Subgroup Analysis Shows High COVID-19 Burden Is Associated With Increased Adverse Drug Effect Related Mortality in The United States: A Retrospective Cohort Study

Liang Xiong[1]

[1]China Pharmaceutical University

November 9, 2023

Abstract

COVID-19 caused substantial damage for the world and more than one million individuals succumbed to this contagious disease. During the 2020-2021 autumn-winter season, there was a huge wave of new COVID-19 infection cases in the United States (US). We intend to investigate whether this high COVID-19 burden had a link to adverse drug reactions in the US, thus we extracted online data from the US Food and Drug Administration (FDA) comparing the adverse drug effect-related mortality between two autumn-winter seasons (2020/2021 cohort 1 vs 2022/2023 cohort 2). The primary outcome is measured via multi-variable logistic regression models which adjust age, sex, and drug indication. A second analysis investigated the association between the high COVID-19 burden and the adverse drug effect mortality for the 25 most reported drugs during the two seasons. The average age is 58.87 vs 59.27 years, respectively. In Cohort 1 54.29% are females and in Cohort 2 the percentage is 55.32%. The crude mortality in Cohort 1 is 19.80% and in Cohort 2 it is 20.72%. We did not find a positively significant primary outcome and the odd ratio (OR) of high COVID-19 burden for adverse drug effect mortality is 0.946 (95%CI 0.926-0.965, $p < .0001$). However, the subgroup analysis shows for some drugs, most of which compromise the immune response, the high COVID-19 burden is linked to increased risk of death significantly. They include adalimumab, clozapine, duplilumab, lendlidomide, palbocicib, pomalidomide, rivaroxaban, tofacitib, ibrutinib, and updadacit. Our study probably provides preliminary evidence supposing that patients suffering an adverse drug effect involving the immune system from medications might be at increased risk for deteriorating outcomes during the high pandemic burden period of a serious and contagious disease. However, future prospective studies are needed to confirm the results. We think an adverse drug reaction mitigation strategy during future pandemics is needed to better protect those who take these drugs.

Subgroup Analysis Shows High COVID-19 Burden Is Associated With Increased Adverse Drug Effect Related Mortality in The United States: A Retrospective Cohort Study

Authors

First author: Liang Xiong

Correspond author: Liang Xiong

Affiliation of Authors

China Pharmaceutical University Ringgold standard institution

Nanjing, Jiangsu

China

tom.hsiung@outlook.comsmu.edu.cn

Acknowledgments

All authors have contributed to the research work, L.X. designed the study and was responsible for all of the research work, including data cleaning, statistical analysis, results interpretation, and writing the draft.

Conflict of Interest Statement

There is no conflict of interest for all authors.

Other Statements

This research has not been posted in other places and there is no sponsor for this research.

Abstract

COVID-19 caused substantial damage for the world and more than one million individuals succumbed to this contagious disease. During the 2020-2021 autumn-winter season, there was a huge wave of new COVID-19 infection cases in the United States (US). We intend to investigate whether this high COVID-19 burden had a link to adverse drug reactions in the US, thus we extracted online data from the US Food and Drug Administration (FDA) comparing the adverse drug effect-related mortality between two autumn-winter seasons (2020/2021 cohort 1 vs 2022/2023 cohort 2). The primary outcome is measured via multi-variable logistic regression models which adjust age, sex, and drug indication. A second analysis investigated the association between the high COVID-19 burden and the adverse drug effect mortality for the 25 most reported drugs during the two seasons. The average age is 58.87 vs 59.27 years, respectively. In Cohort 1 54.29% are females and in Cohort 2 the percentage is 55.32%. The crude mortality in Cohort 1 is 19.80% and in Cohort 2 it is 20.72%. We did not find a positively significant primary outcome and the odd ratio (OR) of high COVID-19 burden for adverse drug effect mortality is 0.946 (95%CI 0.926-0.965, $p < .0001$). However, the subgroup analysis shows for some drugs, most of which compromise the immune response, the high COVID-19 burden is linked to increased risk of death significantly. They include adalimumab, clozapine, duplilumab, lendlidomide, palbocicib, pomalidomide, rivaroxaban, tofacitib, ibrutinib, and updadacit. Our study probably provides preliminary evidence supposing that patients suffering an adverse drug effect involving the immune system from medications might be at increased risk for deteriorating outcomes during the high pandemic burden period of a serious and contagious disease. However, future prospective studies are needed to confirm the results. We think an adverse drug reaction mitigation strategy during future pandemics is needed to better protect those who take these drugs.

