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Polypharmacy and the occurence of potential drug interactions in geriatric Covid-19 patients in Karawang General Regional Hospital, Indonesia

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ABSTRACT: The management of COVID-19 treatment continues to evolve by involving various types of drugs both symptomatic and supportive therapy. COVID-19 infection with comorbid conditions in geriatric patients can have an effect on increasing drug use and the potential for drug interactions. The purpose of the study was to determine whether there is a relationship between the level of polypharmacy and the incidence of potential drug interactions at Karawang Regency Hospital for the period January to December 2021. The research method used was a cross-sectional study design. The data collected was hospital secondary data with retrospective data type and statistical analysis using Spearman Rho. The research material used was medical record data from 182 samples using the total sampling method. Based on the results of the study, it was found that as many as 108 (59.3%) patients received treatment with a total of 5-9 types of drugs. Potential drug interactions were experienced by 148 (81.3%) patients with a total of 764 events. There is a relationship between the level of polypharmacy and the potential incidence of drug interactions (r: 0.537, p: <0.001).

KEYWORDS: COVID-19; drug interactions; geriatric; polypharmacy.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a new type of coronavirus that can cause severe respiratory infections. The Corona Virus Disease (COVID-19) pandemic has paralysed the global health sector due to the uncontrollable spread of the disease [1]. Indonesia ranks fourteenth and is the country with the highest confirmed cases in the Southeast Asia region [2]. As of 31 December 2021, there were 4.2 million confirmed cases, the percentage of death cases nationally was 3.0% with the highest death rate in patients aged ≥60 years [3].

Indonesian government determines that if a person is ≥60 years old, they are categorised as elderly [4]. The decline in overall function causes elderly people to experience multi-pathological conditions and if infected with COVID-19, the risk of death is higher. Comorbid factors and clinical conditions caused by COVID-19 infection make the elderly vulnerable to polypharmacy treatment.

The simultaneous use of five or more drugs by a patient including the use of OTC (Over The Counter) drugs, herbs and complementary drugs such as vitamins and minerals can be a general definition of polypharmacy [5-7]. Polypharmacy can cause new problems in elderly patients, because the more drugs used, the greater the risk of DRP's (Drug Related Problems) such as side effects and drug interactions.

Drug interactions are when two or more drugs administered at the same time can have their own effects or interact with each other. These interactions may potentiate or antagonise one drug by another, or may sometimes have other effects [6]. Generally, there are two mechanisms of drug interactions, namely pharmacodynamic and pharmacokinetic. Pharmacodynamic drug interactions are through pharmacological effects on the same site of action or receptor by each drug that are synergistic or antagonistic and pharmacokinetic mechanisms of interaction involve the stages of absorption, distribution, metabolism and excretion [7].

The severity of interactions can be classified into three levels: minor, moderate and major. Minor if the interaction is likely to occur in the patient due to negligence. Moderate category if the interaction occurs in the patient and monitoring should be done. The effect of a moderate interaction may cause a change in the patient's

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clinical status, lead to additional treatment or a longer hospital stay. An interaction is categorised as major severity if the interaction endangers the patient including the patient's life and damage/disability may occur [8].

There were 78% drug interaction cases (259 cases) of elderly patients with metabolic diseases that occurred in the outpatient department of the Haji Adam Malik Medan Central General Hospital in 2015. The 500 drug interactions identified included pharmacodynamic interactions (22.8%), pharmacokinetic interactions (63.6%) and unknown interactions (13.6%). The severity of interactions that occurred were major (6.8%), moderate (69.8%) and minor (23.4%) [8]. Based on the above, the aim of the research is to find out whether there is a relationship between the level of polypharmacy and the incidence of potential drug interactions in the Karawang District Hospital for the period January - December 2021.

▪ MATERIALS AND METHODS

Materials

The materials used in this study were medical record data for geriatric patients with confirmed COVID-19 who were admitted to the isolation room who received 5 or more than 5 (polypharmacy) medications during treatment of the Karawang Regency General Hospital from January to December 2021.

Study design

This research has obtained a research ethics permit from the Palembang Health Polytechnic number 0008/KEPK/adm2/I/2022. Study design cross-sectional observation study. The data collected was hospital secondary data with retrospective data type. The source of research data was secondary data from medical records in the medical facility and other supporting data from the pharmacy. The data were processed using SPSS to provide conclusions using descriptive statistical tests and Spearman's Rho correlation tests.

