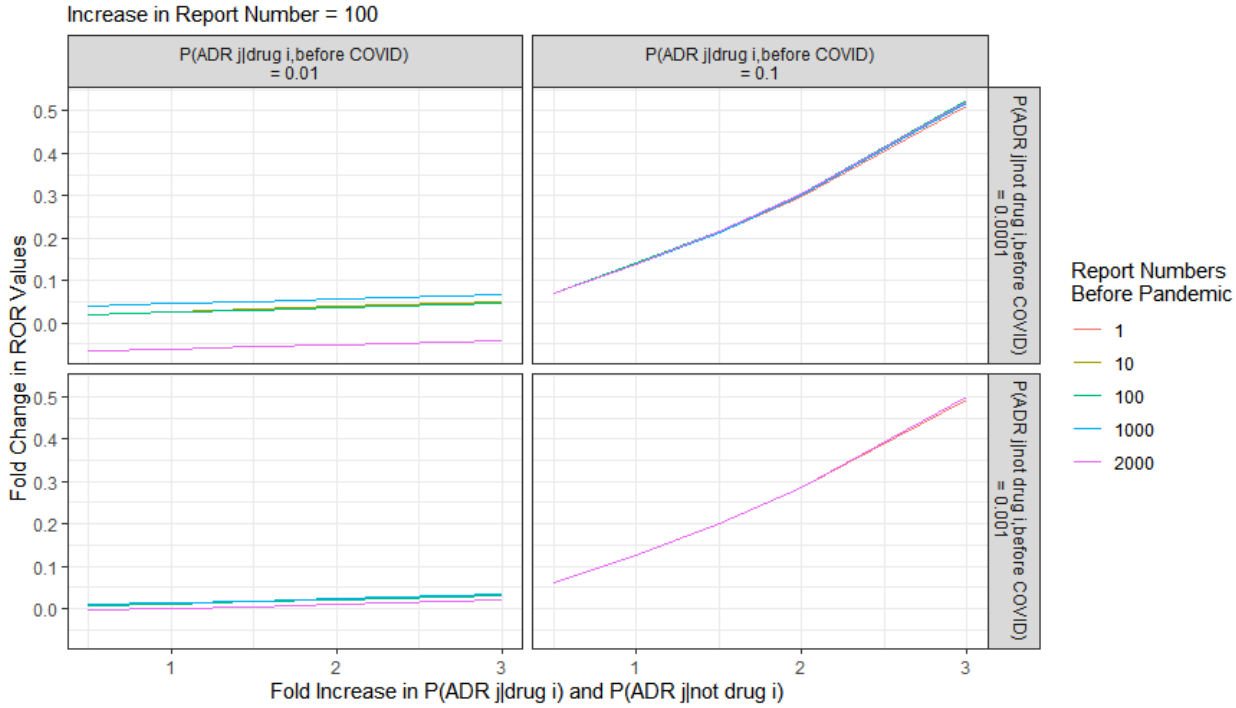
Appendix Figure 3 Relationship of Signal Ranking and Observed-to-expected Ratio
Rankings by IC, and ROR are overlaid on one plot. Dot sizes reflect the total numbers of expected reports of the signals over one year (from September 11, 2019 to September 11, 2020).



Appendix Figure 4 Fold Change in ROR with Increase in Report Numbers



Appendix Figure 5 Fold Change in ROR with Increase in P(ADR j|drug i)



Appendix Figure 6 Fold Change in ROR with Increase in P(ADR j|drug i) and P(ADR j|not drug i)

Appendix B Supplementary Tables

Appendix Table 1 Signals Detected Only by One Disproportionality Measure for Repurposed Drugs