Keywords

ADR, COVID-19, mortality, cancer

Key Points

- Mortality from FAERS-collected adverse drug reactions in the United States is around 1 in 5.
- The COVID-19 high burden is associated with increased death risk from adverse drug reactions of some drugs.
- Subgroup analysis demonstrates most of the drugs whose deleterious outcomes are associated with the high COVID-19 burden are drugs that weaken the immune system.
- Compared with the low COVID-19 burden period, patients who are taking clozapine are at the highest risk of death due to the drug's adverse reaction when the COVID-19 burden is high.
- For direct oral anticoagulant rivaroxaban, the COVID-19 burden is associated with mortality from adverse drug reactions.

Plain Language Summary

We used the adverse reaction reports data from the FDA to analyze the risk of death due to adverse drug reactions between the 2020/2021 and 2022/2023 autumn seasons. One major difference between the two seasons is the number of new confirmed COVID-19 cases. We aim to investigate whether there is an association between the COVID-19 burden and the risk of death due to adverse drug reactions. We found

there was a negative association between the COVID-19 burden and the risk of death due to adverse drug reactions. However, subgroup analysis shows for some drugs, the risk of death was increased during the high COVID-19 burden season. We conclude our research probably provides some evidence about the association between the COVID-19 burden and the mortality of adverse drug reactions.

Ethics Statement

This research is a retrospective cohort study using FAERS publicized data. We follow the rules of using these data required by FDA.

Introduction

The COVID-19 pandemic has caused substantial suffering for the world. Economically, it is estimated that COVID-19 caused a large economic burden[1][5]. One system review investigated studies that assessed the economic burden of COVID-19 and the authors found a considerable economic burden was pressed on patients and the general population[1]. In addition, the COVID-19 pandemic had a harmful effect on the mental health of people. A system review that identified 5683 unique data sources found that SARS-CoV-2 infection rates were associated with an increased prevalence of major depressive disorder and anxiety disorders[4]. A study in the United Kingdom which includes 3077 adults found the rates of suicidal thoughts were increasing across waves[2]. Another Slovenia study using cross-sectional survey data found positive mental health of the population worsened during the pandemic[3]. Most importantly, deaths caused by the pandemic have approached 7 million according to the statistics of the World Health Organization (WHO). For the healthcare system, during the early pandemic, both hospitalization and intensive care unit (ICU) admissions significantly increased.

On Jan 31, 2020, President Trump first declared a public national health emergency due to COVID-19. This national public health emergency status expired at the end of the day on May 11, 2023. During this three-year period, the United States (US) experienced multiple waves of increased COVID-19 spreading and cases. During the first full autumn-winter season after the declaration of a national public health emergency, the United States experienced a then-record-high rate of new COVID-19 cases, hospitalizations, and ICU admissions. At that time point, wide population COVID-19 vaccination had not been formed and Paxlovid and molnupiravir emergency use authorizations would come a year later. Therefore, the healthcare system in the United States probably encountered a high COVID-19 burden during the autumn-winter season in 2020/2021.

According to the US Centers for Disease Control and Prevention (CDC), there are approximately 1.3 million emergency department visits annually, and about 350000 patients each year need hospitalization due to adverse drug events. The US Food and Drug Administration (FDA) defines adverse events as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. The FDA Office of Surveillance and Epidemiology 2020 Annual Report found there were 2222711 reports received and over 50% were expedited reports. There are some risk factors for adverse drug events, and they include hereditary factors, gender, certain preexisting diseases, pregnancy, older age, and use of several drugs[6][7][8][9][10][11]. However, among adverse drug events, whether there is an association between the healthcare system's high COVID-19 pandemic burden and a deleterious outcome due to adverse drug events remains to be clear.