Sample criteria

The samples in this study were geriatric patients with confirmed COVID-19 from medical records, with inclusion and exclusion criteria. Inclusion criteria: Patients with age ≥60 years, confirmed COVID-19 patients as indicated by the results of antigen swab or PCR and treated in the isolation room of Karawang Regional Hospital, COVID-19 geriatric patients with polypharmacy treatment. Exclusion criteria: Incomplete patient data in the medical records.

Data collection

The study was designed to identify geriatric patients with confirmed COVID-19 in the isolation ward based on their treatment and clinical outcomes. The data were entered into the data collection form. The tabular summary includes Patient demographic and clinical data (name, age, gender, reported symptoms related to patients with COVID-19, comorbidities). Treatment profile data including drug name, number of drugs, drug dosage and identification of polypharmacy and drug interactions; Drug interactions in COVID-19 geriatric patients were analysed using Drugs.com or covid19-druginteractions.org. Data were grouped and then percentages calculated based on type of interaction mechanism and severity. The drug interaction classification in this study was obtained directly from the platform used. clinical outcome, treatment duration and post-treatment status (recovery or death); data collected per patient who met inclusion criteria at Karawang Regency Regional General Hospital.

Statistical analysis

The statistical analysis performed in this study was descriptive quantitative and correlation analysis using Spearman's Rho test for correlation drug interaction with polypharmacy, lenght of stay and commorbidities. Spearman Rho is used for correlation, with non-parametric data types. The data presented are in the form of frequency distribution, percent and strength and direction of correlation based on medical record data from Karawang Regional Hospital.

RESULTS

Patient characteristics

The total number of geriatric patients diagnosed with COVID-19 based on population data obtained from the Karawang Regional Hospital Medical Records Installation in 2021 was 315 patients. Samples were collected using a total sampling technique where there were 182 patients who met the inclusion and exclusion criteria. The samples included in the exclusion criteria were due to patients who died, referred patients, non-polypharmacy patients, patients with incomplete medical record data with a total of 133 patients. Data collected included gender, age, COVID-19 level, type of comorbidity, number of comorbidities and length of stay. These are shown in Table 1 below.

Table 1. Patient characteristics.

Patient Characteristics	n (patients)	%
Gender		
Male	95	52.2
Female	87	47.8
COVID-19 Severity level		
Medium	150	82.42
Severe	32	17.58
Length of Stay (day)		
1-14	168	92.3
> 14	14	7.7
Comorbidities		
Hypertension	67	36.81
Diabetes mellitus	60	32.97
Chronic Kidney disease	38	20.88
Heart disease	26	14.29
Stroke	9	4.95
Others	17	9.34

Treatment profile overview

COVID-19 geriatric patients suffering from multiple pathologies are certainly at risk in terms of treatment, in particular the risk of polypharmacy. One of the effects of polypharmacy is the potential for adverse drug interactions, which can be harmful to patients. In this trial, drugs that are a combination of several types of drugs were tested. Table 2 describes the number of drugs used.

Table 2. Overview of polypharmacy and use of COVID-19 drugs.

Drugs quantity	n (patients)	%
5-9	108	59.34
≥ 10	74	40.66

Characteristics of drug interactions in patients

The results showed that 148 patients (81.3%) in the sample experienced potential drug interactions during treatment at Karawang Regional Hospital. Based on this number, it is known that patients who have the potential to experience drug interactions have at least 1 to at most 35 pairs of drugs that interaction with each other. In the table 3, total incidence of potential drug interactions was 764 events with minor (9.33%), moderate (71.34%), major (9.95%) and unknown (9.16%) interaction levels.

Table 3. Overview of potential drug ınteractions.

Category	Ammount	%
Number of drug interactions (n = 182)		
0	34	18.68
1-2	58	31.87
3-4	43	23.63
≥5	47	25.82
Severity of drug interaction (n = 764)		
Unknown	70	9.16
Minor	73	9.55
Moderate	545	71.34
Mayor	76	9.95
Type of drug interaction (n = 764)		
Pharmacodynamics	457	59.82
Pharmacokinetics	284	37.17
Unknown	23	3.01

Analysis of the correlation polypharmacy levels and potential drug interactions

In this study, an analysis was conducted to determine whether there is a significant relationship between polypharmacy and potential drug interactions. Researchers will also compare other factors such as the number of comorbidities and length of stay to the potential for drug interactions in COVID-19 geriatric patients at Karawang Regency Hospital. It is known that the type of measurement scale in each variable is ordinal and the results of the normality test show an abnormal distribution of data, so based on these provisions, the analysis is carried out using the Spearman's Rho correlation test. The results of the correlation test can be observed based on table 4.