Drug Name	Adverse Event	Measure	N_{before}	N_{during}	E_{before}	E_{during}
Azathioprine	Stillbirth and foetal death	IC	2	5	0.20	0.27
Colchicine	Myopathies	IC	2	5	0.15	0.29
Prednisone	Toxoplasma infections	IC	2	10	0.77	2.32
Apixaban	Abdominal wall conditions NEC	ROR	4	3	1.88	0.74
Apixaban	Gastrointestinal neoplasms malignancy unspecified NEC	ROR	2	3	3.51	2.7
Apixaban	Non-site specific embolism and thrombosis	ROR	208	438	103.57	126.3
Clozapine	Hodgkin's disease NEC	ROR	3	6	2.3	2.41
Clozapine	Schizoaffective and schizophreniform disorders	ROR	5	11	0.4	0.66
Dexamethasone	Abnormal reflexes	ROR	2	3	0.89	0.68
Methotrexate	Arterial infections and inflammations	ROR	5	16	6.39	10.59
Methotrexate	Bladder infections and inflammations	ROR	3	14	6.11	13.71
Methylprednisolone	B-cell lymphomas NEC	ROR	2	3	1.6	1.22
Mycophenolate Mofetil	Renal structural abnormalities and trauma	ROR	2	2	0.3	0.14
Prednisone	Cataract conditions	ROR	11	32	32.73	31.56
Prednisone	Connective tissue disorders NEC	ROR	6	14	6.41	7.58
Prednisone	Deliria	ROR	5	11	5.69	6.36
Prednisone	Hepatitis virus infections	ROR	15	25	12.52	10.4
Prednisone	Hypoglycaemic conditions NEC	ROR	2	5	5.22	4.83
Tacrolimus	Acnes	ROR	11	29	13.83	18.38
Tacrolimus	Magnesium metabolism disorders	ROR	5	12	1.24	1.77
Tocilizumab	Gastrointestinal ulcers and perforation, site unspecified	ROR	7	15	8.44	9.27

(Measure: the disproportionality measure that detects the DEC as a signal; N_{before}: number of observed reports before pandemic outbreak; N_{during}: number of observed reports during pandemic; E_{before}: number of expected reports during pandemic outbreak; E_{during}: number of expected reports during the pandemic.)

Appendix Table 2 Signals Detected Only by One Disproportionality Measure for Remdesivir

Drug Name	Adverse Event	Measure	N	E
Remdesivir	Abnormal reflexes	ROR	2	0.46
Remdesivir	Angioedemas	ROR	5	2.68
Remdesivir	Body temperature altered	ROR	12	1.87
Remdesivir	Coagulopathies	ROR	2	6.14
Remdesivir	Enterobacter infections	ROR	3	0.4
Remdesivir	Hyperlipidaemias NEC	ROR	6	0.74
Remdesivir	Klebsiella infections	ROR	2	2.31
Remdesivir	Mediastinal disorders	ROR	14	0.36
Remdesivir	Mental disorders NEC	ROR	14	7.72
Remdesivir	Respiratory tract and thoracic cavity procedural complications	ROR	2	0.3
Remdesivir	Thrombocytoses	ROR	3	0.91
Remdesivir	Tracheal disorders (excl infections and neoplasms)	ROR	2	0.2

(Measure: the disproportionality measure that detects the DEC as a signal; N: number of observed reports during the pandemic; E: number of expected reports during the pandemic)

Appendix Table 3 Common Signals with High Statistical Significance for the 19 Repurposed Drugs