On May 5 2023 WHO head declared "with great hope" an end to COVID-19 as a public health emergency and one week later the US national public health emergency state was ended. During the 2022/2023 autumn-winter season, new daily COVID-19 cases, hospitalization, and ICU admissions had decreased compared with two years earlier. Based on the chronological change of the COVID-19 pandemic and the availability of online data we think it is possible to make a retrospective analysis about COVID-19 burden and adverse drug reaction. Therefore, in this study, we aim to investigate the association between the healthcare system's COVID-19 burden and the mortality due to adverse drug events during these two autumn-winter seasons using online data publicized by the US FDA.

Methods

We conducted a retrospective cohort study using publicized data from the FDA Adverse Event Reporting System (FAERS). The FAERS quarterly publishes data file summaries of reported cases. The data we extracted were from three tables which store demographic and administrative information, drug information, and patient outcome information, respectively. The quarters of data files we use for analysis include the 4th quarter of 2020 (2020_Q4), the 1st quarter of 2021(2021_Q1), the 4th quarter of 2022(2022_Q4), and the 1st quarter of 2023(2023_Q1). The exposure we aim to investigate is high COVID-19 burdens and the period this exposure occurred was during the 4th quarter 2020 and 1st quarter 2021.

We extracted the information stored in FAERS data file DEMO20Q4.txt, DRUG20Q4.txt, OUTC20Q4.txt, DEMO21Q1.txt, DRUG21Q1.txt, and OUTC21Q1.txt to construct as the exposed cohort and we use data from DEMO22Q4.txt, DRUG22Q4.txt, OUTC22Q4.txt, DEMO23Q1.txt, DRUG23Q1.txt, and OUTC23Q1.txt to construct the unexposed cohort. We match the DEMO table, DRUG table, and OUTC table by table column variables PRIMARYID and CASEID. To derive observations with unique PRIMARYID-CASEID pairs, we filtered out drug records in the DRUG table which have role_cod parameters other than "PS". In the case of duplication with the same PRIMARYID-CASEID but different outcomes in the DEMO table, we only kept one record. Should the records with the same PRIMARYID-CASEID pair have a fatal record, only the record with a fatal outcome was kept. If the same PRIMARYID-CASEID pair has multiple outcome records but no fatal record, only one record was kept based on the alphabet sequence of outcomes abbreviations. The data flow is shown in Figure 1.

The primary outcome is mortality due to adverse drug events recorded in the FAERS. The difference in this mortality between the two autumn-winter seasons is estimated by an odd ratio. We constructed a logistic regression model to estimate the odds ratio and its confidence interval. Covariates contained in the model include gender and age. We did not contain weight in the model because the raw data has many errors that are not possible to rectify. We first made a primary analysis to check the association between COVID-19 burden and mortality. Then, we did a subgroup analysis for the leading 25 drugs in the numbers of reports from the final data we derived from FAERS. These 25 drug in a descending order of numbers of reports are ranitidine(RANITIDI), lenalidomide(LENALIDO), apixaban(APIXABAN), adalimumab(ADALIMUM), tofacitinib(TOFACITI), fentanyl(FENTANYL), rivaroxaban(RIVAROXA), tenofovir(TENOFOVI), acetaminophen(ACETAMIN), oxycodone(OXYCODON), palbociclib(PALBOCIC), pomalidomide(POMALIDO), treprostinil(TREPROST), pimavanserin(PIMAVANS), emtricitabine(EMTRICIT), nivolumab(NIVOLUMA), ibrutinib(IBRUTINI), dupilumab(DUPILUMA), immunoglobulin(HUMAN IM), and clozapine(CLOZAPIN), bamlanivimab(BAMLANIV), pregabalin(PREGABAL), upadacitinib(UPADACIT), insulin (INSULIN), risankizumab(RISANKIZ).