Number of drug interactions	R	Sig. (p-value)
Polypharmacy	0.537	< 0.001*
Lenght of stay	0.236	0.001*
Comorbidities number	0.053	0.481

Notes: r = correlation value korelasi based on *Spearman's rho*; p = signifikansi; *highly significant correlation (p<0.05)

▪ DISCUSSION

Based on table 1, it is known that the number of male patients is 95 patients (52.2%) more than the number of female patients, namely 87 patients (47.8%). The results of this study are in accordance with previous research conducted by Cantudo-Cuenca et al, namely from the total patients analyzed (n = 174) it is known that the number of male patients (50.6%) is more than female patients [9]. Zulkarnaini et al. also stated in their study that there were 360 (58.25%) male patients who were known to be more than female patients (41.75%) [10]. The results of the study are also in accordance with the data issued by the Karawang Regency COVID-19 task force, namely the number of positive confirmations of male patients (57.80%) more than female patients (42.20%) [11]. Population data based on gender from the Karawang Regional Statistics Agency in 2020 shows that the male population is more than female [12]. As for other factors based on previous studies published by Chang, women have better immunity than men, so in general, in several studies on COVID-19, men are more infected [13]. Lifestyle and concern for health are also supporting factors why men are more infected with COVID-19 than women [14].

The number of co-morbidities per patient also varies, from none comorbidities to 5 different types of comorbidities. Based on the sample obtained, 72 patients (40.1%) suffered from one type of comorbidity. The results of this study are in line with the research conducted by Karya, et al, at Bhayangkara Denpasar Hospital, namely hypertension comorbidities were found in 33 patients (21.57%), where hypertension was the comorbidity most suffered by patients, followed by diabetes mellitus, chronic kidney disease and heart disease. According to the theory, hypertension causes a weakening of the immune system, and the use of antihypertensive medication, in particular ACE-I, is one of the factors that increase susceptibility to COVID-19 infection [15].

This event is connected to research into how the COVID-19 virus binds to the angiotensin converting enzyme-2 (ACE-2) receptor when infecting humans. People with hypertension and ACE-i use may have increased expression of ACE-2 receptors, increasing the risk of infection. Diabetes mellitus also has an influence on increasing COVID-19 infection by reducing the ability of phagocytic cells. Diabetes mellitus patients have higher levels of furin expression compared to normal people; furin is a type 1 membrane-bound protease that can act as a viral activator after binding to the ACE-2 receptor, so the increase in lung inflammation is higher [15].

Medical record data also showed the clinical condition of geriatric COVID-19 patients, with more patients showing moderate clinical grades (82.42%), the main symptoms being cough, breathlessness and fever. This is consistent with research by Chang and Karya, et al, that more than 80% of COVID-19 patients showed moderate symptoms with the most common symptoms being shortness of breath, fever and cough [12-15]. The length of stay for geriatric COVID-19 patients in this research sample was categorised into two groups, namely 1-14 days and ≥14 days. A total of 168 patients (92.3%) were treated for 1-14 days with an average stay of 10-11 days. Rahmatillah et al. also found in their study that 52 patients (72.22%) isolated in hospitals in Jakarta were treated for a maximum of 1-14 days with an average of 12.5 days. The length of stay for geriatric COVID-19 patients is influenced by various aspects such as the time difference between exposure to the virus and the onset of symptoms, the time the patient is admitted to hospital, and various other specific aspects. Obviously, individual responses and disease patterns within a locality or country will vary and may influence the length of hospital stay [16].

The level of polypharmacy analysed was a minimum of 5 drugs and a maximum of 17 drugs received by patients during treatment, based on 182 samples. It is known that 108 patients (59.34%) were treated with 5-9 drugs and 74 patients (40.66%) were treated with ≥ 10 drugs. The results of this study are in line with two studies on polypharmacy and excessive polypharmacy by Jyrkka et al. and O'Dyner et al. who found that more than 60% were treated with 5-9 drugs. This number is higher compared to patients taking ≥ 10 drugs. This study found that the factors closely associated with the high number of drugs used were the clinical conditions and comorbidities of the patient [17-18].

The use of high doses of medication in older people with COVID-19 is, of course, strongly related to their clinical status at the time of treatment and to their medical history. The patients in this study had an average COVID-19 condition with moderate clinical severity, such that patients did not require additional medications such as corticosteroids according to the COVID-19 management guidelines. In addition, the patient's medical history shows that most patients have only one type of comorbid condition and therefore have little need for additional medication [19].

