

IAI SPECIAL EDITION

RESEARCH ARTICLE

# Analysis of polypharmacy events and drug-drug interaction in COVID-19 therapy

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## Keywords

COVID-19  
Drug interaction  
Polypharmacy

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## Abstract

**Background:** Polypharmacy is the use of five or more types of drugs in a therapy simultaneously. The use of polypharmacy therapy increases the potential for drug-drug interactions. In COVID-19 therapy, the use of varied antiviral and non-antiviral medications allow for increased polypharmacy and potential drug interactions. **Objective:** To determine the relationship between polypharmacy and drug-drug interactions in COVID-19 therapy. **Method:** This is an analytical observational study with retrospective data retrieval using secondary data sources. The sampling technique used purposive sampling with a total of 91 samples. Tracing potential drug interactions was reviewed through the Micromedex 2.0 application and the results obtained were analysed with the Spearman correlation analysis test. **Result:** The results of data obtained from non-polypharmacy events was 3.20% and polypharmacy events was 96.80%. The potential for drug interactions was at the Contraindicated category (3.78%), the Major Category (66.19%), the Moderate category (27.87%) and the Minor category (2.16%). The results from the test showed a very strong positive correlation between polypharmacy and potential drug interactions characterised by a  $p$ -value of 0.0001 and a correlation coefficient of 0.874. **Conclusion:** The higher the increase in polypharmacy, the higher the potential for drug interactions. Handling of drug interactions that occur can be given by giving a pause in the time of drug use, dose adjustment, and drug turnover.

## Introduction

Pharmacological therapies mainly used during the pandemic to manage COVID-19 include antiviral treatment, antibiotic therapy, and adjuvant therapy. Some of the antiviral medicines used include remdesivir, oseltamivir, lopinavir + ritonavir, and favipiravir; The antibiotic therapies used include chloroquine, and azithromycin while adjuvant therapy includes anticoagulants, bronchodilators, corticosteroids, immunomodulators, and NSAIDs (BPOM, 2020; Burhan *et al.*, 2020; Smith *et al.*, 2020). In COVID-19 patients, various use of medications might increase the potential for drug-drug interactions. Inappropriate polypharmacy can be identified by no evidence-based indications, improper indications, too high doses, therapy that is not able to liquefy therapeutic effects, and the occurrence of drug

interaction (Jones *et al.*, 2014). Drug interactions are the effects of two or more drugs interacting negatively and affecting the body's response to treatment. This ultimately leads to increased or decreased effects that can affect the patient's therapeutic outcome (Yasin *et al.*, 2005). Interactions based on severity are divided into major, moderate, and minor interactions. Major interactions have a considerable effect that can endanger lives or result in permanent damage, and moderate interactions can cause changes in the patient's clinical status. At the same time, minor interactions have effects that are not too disruptive so that they do not require additional therapy or can be considered harmless. Based on previous research, research can be carried out to determine the relationship between the incidence of polypharmacy and potential drug interactions in COVID-19 therapy.

**Methods**

This is an analytical observational study with retrospective data retrieval using secondary data sources. Medical data were obtained from one of the West Nusa Tenggara province hospitals in June-November 2021. The sampling technique used purposive sampling based on certain inclusion and exclusion criteria. The Slovin formula was used to calculate the number of samples. Tracing potential drug interactions was reviewed through the Micromedex 2.0 application, and the results obtained were analysed with the Spearman correlation analysis test using SPSS 24. This study has fulfilled the Ethical eligibility with Number 29/EC-04/FK-06/UNIZAR/V/2022.

**Results**

**Demographic data**

The study’s results, as depicted in Table I, showed that, in terms of gender, the demographic data of male patients were more exposed to COVID-19, i.e., 54.9% compared to the female ones by 45.1%. The most common age range was found in the age of 26 to 35 years, i.e. 23.1%. The lowest age was in the range of 0 to 5 years and 6 to 11 years, giving a percentage of 1.1%. COVID-19 patients had a length of treatment that varied between 1 to 21 days. In this study, patients had the most length of therapy for nine days, i.e. 12.1%. At the same time, the least was for 15, 17, and 21 days, i.e., 1.1%.

**Drug class and types of drugs**

The most administered class of medications given were multivitamins (13.6%), antibiotics (11.4%), supplements (9.2%), mucolytics (7.5%), antivirals (7.2%), antipyretics (4.8%), anticoagulants (4.6%), corticosteroids (4.3%), non-steroidal anti-inflammatory agents (4.3%) and proton pump inhibitors (3.5%). Other classes of drugs were spread across the adjuvant therapies that are adapted to the patient's condition, which include medications like vitamin C (6.2%), vitamin D (6.1%), Acetylcysteine (5.7%), Zinc (5.5%), Paracetamol (4.8%), Favipiravir (2.8%), Azithromycin (2.8%), Remdesivir (2.7%) and Methylprednisolone (2.5%).