Results

After data verification and pairing, there are a total of 232828 adverse drug effect reports available for analysis. These reports are divided into a high COVID-19 burden group (cohort 1) and a reference COVID-19 (cohort 2) burden group based on the chronical COVID-19 history in the United States, i.e. 2020-2021 autumn-winter season (Cohort 1, n=134342) vs 2022-2023 autumn-winter season (Cohort 2, n=98486). The average age is 58.87 vs 59.27 years, respectively. In Cohort 1 54.29% are females and in Cohort 2 the percentage is 55.32%. The crude mortality in Cohort 1 is 19.80% and in Cohort 2 it is 20.72%. After the adjustment of the confounders age and gender, the OR of high COVID-19 burden is 0.946 (95%CI 0.926-0.965, $p < .0001$).

Later, we did a subgroup analysis based on generic drug names for the 25 leading reported drugs. Of note, bamlanivimab (BAMLANIV) has to be removed from the analysis because it was not available in the 2020/2021 autumn-winter period. The result is shown in Table 1. In combination, these 25 drugs accounted for 43.31% of the 232828 cases reported (n=119867). Among these drugs, the COVID-19 burden related adjusted ORs for fatality were significantly increased for adalimum, clozapin, dupliluma, ibrutini, lenalido, palbocic, pomalido, rivaroxa, and tofaciti. The detailed results are listed in Table 1.

Among these 25 leading drugs, some of them are only indicated for cancers, some are used to treat cancer or non-cancer disease, and some are less likely to be used for cancer treatment. Therefore, we probably can link each adverse drug reaction report and the comorbidity of cancer through the labeled indication of each drug. As a result, we are able to construct the new cofactor of cancer comorbidity and it might be useful for confounder control in the statistic model. We divide these 25 leading reported drugs based on their possibility of being used for cancer into three categories, including group A definitely, group B likely, and group C, less likely. Then, we assigned values for the cofactor of cancer to each observation based on the group the reported drug is within. By default, we treat observations of which reported drug is in group A as suffering cancer, and observations of which reported drug is in group C as non-cancer cases. We treat drugs in group B as either for cancer treatment or not, so we constructed two separate models, one treats group B as being used for cancer (model 1), and the other treats group B as being indicated for non-cancer disease (model 2). After controlling the indication of cancer, both model 1 and model 2 show a significant association between high COVID-19 burden and risk of death among adverse effect reports of these 25 drugs. The complete results for model 1 and model 2 are listed in Table 2. The grouping of the leading reported drugs is shown in Table 3.

Discussion

To our knowledge, there is little research investigating the impact of the COVID-19 pandemic on clinical outcomes of adverse drug reactions. Douros A. et al (2021) did a research about the characteristics of adverse event reporting in the United States FAERS. In their study, they compared the reporting characteristics before and after the COVID-19 outbreak[12]. Another study in Poland by Schetz D. et al investigated adverse drug reaction-reporting behavior of psychotropic drugs [14]. Filippelli A. et al did a study to investigate drug-to-drug interactions leading to adverse clinical outcomes among COVID-19 patients [13]. However, among these studies, we did not find any focus on the impact of COVID-19 burden on mortality related to adverse drug reactions. Therefore, our study which focused on the mortality of adverse drug effects as the primary endpoint might provide evidence from a different perspective.

In this retrospective cohort study, we did not find there was a significant adjusted positive association between high COVID-19 endemic in the United States and reported adverse drug effect mortality, using publicized data from the FAERS database. However, a subgroup analysis for the 25 (Note: Bamlanivimab is removed from the analysis because it is chronically not available to Cohort 1 patients.) leading reported medications during and after the high COVID-19 high burden period found for \sout810 of them there is a significant association between the COVID-19 high burden and the increased risk of adverse drug effect-related death. According to the FDA official drug labels, all of them but rivaroxaban have documented adverse drug reactions related to the compromise of the immune system, including neutropenia, hematologic toxicity, and immunological signal disruption, under which cases patients who take these drugs are prone to serious infections. Among these drugs, adalimumab binds specifically to TNF-alpha and blocks its interaction with TNF receptors and it is used primarily for rheumatoid arthritis and some other autoimmune diseases. Clozapine, lenalidomide, palbociclib, and pomalidomide can cause neutropenia. Tofacitinib and upadacitinib are JAK inhibitors that block the transmission of signals arising from cytokine to influence immune cell function and are primarily indicated for rheumatoid arthritis too. Ibrutinib is an inhibitor of Bruton's tyrosine kinase, which inhibits the signaling of B-cell surface receptors. Finally, dupilumab is a human monoclonal antibody targeting interleukin-4 and interleukin-13 and its treatment can decrease certain biomarkers of inflammation. Therefore, we think the most probable explanation for our observation in the subgroup analysis of the association between high COVID-19 burden and increased adverse drug effect mortality is credited to the disruption or weakening pharmacodynamic effects of these drugs on the immune system of patients. One interesting observation of our analysis is, that among the subgroup who used nivolumab, a PD-1 pathway blockade drug, the high COVID-19 burden was associated with a lower risk of death due to this drug (OR 0.715, 95%CI 0.589-0.869). In addition, another monoclonal antibody Risankizumab that selectively binds to and inhibits interleukin-23 did not show an increased risk of death (OR 1.06, 95%CI 0.676-1.662), which is different from other immune disrupting drugs.