Geriatric COVID-19 patients will receive drug therapy based on the symptoms and clinical severity experienced when infected with COVID-19, as described in the COVID-19 Management Guidelines. The treatment profile of the study consists of two categories, namely COVID-19 and non-COVID-19 treatment. Treatment for COVID-19 in patients isolated at RSUD consists of antivirals, antibiotics, vitamins, anticoagulants and immunomodulators. The most common antiviral used in COVID-19 therapy in this study was favipiravir, used in 123 patients (67.58%). The results of this study are in line with research by Suryanti et al. that 254 patients (90.54%) at Murjani-Sampit Regional Hospital received antiviral treatment with favipravir compared to the use of remdesivir and oseltamivir. The use of favipiravir is classified as high because more patients have moderate clinical conditions [20]. Favipiravir in its active form has a role in inhibiting the viral RNA-dependent RNA polymerase (RdRp) enzyme so that it can stop the COVID-19 virus replicating in the body [21].

The antibiotic azithromycin was used as a single or combination treatment to treat COVID-19 infection in 73.08% of the total sample. According to research conducted by several experts in the treatment of COVID-19, azithromycin is a macrolide antibiotic that also has an immunodulatory function that is effective in controlling cytokine production, preserving lung epithelial cells and protecting ventilatory function, so its use in combination with COVID-19 treatment is believed to be beneficial. [21]. The most common antibiotic used for prophylaxis and treatment of pneumonia in geriatric COVID-19 patients is levofloxacin (36.81%), with levofloxacin being the first-line treatment for pneumonia due to COVID-19 infection as indicated by radiological findings. Hospitalised COVID-19 patients are prone to co-infections with pathogenic microbes such as S. pneumoniae. This condition is caused by respiratory problems due to inflammation of the lung

lining and impaired immunity in COVID-19 patients [22]. Research conducted by Alwan found that the use of levofloxacin also has potential as an antiviral agent, so its use can increase the effectiveness of therapy and reduce the cost of patient care [22].

The use of vitamin C and vitamin D in geriatric COVID-19 patients has great potential to reduce the impact of coronavirus infection. In addition to its primary role as an immunomodulator, observational studies have shown that vitamin D deficiency increases the risk of respiratory viral infections. Vitamin D may reduce the risk of infection by several mechanisms, such as the induction of cathelicidins and defensins, which can interfere with the rate of viral replication and reduce the concentration of pro-inflammatory cytokines. Fahmi et al showed that after treatment of COVID-19 with vitamin C, the levels of D-dimer and ferritin in patients could be significantly reduced. There are no side effects directly related to vitamin C, so it is considered safe to use in patients with moderate to severe clinical conditions [21].

The use of corticosteroids in geriatric COVID-19 patients with severe to critical clinical conditions is recommended to overcome the problem of severe inflammation caused by COVID-19 virus infection. In this study, the use of dexamethasone (10.44%) was found to be higher than that of methylprednisolone. The use of ultra-fractionated heparin (UFH) and low molecular weight heparin (LMWH) is also used to treat geriatric COVID-19 patients with coagulation disorders and thrombosis, which can be identified by testing D-dimer, platelet and fibrinogen levels. The incidence of pulmonary embolism in COVID-19 patients has been found to be around 30%, so the use of heparin is very necessary, although side effects such as thrombocytopenia can also threaten patients, so the use of the drug needs to be closely monitored [19].

The potential for drug-drug interactions in geriatric COVID-19 patients is closely related to treatment, for which there is currently no outcome measure to determine which drugs are really useful in the treatment of COVID-19, apart from comorbidity factors that influence the level of drug use [9]. The most common potential drug-drug interactions of low severity were between acetylsalicylic acid and omeprazole. A total of 12 patients were identified as having a potential drug interaction due to receiving these drugs during treatment. In general, this interaction can lead to a reduction in the bioavailability of acetylsalicylic acid in the blood due to impaired absorption caused by an increase in gastric pH when omeprazole is used, and has the potential to disrupt blood coagulation. In these circumstances, administration of enteric-coated acetylsalicylic acid may minimise the potential for drug interactions. Other infrequent interactions included furosemide/acetylsalicylic acid (7 events and increased risk of forosemide toxicity) and paracetamol/ranitidine (6 events and risk of hepatotoxicity) [7],[23].

