International Journal of Scientific Research and Management (IJSRM)
||Volume||10||Issue||12||Pages||MP-2022-731-739||2022||
Website: www.ijsrm.in ISSN (e): 2321-3418
DOI: 10.18535/ijsrm/v10i12.mp01

Analysis of Drug Accuracy, Dosage and Drug Interactions in Comorbid Hypertension COVID-19 Patients at Hospital X in Central Java Period 2021

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Abstract
Treatment of COVID-19 comorbid hypertension involves many drugs with therapeutic risk of non-guidelines and potential drug interactions. The purpose of the study was to identify the demographic characteristics, clinical level, accuracy of medications and doses and potential drug interactions. Study design was cross-sectional through retrospective data collection. Samples of inclusion criteria obtained 70. The results showed a 51.4% female sample, an average age of 46 to 59 years old (48.6%), moderate COVID-19 level 61.4%, grade 1 hypertention 48.6% and stay longer than 14 days (51.4%) at hospital. Drug accuracy of COVID-19 is 78,6% accurate and 21,4% inaccurate and dose accuracy 100% accurate. The accuracy of antihypertensive were 82.9% accurate drug, 17.1% inaccurate drug, 95.7% accurate dose and 4.3% inaccurate dose. The percentage of samples with potential medication interaction was 97.1% the most interactions werw 1-5 events (51.9%) and the severity distribution was 60.2% moderate, 20.1% minor 13.2% major and 6.5% unkown. Correlation test results sig. (p-value) 0.237. Conclusion, the majority of samples were female, aged 46 to 59, moderate grade COVID-19 patients, with grade 1 hypertention, and length of stay >14 days. There is no coorelation between duration of stay and possible drug interactions, accuracy or inaccuracy of drugs and doses, however there is accuracy in the use if drugs and doses.

Keywords: Drug, Dosage, Accuracy, Drug Interaction, COVID-19 Comorbid Hypertension, Hospitalization

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). Cases in Indonesia until December 31 2021 reported 4,262,720 confirmed cases. The top three provinces with the most confirmed cases of COVID-19 are DKI Jakarta (20.3%), West Java (16.6%) and Central Java (11.4%) (2). The confirmed cases of COVID-19 in Sragen Regency until 31 December 2021 16,676; 1,395 cases of death and 15,280 cases of recovery (3). The selection of drugs and the right dose needs to be observed and irrational drug use (4). The rational drug according to the Ministry of Health of the Republic of Indonesia, patients receive drugs their needs, for an adequate period of time and at the cheapest prices for patients and society (5). Medication given together with other drugs, herbs, food, drinks, or other chemicals lead drug interactions by increasing the toxicity or reducing the efficacy of drug (6). The more of drugs used patients, the higher potential for drug interactions (7). The presence of comorbidities in COVID-19 patients results in a longer duration of patient hospitalization and the use of multiple drugs or polypharmacy, thereby increasing the risk of drug interactions (8). Drug interactions with drugs that have the potential to occur in the treatment of COVID-19 comorbid hypertension need to be known because they can cause adverse drug reactions (ADR) thereby increasing the risk of hospitalization, long recovery time, or death in severe cases (9). This study aims to determine demographic characteristics, clinical degree, drug accuracy, dosage accuracy and potential drug interactions in comorbid hypertension COVID-19 inpatients at hospital X in Central Java 2021 period.

Materials and Methods

Materials

Data on medical records of patients with comorbid hypertension with COVID-19 obtained from the Medical Recording and Health Information Installation at hospital X 2021 period.

Tool

Data collection forms and stationery, SPSS programs, Therapy guidelines from the Hospital Clinical Practice Guideline (PPK), COVID-19 Management Guidelines Edition 2 and Edition 3, Hypertension Management

Consensus 2019, Sites that provide drug interaction checkers such as drugs.com and/or Medscape and/or covid19-druginteractions.org.

Data Collection and Organization. Sample data were collected from secondary data sources from medical records of inpatients at hospital X were confirmed to have comorbid hypertension with COVID-19 for the 2021 period. The data collected in this study included gender, age, diagnosis, drug therapy

Methods

Type research is descriptive non-experimental with a cross-sectional study design through retrospective data collection. Inclusion criteria inpatients at Hospital X for the 2021 period, the patient is > 18 years old, and the patient is confirmed comorbid hypertension with COVID-19.

Data analysis.

The data has been analyzed using descriptive statistics including the patient's demographic characteristics. Hospital Clinical Practice Guideline and the COVID-19 Management Guidelines Edition 2 and Edition 3 compared to the therapy given. Hypertension Management Consensus

Results and Discussion

Demographic Characteristics.