For direct oral anticoagulants, the result is inconsistent. We observed an increased OR of death for rivaroxaban (OR 5.501, 95%CI 3.737-8.099), while another anticoagulant apixaban is associated with decreased OR of fatality (OR 0.834, 95%CI 0.741-0.938). We searched references comparing the safety outcomes of rivaroxaban and apixaban. In a population-based study published in 2022, Hennessy S. et al found apixaban was linked to a lower risk of bleeding compared with rivaroxaban[17]. Another large sample retrospective cohort study conducted by Murray K.T. et al demonstrated a lower risk of major hemorrhagic events for apixaban[19]. However, this study only focuses on patients 65 years or older. Inconsistence also exists, a study conducted by Segal E. et al comparing rivaroxaban and apixaban had mixed results, where rivaroxaban demonstrated a lower rate of intracranial hemorrhage while having a higher risk of gastrointestinal bleeding[18]. Finally, a meta-analysis publicized in 2022 by Mitchell S.A. et al concluded major bleeding was significantly lower with apixaban compared with rivaroxaban[20]. Based on these studies, we attribute the inconsistent result between apixaban and rivaroxaban in our study partially to the safety profile of each drug itself. Therefore, our retrospective analysis indirectly provides data trends supporting a possible safety advantage of apixaban over rivaroxaban during high COVID-19 burden. However, this needs further confirmed by prospective studies.

Among drugs included in our subgroup analysis, clozapine has the highest odd ratio for death during and after the highest COVID-19 burden. Clozapine not only has an adverse reaction of severe neutropenia but also is used to treat schizophrenia. Therefore, those who reported and took clozapine probably suffer from schizophrenia and as a result, this disease might have an additive effect on the mortality. In a large-scale retrospective cohort study, Feingold D. et al found patients with schizophrenia were 3 times more likely to experience COVID-19 mortality[15]. Another nationwide population-based cohort study by Duclos A. et al found hospitalized patients with schizophrenia have an increased 90-day non-COVID-19 mortality compared with controls[16].

However, direct information about comorbidity is lacking from the FAERS online data meanwhile comorbidity probably potentially is an important confounder for our analysis. Therefore, we use the mentioned strategy in the result section to reconstruct a parameter for whether a report is related to cancer treatment. With this tactic, we added the comorbidity of cancer as another confounder in our next analysis and next, we further analyze the relationship between COVID-19 burden and adverse drug effect mortality for reported cases involving the leading 24 drugs. The results of both model 1 and model 2 show high COVID-19 burden retains its negative association with the risk of death due to adverse drug effects when age, gender, and indication for cancer are controlled (Model 1: OR 0.950, 95%CI 0.920-0.982; Model 2: OR 0.932, 95%CI 0.903-0.961).

Although overall the high COVID-19 burden is not associated with a higher risk of death due to adverse drug effects, our subgroup analysis did show for some drugs there indeed is a link between adverse reaction mortality and high COVID-19 burden. Most of these drugs have labeled adverse reactions which disrupt or weaken the immune system of the host. So, our study probably provides preliminary evidence supposing that patients suffering an adverse drug effect involving the immune system from medications are probably at increased risk for deteriorating outcomes during the high pandemic burden period of a serious and contagious disease. This discovery potentially is a warning from the public health perspective for healthcare staff and policymakers that patients on these drugs are more fragile than other patients during a pandemic and need a special migration strategy to lower the danger of bad outcomes.