**Polypharmacy events and drug interactions**

The various COVID-19 therapies increased polypharmacy in patients. This can be seen in Table II, presenting the data on the number of drugs obtained by patients. There was 96.70% of the patients obtained more than five medications, and 3.30% of the patients obtained less than five medications.

**Table I: Demographic data**

Gender	Frequency	%
Male	50	54,9
Female	41	45,1
Age range (years)	Frequency	%
0-5	1	1.1
6-11	1	1.1
17-25	15	16.5
26-35	21	23.1
36-45	11	12.1
46-55	14	15.4
56-65	11	12.1
>65	17	18.7
Length of care	Number of days	%
1.0	5	5.5
2.0	8	8.8
3.0	9	9.9
4.0	4	4.4
5.0	6	6.6
6.0	6	6.6
7.0	10	11.0
8.0	4	4.4
9.0	11	12.1
10.0	4	4.4
11.0	9	9.9
12.0	8	8.8
13.0	2	2.2
15.0	1	1.1
16.0	2	2.2
17.0	1	1.1
21.0	1	1.1
Number of drugs	Frequency	%
3.0	2	2.2
5.0	1	1.1
6.0	2	2.2
7.0	1	1.1
8.0	7	7.7
9.0	7	7.7
10.0	5	5.5
11.0	6	6.6
12.0	6	6.6
13.0	11	12.1
14.0	2	2.2
15.0	5	5.5
16.0	3	3.3
17.0	3	3.3
18.0	7	7.7
19.0	3	3.3
20.0	5	5.5
21.0	3	3.3
22.0	3	3.3
23.0	2	2.2
24.0	3	3.3
25.0	3	3.3
29.0	1	1.1
<b>Total</b>	<b>91</b>	<b>100.0</b>

Multivitamins became the most widely administered class of medicine by 13.6%, with Vitamin C as the most prominent with a percentage of 6.2%. The more the number of drugs, the higher the risk of drug-drug interactions, representing 45.14%. Drug interactions in this study were divided into several categories, as seen in Table II. The drug interaction category is divided into the categories of contraindications (3.78%), major (66.19%), moderate (27.87%), and minor (2.16%). Data shows that the highest potential for drug interactions was seen in levofloxacin and zinc, with 42 cases of the moderate category, levofloxacin and methylprednisolone with 27 points of the major

category, azithromycin, and ondansetron, with 15 cases of the major category, ondansetron and tramadol with 12 instances of minor categories. Dexamethasone and ketorolac, fentanyl and ondansetron, fentanyl and tramadol had 11 cases of substantial categories; dexamethasone had the potential to cause drug interaction with fentanyl and tramadol with the same number of ten cases of considerable category. Levofloxacin and ondansetron with nine cases of major category. Some drugs intersected with other drugs with lower and diverse cases.

**Table II: Polypharmacy events and drug interactions**

Number of drugs	Number of patients	%	Polypharmacy events	Drug interactions	%
<5	3	3.30	Non-Polypharmacy	0	0
5-10	22	24.2	Polypharmacy	28	5.03
11-15	30	33.0	Polypharmacy	83	14.92
16-20	21	23.1	Polypharmacy	194	34.89
>20	15	16.5	Polypharmacy	251	45.14
<b>Total</b>	<b>91</b>	<b>100</b>		<b>556</b>	<b>100</b>

**Correlation analysis testing**

Analytical testing between patients’ treatment length and the number of drugs aimed to determine the relationship between the two variables. The test was carried out using the Shapiro-Wilk normality test, which obtained some significant results for the duration of treatment of 0.083 ( $p < 0.10$ ), so it can be estimated that the data were normally distributed. The significant value for the number of drugs obtained was 0.006 ( $p < 0.10$ ), so it can be estimated that the data was not normally distributed. The next test used the Spearman Correlation Analysis Non-Parametric Test, which obtained a significant result of 0.456 ( $p > 0.10$ ) with a correlation coefficient of 0.079. Thus, it could be stated that the two variables were uncorrelated.

Testing the relationship between the incidence of polypharmacy and potential drug interactions was conducted using the Shapiro-Wilk Normality Test with a significance of 0.083 ( $p < 0.10$ ). Then, it can be stated that the distributed data were normal. Meanwhile, the significance of drug interactions is  $p < 0,001$ , indicating that the distributed data were abnormal. Correlation analysis testing using the Spearman correlation analysis test showed a significant  $p < 0.001$  with a correlation coefficient of 0.874. Thus, it can be stated that there was a robust correlation with the direction of the positive correlation between the two variables.