The most potential drug interactions of moderate severity were found between azithromycin and levofloxacin with a frequency of 40 patients. Potential interactions occur through pharmacodynamic mechanisms in the form of drug synergism affecting QT interval prolongation. The potential for similar events was also found with azithromycin and ondancetron, where the co-administration of both drugs in this study was quite high, occurring in 24 patients. The QT interval is the time it takes for the heart to repolarise after depolarisation. The electrogram is characterised by Q and T waves approaching the time when the heart contracts to relax. Prolongation of the QT interval may increase the risk of arrhythmias and more serious toxicities, including sudden death, but evidence on the risks of this combination is limited. To avoid the risk of this drug interaction, it is recommended that alternatives to this combination be considered. If this is not possible, monitor QT interval and arrhythmias. There are several risk factors that need to be considered when using drugs that affect the QT interval because they have toxic effects that tend to increase the risk, including older age, female sex, bradycardia, heart disease, and high drug concentrations [24].

At the mayor severity level, the highest potential interaction was found between the use of levofloxacin and dexamethasone, potentially occurring in 17 patients receiving this treatment. Concomitant use of these drugs may increase the risk of tendonitis and tendon rupture. The risk is increased in elderly users due to reduced bone density and joint elasticity. The potential for serious interactions also occurred with the use of levofloxacin and insulin in 15 patients who received this therapy with a risk of severe hypoglycaemia. At the level of unknown interactions, the combination of favipiravir and acetaminophen may increase the AUC of acetaminophen by up to 20%. Favipiravir is known to increase paracetamol concentrations by inhibiting phase 2 metabolism between paracetamol and sulphate, so it may inhibit the elimination of some paracetamol metabolites [25].

In this study, other factors that could influence the high incidence of potential drug-drug interactions were also analysed. There was a significant association between length of stay (p-value 0.001) but not between number of comorbid conditions (p-value 0.481) and potential drug interactions. This is consistent with research by Kusumawardani et al, who found that the number of medications had a very significant correlation with the incidence of drug-drug interactions. Other factors that influence the high potential for drug interactions are the length of hospitalisation and the number of comorbidities the patient has [23].

The insignificant relationship could be caused by the number and type of patients' comorbidities, which do not really affect the amount of medication taken and therefore do not affect the potential for interacting with other drugs. Drug use in patients with more than one type of co-morbidity and in patients with many co-morbidities, i.e. high blood pressure and diabetes, is adjusted according to the treatment algorithm and the patient's needs. The use of one or two drug combinations is more common in hypertensive and diabetic patients, so the number of drugs used does not increase significantly. A significant relationship with potential drug interactions was found in the results of the correlation test for length of stay. According to Tanzil et al, length of stay may be related to disease severity, so it can significantly influence the number of medications a patient takes. Polypharmacy is the key to increasing the risk of interacting [25].

In fact, polypharmacy is one of the factors that cause drug-drug interactions. It is therefore important to recognise that the simultaneous use of large numbers of drugs carries a risk of reducing the safety and effectiveness of treatment. The increasing use of medicines in treatment cannot be dissociated from many factors, such as the availability of more effective and safer medicines, the promotion of consistent treatment, chronic diseases that require some patients to take more medicines, and the lack of intervention in treatment by pharmacists. Polypharmacy is not always potentially dangerous, but it cannot be ignored either because of the limited understanding between theory and reality of how to manage and prevent complex drug use problems [26].

▪ CONCLUSION

The incidence of drug interactions should be overcome by administering drugs that are appropriate to the patient's condition. There is a significant relationship between polypharmacy and tdrug interactions, $p < 0.001$ and r 0.537, meaning that the likelihood of drug-drug interactions rises with the number of drugs used.

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REFERENCES

[1] Ministry of Health Indonesia. Guidelines for Prevention and Control of Coronavirus Disease 2019 (COVID-19) 5th Revision. Jakarta: *Directorate General of Disease Prevention and Control*, 2020, pp 17.

[2] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Taken from: https://COVID19.who.int/Accessed 13 August 2021

[3] Task Force for Handling COVID-19. Taken from: https://COVID19.go.id/peta-sebaran-COVID19. Accessed August 13, 2021.

[4] Law Number 13 of 1998 concerning the Welfare of the Elderly www.bpkp.go.id/unit/ Hukum/uu/1998/13-98 Accessed 13 August 2021.

[5] World Health Organization. *Medication Safety in Polypharmacy. Medication Without Harm*. 2019, pp 11-12.

[6] Republic of Indonesia Food and Drug Supervisory Agency. *Indonesian National Drug Informatorium*, 2008. Jakarta: Sagung Seto; 2008.