The strength of our study lies in the fact we used real-world data from the FAERS database for analysis. In addition, the sample size is relatively large. However, there are some limitations of our analysis. First, the confounders we integrated into our regression models only include age, gender, and in later analysis the comorbidity of cancer. There are many other factors linked to mortality for which we don't have control. Second, the many observations in the FDA publicized data have missing data or errors, which resulted in a large number of data removals during our data verification and matching process. Third, when determining whether a drug use links to cancer treatment, cases might exist that the reported drug was not for cancer treatment but the patient actually suffers from cancer, which would introduce mids-categorizing in our

analysis. Nevertheless, our study provides a direction for future research, drug safety surveillance, and maybe clinical practice strategies for the mitigation of adverse drug mortality during future public health crises.

Conclusion

In conclusion, the high COVID-19 burden is negatively associated with increased mortality from adverse drug effects in the United States. Subgroup analysis shows for some drugs there is a link between high COVID-19 burden and increased risk of death due to adverse drug effects. More stringent prospective studies are needed to confirm this observation.

References

1.Richards F, Kodjamanova P, Chen X, et al. Economic Burden of COVID-19: A Systematic Review. *Clin Outcomes Res: CEOR* . 2022;14:293-307. doi:10.2147/ceor.s338225

2.O'Connor RC, Wetherall K, Cleare S, et al. Mental health and well-being during the COVID-19 pandemic: longitudinal analyses of adults in the UK COVID-19 Mental Health & Wellbeing study. *Br J Psychiatry* . 2021;218(6):326-333. doi:10.1192/bjp.2020.212

3.Vinko M, Mikolič P, Roškar S, Klanšček HJ. Positive mental health in Slovenia before and during the COVID-19 pandemic. *Front Public Heal* . 2022;10:963545. doi:10.3389/fpubh.2022.963545

4.Collaborators C 19 MD, Santomauro DF, Herrera AMM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic.*Lancet* . 2021;398(10312):1700-1712. doi:10.1016/s0140-6736(21)02143-7

5.Ohsfeldt RL, Choong CKC, Collam PLM, Abedtash H, Kelton KA, Burge R. Inpatient Hospital Costs for COVID-19 Patients in the United States.*Adv Ther* . 2021;38(11):5557-5595. doi:10.1007/s12325-021-01887-4

6.Jiang J, Tang Q, Feng J, et al. Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: A meta-analysis.*SpringerPlus* . 2016;5(1):1368. doi:10.1186/s40064-016-2912-z

7.Drici MD, Clément N. Is Gender a Risk Factor for Adverse Drug Reactions? *Drug Saf* . 2001;24(8):575-585. doi:10.2165/00002018-200124080-00002

8.O'Mahony D, O'Connor MN, Eustace J, Byrne S, Petrovic M, Gallagher P. The adverse drug reaction risk in older persons (ADRROP) prediction scale: derivation and prospective validation of an ADR risk assessment tool in older multi-morbid patients. *Eur Geriatr Med* . 2018;9(2):191-199. doi:10.1007/s41999-018-0030-x

9.Han Y zhong, Guo Y ming, Xiong P, et al. Age-Associated Risk of Liver-Related Adverse Drug Reactions. *Front Med* . 2022;9:832557. doi:10.3389/fmed.2022.832557

10.Silva KDL da, Fernandes FEM, Pessoa T de L, Lima SIVC, Oliveira AG, Martins RR. Prevalence and profile of adverse drug reactions in high-risk pregnancy: a cohort study. *BMC Pregnancy Childbirth* . 2019;19(1):199. doi:10.1186/s12884-019-2321-8

11.Bassi PU, Osakwe AI, Ogar CK, et al. Impact of comorbidity on adverse drug reaction profile in a cohort of patients treated with Artemisinin combination therapies for uncomplicated malaria in Nigeria.*Pharmacol Res Perspect* . 2017;5(2):e00302. doi:10.1002/prp2.302