**Discussion**

This study showed a higher number of male patients than women. The difference in the incidence rate based on gender implies that women have a heightened concern for environmental conditions compared to men. Also, women had more leisure time than men, so they had more time to discuss and read about how to prevent exposure to COVID-19 (Wulandari et al., 2020). The age range was between 26 to 35 years old. This is in line with previous studies by Elviani and colleagues (Elviani et al., 2021) suggesting that patients aged 26 to 36 had higher productivity, so the possibility of exposure to COVID-19 was more significant in this age range than in other age ranges. This is influenced by high morbidity and activities outside the home. The frequency of social interactions is normally high in the productive age range. Another age range with a high number of cases of exposure to COVID-19 was the elderly, i.e., over 65 years old. Patients over 60 years experience a decrease in tissue and organ function; hence they are easily exposed to infections. Decreased immunity and reduced elasticity of the lung tissue cause an increased risk of comorbidities, exposing them to COVID-19 infection (Ernawati, 2021). Other age ranges had a lower exposure risk than productive and old age.

In this study, non-polypharmacy therapy was 3.20%, and polypharmacy therapy was 96.80%. Polypharmacy

therapies increase the chances of drug-drug interactions more than non-polypharmacy therapies. The tremendous potential for drug interactions is found in polypharmacy therapy, with the number of drugs more than 20 types of drugs, which is 45.14%.

The administration of drugs to patients is influenced by several factors, including consideration of benefits and risks, the use of more effective and clinically tested drugs, adjustment of medications to patient needs, and selection of the safest way of administering drugs (Junaidi, 2021). The most widely used multivitamin was vitamin C. The major mechanism of action of vitamin C, among others, includes reducing oxidative stress, improving neutrophilic function, and accelerating the improvement in patients exposed to COVID-19 disease (Adondis et al., 2019; Simanjuntak et al., 2020; Suryaningsih et al., 2021). A higher amount of vitamin C given to the patients will definitely increase their quality of life of patients. Administering high doses of vitamin C can ward off exposure and accelerate the healing of COVID-19 patients.

Use of vitamin C in tablet preparations is given a dosage of up to 1000mg at a dose of 500mg, twice a day with one tablet, while for intravenous administration, it is given at a dose of 100 mg, i.e., once in 1 day. This therapy is provided for 14 days or during recovery (Simanjuntak et al., 2020). Another multivitamin that is highly used in COVID-19 patients is vitamin D, which plays a role in calcium homeostasis and bone metabolism and reduces inflammatory processes. Calcitriol is an active form of vitamin D that regulates innate and adaptive immune responses, such as modulating the expression of cytokines and chemokines (Anggiswari et al., 2021).

Patients on more medications have a higher potential for drug interactions (Kusumawardani et al., 2021). Previous studies stated that the incidence of drug interactions with a higher potential for drug interactions occurred in patients with polypharmacy therapy (Yuniar et al., 2022). The highest potential for drug interactions includes levofloxacin and zinc, and there are 42 cases in the moderate category. The effect of this drug interaction is a decrease in levofloxacin activity. Zinc has a higher affinity for Calf-thymus DNA (CT DNA) than levofloxacin, so it can reduce levofloxacin activity (Psomas & Kessissoglou, 2013). The use of multivitamins or supplements such as aluminium, magnesium, calcium, and zinc can influence the use of levofloxacin. Levofloxacin and metals can form chelates that occur due to the presence of insoluble and absorbable multivalent cations. This interaction can potentially decrease levofloxacin's effectiveness (Sultana et al., 2004).

Levofloxacin increases the risk of Achilles tendon rupture. This risk is increased by corticosteroids (Bartlett, 2004; Wise et al., 2012). Other drug interactions include azithromycin and ondansetron, with interactions causing QTC prolongation (Nachimuthu et al., 2012; Tisdale et al., 2013; Moffett et al., 2016). Co-administration of ondansetron and tramadol has a drug interaction effect in the form of cytokine syndrome severity (Beakley et al., 2015). Concomitant use of immunosuppressants can decrease the effectiveness of fentanyl. This is due to the inhibition of CYP3A4 by immunosuppressants (Kitazawa et al., 2017). Co-administration of dexamethasone and tramadol decreases tramadol metabolism. Tramadol is a CYP3A4 substrate, in which its use in conjunction with CYP3A4 inhibitors can increase plasma concentrations to increase the side effects of drugs. The inhibition of metabolic pathways will increase metabolism in CYP2D6, which results in a more potent active metabolite of tramadol. Levofloxacin and ondansetron have a moderate QTC elongation effect, so if the two drugs are combined, it will cause an interval prolongation, which is a risk factor for the occurrence of ventricular arrhythmias (Tisdale et al., 2013). The results of the Spearman correlation test analysis conducted to see the relationship between polypharmacy events and potential drug interactions resulted in a p-value<0,001 with a correlation efficiency of 0.874. It can be concluded that there is a correlation between the incidence of polypharmacy and the potential for drug interactions in the therapy of COVID-19 patients with a robust, strong correlation relationship, and the direction of the relationship is positive.