Drug Name	Adverse Event	N_{before}	N_{during}	E_{before}	E_{during}	IC Increase [Rank]	ROR Fold Increase [Rank]	Causal
Clozapine	Substance related and addictive disorders	9	83	6.55	11.17	2.48[1]	6.14[1]	Yes
Apixaban	Alzheimer's disease (incl subtypes)	7	46	6.53	9.48	2.21[2]	5.87[2]	No
Methylprednisolone	Leukocytoses NEC	5	20	6.49	6.69	1.95[3]	3.04[4]	Yes
Apixaban	Cortical dysfunction NEC	8	25	24.4	22.71	1.75[4]	2.60[6]	No
Azathioprine	Hepatic fibrosis and cirrhosis	6	26	1.13	1.61	1.74[5]	2.31[8]	No
Apixaban	Hearing losses	64	249	88.64	113.31	1.61[6]	2.54[7]	No
Tacrolimus	Acquired immunodeficiency syndromes	5	26	0.67	1.56	1.55[7]	4.38[3]	No
Apixaban	Parkinson's disease and parkinsonism	11	31	23.02	22.96	1.49[8]	2.06[10]	No
Methotrexate	Protein metabolism disorders NEC	5	37	6.68	18.69	1.47[9]	2.71[5]	Yes
Tacrolimus	Hepatitis virus infections	10	28	9.87	10.9	1.36[10]	1.72[11]	Yes
Methylprednisolone	Aspergillus infections	10	24	2.77	2.81	1.26[11]	1.58[12]	No
Apixaban	Dementia (excl Alzheimer's type)	48	142	26.04	32.35	1.25[12]	2.18[9]	No
Prednisone	Atypical mycobacterial infections	11	24	4.76	4.63	1.16[13]	1.57[13]	No
Dexamethasone	Bone disorders NEC	15	38	26.74	31.38	1.11[14]	1.21[15]	Yes
Apixaban	Retinal structural change, deposit and degeneration	14	34	27.51	31.21	1.10[15]	1.25[14]	No

(N_{before}: number of observed reports before pandemic outbreak; N_{during}: number of observed reports during pandemic; E_{before}: number of expected reports during pandemic outbreak; E_{during}: number of expected reports during the pandemic; Causal: whether the DEC is also detected by both IC and ROR as signals with high confidence in FAERS data reported by healthcare professionals.)

Appendix Table 4 Common Signals with High Statistical Significance for Remdesivir

Drug Name	Adverse Event	N	E	IC [Rank]	ROR [Rank]	Causal
Remdesivir	Infusion site reactions	53	2.88	3.97[1]	29.15[2]	Yes
Remdesivir	Mixed acid-base disorders	14	0.56	3.73[2]	48.92[1]	Yes
Remdesivir	Conditions associated with abnormal gas exchange	96	8.13	3.48[3]	15.62[4]	Yes
Remdesivir	Ventricular arrhythmias and cardiac arrest	189	18.47	3.32[4]	13.35[5]	Yes
Remdesivir	Respiratory failures (excl neonatal)	151	17.56	3.06[5]	10.64[6]	Yes
Remdesivir	Renal vascular and ischaemic conditions	19	2.29	2.77[6]	9.79[7]	Yes
Remdesivir	Renal failure and impairment	432	68.58	2.65[7]	8.01[8]	Yes
Remdesivir	Circulatory collapse and shock	43	6.76	2.57[8]	7.23[10]	Yes
Remdesivir	Right ventricular failures	4	0.26	2.41[9]	21.67[3]	Yes
Remdesivir	Metabolic acidoses (excl diabetic acidoses)	21	3.84	2.28[10]	6.05[11]	Yes
Remdesivir	Rate and rhythm disorders NEC	124	25.63	2.25[11]	5.42[12]	Yes
Remdesivir	Pupil disorders	5	0.74	2.02[12]	7.62[9]	Yes
Remdesivir	Pulmonary oedemas	52	17.28	1.55[13]	3.17[13]	Yes
Remdesivir	Vascular hypotensive disorders	105	35.83	1.53[14]	3.12[14]	Yes
Remdesivir	Pseudomonal infections	8	2.7	1.33[15]	3.10[15]	No
Remdesivir	Hepatic failure and associated disorders	12	5.21	1.07[16]	2.37[16]	No
Remdesivir	Supraventricular arrhythmias	64	30.11	1.06[17]	2.20[17]	Yes
Remdesivir	Coagulopathies	12	6.14	0.86[18]	2.00[18]	No
Remdesivir	Potassium imbalance	14	7.52	0.80[19]	1.90[19]	No
Remdesivir	Sepsis, bacteraemia, viraemia and fungaemia NEC	60	41.74	0.51[20]	1.46[20]	No
Remdesivir	Death and sudden death	216	152.97	0.49[21]	1.45[21]	Yes
Remdesivir	Breathing abnormalities	119	96.52	0.29[22]	1.25[22]	Yes

(N: number of observed reports during the pandemic; E: number of expected reports during the pandemic; Causal: whether the DEC is also detected by both IC and ROR as signals with high confidence in FAERS data reported by healthcare professionals.)