12.Dörks M, Jobski K, Hoffmann F, Douros A. Global COVID-19 pandemic and reporting behavior - An analysis of the Food and Drug Administration adverse events reporting system. *Pharmacoepidemiol Drug Saf* . 2021;30(6):707-715. doi:10.1002/pds.5217

13.Conti V, Sellitto C, Torsiello M, et al. Identification of Drug Interaction Adverse Events in Patients With COVID-19. *JAMA Netw Open* . 2022;5(4):e227970. doi:10.1001/jamanetworkopen.2022.7970

14.Schetz D, Scott TE, Waldman W, Anand JS, Wiergowski M, Kocić I. Reports analysis of psychotropic drugs related adverse reactions in Australia and Poland during the COVID 19 pandemic. *Biomed Pharmacother* . 2023;162:114681. doi:10.1016/j.biopha.2023.114681

15.Schetz D, Scott TE, Waldman W, Anand JS, Wiergowski M, Kocić I. Reports analysis of psychotropic drugs related adverse reactions in Australia and Poland during the COVID 19 pandemic. *Biomed Pharmacother* . 2023;162:114681. doi:10.1016/j.biopha.2023.114681

16.Boyer L, Fond G, Pauly V, et al. Impact of the COVID-19 pandemic on non-COVID-19 hospital mortality in patients with schizophrenia: a nationwide population-based cohort study. *Mol Psychiatry* . 2022;27(12):5186-5194. doi:10.1038/s41380-022-01803-4

17.Dawwas GK, Cuker A, Barnes GD, Lewis JD, Hennessy S. Apixaban Versus Rivaroxaban in Patients With Atrial Fibrillation and Valvular Heart Disease: A Population-Based Study. *Ann Intern Med* . 2022;175(11):1506-1514. doi:10.7326/m22-0318

18.Talmor-Barkan Y, Yacovzada NS, Rossman H, et al. Head-to-head efficacy and safety of rivaroxaban, apixaban, and dabigatran in an observational nationwide targeted trial. *Eur Hear J - Cardiovasc Pharmacother* . 2022;9(1):26-37. doi:10.1093/ehjcvp/pvac063

19.Ray WA, Chung CP, Stein CM, et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation. *JAMA* . 2021;326(23):2395-2404. doi:10.1001/jama.2021.21222

20.Mamas MA, Batson S, Pollock KG, et al. Meta-Analysis Comparing Apixaban Versus Rivaroxaban for Management of Patients With Nonvalvular Atrial Fibrillation. *Am J Cardiol* . 2022;166:58-64. doi:10.1016/j.amjcard.2021.11.021

label	mean	lci	uci	n
all	0.946	0.926	0.965	232828
male	0.901	0.875	0.927	105418
female	0.999	0.97	1.03	127410
acetamin	0.514	0.432	0.611	3300
adalimum	2.028	1.617	2.545	7234
apixaban	0.834	0.741	0.938	5611
clozapin	6.173	3.952	9.643	1905
dupliluma	1.963	1.231	3.13	2273
emtricit	1.023	0.591	1.773	3119
fentanyl	0.209	0.158	0.276	3157
human im	0.975	0.681	1.395	2048
ibrutini	1.293	1.079	1.551	2468
insulin	0.425	0.253	0.713	1735
lenalido	1.989	1.776	2.227	9347
nivoluma	0.715	0.589	0.869	1791
oxycodon	0.862	0.659	1.128	2295
palbocic	1.547	1.269	1.887	3297
pimavans	1.142	0.938	1.391	1822
pomalido	2.201	1.828	2.651	2912
pregabal	0.163	0.071	0.373	1967
ranitidi	0.502	0.45	0.559	20957
risankiz	1.06	0.676	1.662	1728
rivaroxa	5.501	3.737	8.099	3830
tenofovi	0.817	0.471	1.416	5150
tofaciti	1.876	1.498	2.35	6730

label	mean	lci	uci	n
treprost	0.664	0.524	0.842	2171
upadacit	2.667	1.632	4.359	1814