## Conclusion

The increased polypharmacy in COVID-19 therapies likely increases the potential for drug-drug interactions. The highest potential for drug interactions in levofloxacin and zinc with moderate categories may lead to a decrease in the effectiveness of levofloxacin. Levofloxacin and methylprednisolone with significant types can cause an increase in tendon rupture. Azithromycin and ondansetron with major categories can cause QTC prolongation. Handling of drug interactions that occur can be given by giving a pause in the time of drug use, dose adjustment, and drug turnover.

## Acknowledgement

This article was presented at the 2022 Annual Scientific Conference of the Indonesian Pharmacist Association. The authors thank all of the subjects for participating in this study.

## Source of funding

Internal Grants of the University of Muhammadiyah Mataram and RisetMu Research Grants Batch VI.

## References

- Adondis, J., Mongi, J., Tiwow, G. A. R., & Palandi, R. R. (2019). Study of potential drug interactions in heart failure patients in the inpatient installation of Manado Adventist Hospital. *Tropical Biopharmaceuticals*, *2*(2), 124–135. <https://doi.org/10.55724/ibiofartrop.v2i2.125>
- Anggiswari, K., Angela, P., & Sutarka, I. N. (2021). The Role of Vitamin D Immunomodulating Effects on COVID-19 Management. *10*(2), 927–933
- Bartlett, J. G. (2004). Global susceptibility patterns for 21 commonly utilized antimicrobial agents tested against 48,440 Enterobacteriaceae in the SENTRY antimicrobial surveillance program (1997-2001). *Infectious Diseases in Clinical Practice*, *12*(2), 142–143. <https://doi.org/10.1097/01.idc.0000121033.62151.b2>
- Beakley, B. D., Kaye, A. M., & Kaye, A. D. (2015). Tramadol, pharmacology, side effects, and serotonin syndrome: A review. *Pain Physician*, *18*(4), 395–400. <https://doi.org/10.36076/ppj.2015/18/395>
- B POM. (2020). COVID-19 Drug Informatorium in Indonesia
- Burhan, E., Susanto, A. D., Nasution, S. A., Ginanjar, E., Pitoyo, C. W., Susilo, A., Firdaus, I., Santoso, A., Juzar, D. A., Arif, S. K., Wulung, N. G. H. L., Damayanti, T., Wiyono, W. H., Prasenhadi, Afiatin, Wahyudi, E. R., Tarigan, T. J. E., Hidayat, R., Muchtar, F., & IDAI, T. C.-19. (2020). COVID-19 Confirmed Patient Management Protocol
- Elviani, R., Anwar, C., & Januar Sitorus, R. (2021). Overview of age at the incidence of COVID-19. *Journal of Medicine and Health*, *9*(1), 204–209. <https://doi.org/10.22437/jmi.v9i1.11263>
- Emyr Jones, Bevan, A., & Pugh-Jone, J. (2014). Polypharmacy : Guidance for Prescribing. All Wales Medicines Strategy Group, July, 1–36. [http://ukclinicalpharmacy.org/wp-content/uploads/2017/07/All\\_Wales\\_Medicines\\_Strategy\\_Group\\_Polypharmacy\\_Guidance\\_for\\_prescribing\\_2014.pdf](http://ukclinicalpharmacy.org/wp-content/uploads/2017/07/All_Wales_Medicines_Strategy_Group_Polypharmacy_Guidance_for_prescribing_2014.pdf)
- Ernawati, A. (2021). Overview of COVID - 19 Cases by Gender, Age Group, and Population Density in Pati Regency. Litbang Journal: Media Information Research, *Development and IPTEK*, *17*(2), 131–146
- Kitazawa, F., Fuchida, S. I., Kado, Y., Ueda, K., Kokufu, T., Okano, A., Hatsuse, M., Murakami, S., Nakayama, Y., Takara, K., & Shimazaki, C. (2017). Pharmacokinetic interaction between tacrolimus and fentanyl in patients receiving allogeneic hematopoietic stem cell transplantation. *Annals of Transplantation*, *22*, 575–580. <https://doi.org/10.12659/AOT.904505>