Appendix Table 5 Common Signals for Repurposed Drugs using FAERS Data Reported by Healthcare Professionals

Drug Name	Adverse Event	N_{before}	N_{during}	E_{before}	E_{during}	IC Increase [Rank]	ROR Fold Increase [Rank]
Clozapine	Substance related and addictive disorders	8	78	6.42	11.54	2.48[1]	7.10[1]
Methylprednisolone	Leukocytoses NEC	5	19	9.18	9.72	1.84[2]	2.74[3]
Prednisone	Cataract conditions	7	23	22.29	22.37	1.71[3]	2.42[5]
Methotrexate	Protein metabolism disorders NEC	4	36	9.23	26.7	1.67[4]	3.29[2]
Apixaban	Site specific vascular disorders NEC	8	17	6.19	4.36	1.55[5]	2.45[4]
Hydroxychloroquine	Hepatocellular damage and hepatitis NEC	6	60	5.3	20.26	1.48[6]	1.78[6]
Cyclosporine	Febrile disorders	6	26	15.45	24.7	1.47[7]	1.76[7]
Tacrolimus	Hepatitis virus infections	10	27	10.96	13.07	1.19[8]	1.45[8]
Dexamethasone	Bone disorders NEC	14	36	25.67	29.25	1.17[9]	1.34[9]
Prednisone	Hepatitis virus infections	13	25	13.85	12.49	1.08[10]	1.29[10]

(N_{before}: number of observed reports before pandemic outbreak; N_{during}: number of observed reports during pandemic; E_{before}: number of expected reports during pandemic outbreak; E_{during}: number of expected reports during the pandemic)

Appendix Table 6 Common Signals for Remdesivir using FAERS Data Reported by Healthcare Professionals

Drug Name	Adverse Event	N	E	IC [Rank]	ROR [Rank]
Remdesivir	Infusion site reactions	50	3.869355	3.52[1]	23.39[2]
Remdesivir	Mixed acid-base disorders	12	0.780971	3.24[2]	32.73[1]
Remdesivir	Conditions associated with abnormal gas exchange	90	10.6141	3.02[3]	12.03[4]
Remdesivir	Ventricular arrhythmias and cardiac arrest	183	23.8906	2.91[4]	10.73[5]
Remdesivir	Respiratory failures (excl neonatal)	144	25.73653	2.46[5]	7.02[6]
Remdesivir	Renal vascular and ischaemic conditions	19	3.443371	2.28[6]	6.65[7]
Remdesivir	Renal failure and impairment	415	92.65152	2.16[7]	5.79[8]
Remdesivir	Right ventricular failures	4	0.425984	2.15[8]	13.60[3]
Remdesivir	Rate and rhythm disorders NEC	120	28.61192	2.05[9]	4.91[10]
Remdesivir	Circulatory collapse and shock	42	9.904128	2.02[10]	4.87[11]
Remdesivir	Metabolic acidoses (excl diabetic acidoses)	20	5.715285	1.70[11]	3.87[12]
Remdesivir	Pupil disorders	4	0.922965	1.52[12]	4.95[9]
Remdesivir	Pulmonary oedemas	50	18.6723	1.38[13]	2.89[13]
Remdesivir	Vascular hypotensive disorders	99	39.75851	1.30[14]	2.69[14]
Remdesivir	Supraventricular arrhythmias	59	30.31586	0.94[15]	2.04[15]
Remdesivir	Death and sudden death	200	137.4153	0.54[16]	1.51[16]
Remdesivir	Breathing abnormalities	113	91.55106	0.30[17]	1.25[17]

(N: number of observed reports during the pandemic; E: number of expected reports during the pandemic)

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