Table 1 Subgroup analysis for the risk of death due to adverse drug effects for the 25 most reported drugs based on a logistic regression model between the two seasons. Note: Bamlanivimab is removed from the analysis because it is chronically not available to Cohort 1 patients.

model 1				
factors	**mean**	**lci**	**uci**	**p**
COVID-19 high endemic	0.95	0.92	0.982	0.0021
male	1.42	1.374	1.467	<.0001
age (per year)	0.999	0.998	1	0.0611
Indicated for cancer	4.216	4.076	4.361	<.0001
model 2				
factors	**mean**	**lci**	**uci**	**p**
COVID-19 high endemic	0.932	0.903	0.961	<.0001
male	1.482	1.437	1.529	<.0001
age (per year)	1.012	1.011	1.013	<.0001
Indicated for cancer	0.867	0.833	0.903	<.0001

Table 2 Result of two separate logistic regressions of the 25 leading reported drugs. The estimated odd ratio measures the risk for adverse drug reaction-related mortality for each factor. Factors included in this model include age, gender, whether indicated for cancer, and COVID-19 high endemic. Note: Bamlanivimab is removed from the analysis because it is chronically not available to Cohort 1 patients.

Drug	Group
acetamin	C
adalimum	C
apixaban	B
clozapin	C
dupliluma	C
emtricit	C
fentanyl	B
human im	C
ibrutini	A
insulin	C
lenalido	A
nivoluma	A
oxycodon	B
palbocic	A
pimavans	C
pomalido	A
pregabal	C
ranitidi	C
risankiz	C
rivaroxa	B
tenofovi	C

Drug	Group
tofaciti	C
treprost	C
upadacit	C

Table 3 Grouping the leading reported drugs based on their likelihood of treating cancer.

Hosted file

`image1.emf` available at https://authorea.com/users/697834/articles/685837-subgroup-analysis-shows-high-covid-19-burden-is-associated-with-increased-adverse-drug-effect-related-mortality-in-the-united-states-a-retrospective-cohort-study

Figure 1 The data flow process of this study.

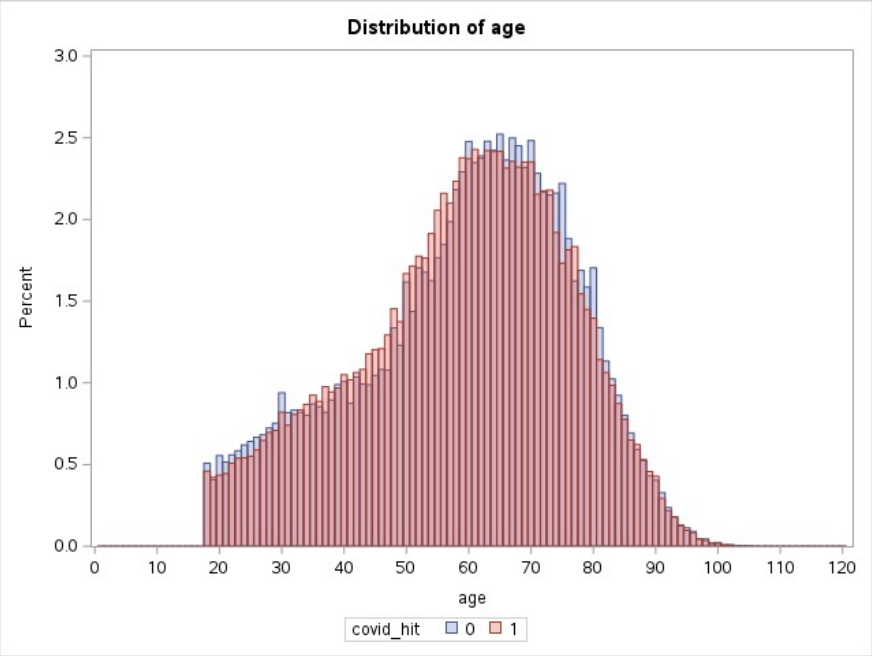

Figure 2 Age distribution of adverse drug effect reports grouped by COVID-19 endemic status. The value of 1 (red) and 0 (blue) of covid_hit means the presence and absence of high COVID-19 endemic in the US, respectively.