[7] Syamsudin. *Drug Interactions: Basic and Clinical Concepts*. Jakarta: UI Press, 2011.

[8] E.S. Dasopang, U. Harahap, D. Lintardo. "Polypharmacy and Drug Interactions in Elderly Outpatients with Metabolic Diseases". *Indonesian Journal of Clinical Pharmacy*, vol. 4, no 4, pp. 235–241, 2015.

[9] M.D. Cantudo-Cuenca, et al. "Drug–Drug Interactions Between Treatment Specific Pharmacotherapy And Concomitant Medication In Patients With COVID 19 In The First Wave In Spain". *Scientific Reports,* vol. 11, no. 12414, 2020.

[10] Zulkarnaini A, Martini RD. "Description of Polypharmacy in Geriatric Patients in Several Polyclinics at RSUP Dr. M. Djamil Padang", *Andalas Health Journal*. vol. 8, pp. 1-6, 2019.

[11] Karawang Regency COVID-19 Handling Task Force. Taken from: https://covid19.karawangkab.go.id/data/Accessed 20 May 2022.

[12] Karawang Regency Central Statistics Agency. Taken from: https://karawangkab.bps.go.id/ Accessed 5 June 2022.

[13] W.H Chang. "Understanding the COVID-19 pandemic from a gender perspective". *Taiwanese Journal of Obstetrics & Gynecology*, vol. 59, pp. 801-807, 2020.

[14] D. Hidayati. *Profile of Population Confirmed Positive for COVID-19 and Died: Cases of Indonesia and DKI Jakarta, Indonesian Population Journal Special Edition on Demography and COVID-19*, pp. 93-100, 2020.

[15] W.S. Kadek, I.M. Suwidnya, B.S. Wijaya, "The Relationship of Comorbid Diseases to the Clinical Degree of COVID-19". *Medical Science Digest*, vol. 12, no. 2, pp. 708-717. 2021.

[16] R. L. Diana, S. Isnaini. "Treatment Profiles And Clinical Outcomes Of COVID-19 Patients At Private Hospital In Jakarta". *PONE Journal*. 2021.

[17] J. Johanna, et al. "Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons results of the Kuopio 75+ Study: A cross-sectional analysis". *Drugs Aging*, vol. 26, no. 6, pp. 493-503, 2009.

[18] O.D. Maire, et al. "Factors associated with polypharmacy and excessive polypharmacy in older people with intellectual disability differ from the general population: a cross-sectional observational nationwide study". *BMJ Open*. 2017.

[19] Team Doctors. Guidelines for Management of COVID-19 edition 3. Jakarta: Indonesian Association of Lung Doctors (PDPI), Indonesian Association of Cardiovascular Specialist Doctors (PERKI), Indonesian Association of Internal Medicine Specialists (PAPDI), Indonesian Association of Anesthesiology and Intensive Therapy Doctors (PERDATIN), Doctors Association Indonesian Children (IDAI). 2020.

[20] S. Etik, A. Rahem, A. Purnamayanti. "Profile of use of COVID-19 antiviral drugs at Dr. Murjani-Sampit". *Ibnu Sina Scientific Journal*, vol. 7, no. 1, pp. 116-123. 2022.

[21] F. N. Islami, S. Sinala, I.Adhayanti, et al, "Medicines as an alternative therapy for COVID-19", *Urban Health*, vol. 3, no. 1, pp. 116-126, 2021.

[22] G.V. Carolina, et al. "Incidence of co-infections and superinfections in hospitalized patients with COVID-19: A retrospective cohort study", *Clinical Microbiology and Infection*, vol. 27, pp. 83-88, 2021.

[23] L.A. Kusumawardani, M. Nisa, N.F. Yumna. "Analysis of Potential Drug Interactions in COVID-19 Inpatients at a Hospital in West Java", *Pharmaceutical Scientific Journal*, vol. 17, no. 2, pp.182-196, 2021.

[24] M.A. Shakir, 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,* vol 10, pp. 105-118. 2022.

[25] I. Tanzil, N. Rivianti, I.Saleh. "Correlation between polypharmacy and length of stay in geriatric patients at Mohammad Hoesin Hospital, Palembang", *Indonesian Journal of Internal Medicine*, vol. 8, no. 4, pp. 204-208, 2020.

[26] Guthrie, et al. The Rising Tide Of Polypharmacy And Drug-Drug Interactions: Population Database Analysis 1995–2010. *BMC Medicine*, vol. 13, no. 74. 2015.