- Moffett, P. M., Cartwright, L., Grossart, E. A., O’Keefe, D., & Kang, C. S. (2016). Intravenous ondansetron and the qt interval in adult emergency department patients: An observational study. *Academic Emergency Medicine*, *23*(1), 102–105. <https://doi.org/10.1111/acem.12836>
- Nachimuthu, S., Assar, M. D., & Schussler, J. M. (2012). Drug-induced QT interval prolongation: Mechanisms and clinical management. *Therapeutic Advances in Drug Safety*, *3*(5), 241–253. <https://doi.org/10.1177/2042098612454283>
- Psomas, G., & Kessissoglou, D. P. (2013). Quinolones and non-steroidal anti-inflammatory drugs interacting with copper(ii), nickel(ii), cobalt(ii) and zinc(ii): Structural features, biological evaluation and perspectives. *Dalton Transactions*, *42*(18), 6252–6276. <https://doi.org/10.1039/c3dt50268f>
- Putra, A. M. P., Wasiaturrahmah, Y., Rahmah, N., & Nahdha. (2021). Potential drug interactions in COVID-19 patients in one of the hospitals in South Kalimantan province. *Pharmaceutical and Pharmacology Magazine*, *25*(3), 94–97. <https://doi.org/10.20956/mff.v25i3.18238>
- Shakir Mahmood Alwan. (2022). Al-Akidi Therapeutic Protocol for Severe Infections Associated with COVID-19: Potential and Effective Treatment by Levofloxacin and Vitamin D3 and Zinc (Part 1). *Journal of Pharmacy and Pharmacology*, *10*(4), 105–118. <https://doi.org/10.17265/2328-2150/2022.04.001>
- Simanjuntak, N., Tewu, Y. S. T., & Makawimbang, R. (2020). Suitability of Vitamin C and Antiviral Pharmacological Therapy Management for Moderate Category COVID Patients at Bitung Regional General Hospital, North Sulawesi Province. *Indonesian Journal of Pharmaceutical Science and Technology*, *X*(1), 61–74
- Smith, T., Bushek, J., Leclair, A., & Prosser, T. (2020). COVID-19 Drug Therapy What’s been updated : Highlights : Elsevier
- Sultana, N., Arayne, M. S., & Sharif, S. (2004). Levofloxacin interactions with essential and trace elements. *Pakistan Journal of Pharmaceutical Sciences*, *17*(2), 67–76. <http://www.ncbi.nlm.nih.gov/pubmed/16414598>
- Suryaningsih, N. P. A., Reganata, G. P., Sutema, I. A. M. P., & Putri, D. W. B. (2021). Rationality in Vitamin C Self-medication during the Covid-19 Pandemic in Denpasar City. *Bali Medika Journal*, *8*(2), 180–190
- Tisdale, J. E., Jaynes, H. A., Kingery, J. R., Mourad, N. A., Trujillo, T. N., Overholser, B. R., & Kovacs, R. J. (2013). Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circulation: Cardiovascular Quality and Outcomes*, *6*(4), 479–487. <https://doi.org/10.1161/CIRCOUTCOMES.113.000152>
- Wise, B. L., Peloquin, C., Choi, H., Lane, N. E., & Zhang, Y. (2012). Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *American Journal of*

*Medicine*, **125**(12), 1228.e23-1228.e28.  
<https://doi.org/10.1016/j.amjmed.2012.05.027>

Wulandari, A., & dkk. (2020). The relationship between individual characteristics and knowledge about the prevention of Coronavirus Disease 2019 in the community in Pungging Mojokerto District. *Indonesian Journal of Public Health*, **15**(1), 42–46. <https://doi.org/10.52646/snj.v4i1.97>

Yasin, T., Ahmed, S., Ahmed, M., & Yoshii, F. (2005). Effect of concentration of polyfunctional monomers on physical properties of acrylonitrile-butadiene rubber under electron-

beam irradiation. *Radiation Physics and Chemistry*, **73**(3), 155–158.  
<https://doi.org/10.1016/j.radphyschem.2004.07.009>

Yuniar, Y., Ramadhiani, A. R., Asyifa, D., Ade Putri, W. K., & Apriliana, W. S. (2022) Potential Drug Interactions in Confirmed COVID-19 Patients with Comorbidities in the Ogan Ward of Dr. Mohammad Hoesin Hospital Palembang for the April-June 2021 period. *Farmaseutics Magazine*, **18**(1), 43.  
<https://doi.org/10.22146/farmaseutik.v18i1.71910>