In the population study of comorbid hypertension COVID-19 patients at hospital X 2021 period, 82 patients met the inclusion criteria. The results in Table 1 showed 36 (51,4%) females, 34 (48,6%) males.

Table 1. Sample Distribution Based on Demographic Characteristics

Sample Demographic Characteristics	**Σ (n = 70)**	**Percentage (%)**
Gender		
Male	34	48,6
Female	36	51,4
Age		
18-30 years old	1	1,4
31-45 years old	8	11,4
46-59 years old	34	48,6
≥ 60 years old	27	38,6

The data on the number of patients confirmed positive for COVID-19 by the Task Force for Handling COVID-19 in Indonesia, shown until May 23 2022 positive confirmed cases were more female than male, namely 52.3% (2). These results are in line with Wang et al study regarding the clinical features of comorbid hypertensive COVID-19 patients compared to the non-hypertensive group, which obtained a larger sample of the female sex, namely 56.1% of hypertensive patients and 52.6% of non-hypertensive patients. (10). Based on the accompanying comorbidities hypertension, the 2018 Riskesdas results also show the prevalence rate of hypertension in residents > 18 years according to characteristics in women 36.9% higher than in men (31.3% (11). Differences in the pathogenesis of COVID-19 in men -men and women are still not well understood, but are probably multifactorial (12). Research by Putri et al's shows that there is no relationship between gender and the incidence of COVID-19 infection (13). The age category of the sample is mostly 46 -59 years is 34 (48.6%) samples. This result is in line with the study of Xu et al's, by the age category of the sample most infected with COVID-19 was in the age range 41-65 years is 53% of samples (14). Based on accompanying comorbidities hypertension, the 2018 Riskesdas results also show a higher prevalence rate with increasing age. The prevalence in the age range 45-54 years is 45.3%, the age range 55-64 years is 55.2%, and the age range of 65-74 was 63.2% (11). There is a relationship between age and the level of innate immunity, where an elderly person is more likely to be infected along with decreased innate immunity (15).

Characteristics of Clinical Degree.

The results in Table 2 show that samples with moderate severity of COVID-19 disease were 61.4% more than those with severe disease severity of 38.6%.

Table 2. Sample Distribution Based on Clinical Degree

Clinical Degree	Σ (n = 70)	Percentage (%)
Degree of Severity COVID-19 Disease		
Moderate	43	61,4
Severe	27	38,6
Degree of Severity Hypertension		
Degree 1	34	48,6
Degree 2	27	38,6
Isolated systole	9	12,9
Length of Stay		
1-14 days	34	48,6
>14 days	36	51,4

The results in Table 2, degree of severity of COVID-19 disease in line with Oktarina et al's study obtained 75% more samples with moderate disease severity compared to 25% with severe disease severity (16). The same results were also obtained in the Pepitasari et al study which showed that samples with moderate disease severity 70.83% were the highest degree of disease severity compared to mild disease severity 13.54%, severe 5.21% and critical 10.42% (17).

Moderate disease severity was assessed from clinical signs of pneumonia (fever, cough, shortness of breath, fast breathing) and SpO2 > 93% without using oxygen. The degree of severity of the disease was assessed from the clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one from a respiratory rate > 30 x/minute, severe respiratory distress, or SpO2 < 93% without using oxygen (18). The results for the highest degree of hypertension severity were grade 1 is 48.6%. This result in line with the study of Sumawa et al which obtained samples with the highest degree of hypertension severity at degree 1 is 79.49% in hospitalized patients (19). Confirmation diagnosis of hypertension could not depends on one examination. Blood pressure measurement for 24 hours including during sleep is an accurate method of confirming the diagnosis of hypertension (20). In this study, the determination of the severity of hypertension was seen from the average blood pressure value on blood pressure measurements for 24 hours recorded in the medical record before patients received antihypertensive drug therapy.

The division of length of stay was based on the duration of recovery are non-prolonged (≤14 days) and prolonged (>14 days) groups (21). From the results in Table 2, discovered the length of stay was the most >14 days (51.4%) compared to the length of stay <14 days (48.6%). The average length of stay of the sample is 16.0 days of treatment. These results are different from the study by Ramatillah et al, which found the most length of stay in COVID-19 patients with comorbid degenerative diseases with a length of stay of <14 days (63.6%) (22). COVID-19 patients with comorbid hypertension, diabetes or cardiovascular disease have a worse prognosis compared to patients no comorbidities. In the study by Hu et al cited by Baihaqi et al showed that there was a significant relationship between hypertension and prolonged hospitalization. This is supported by the theory that infection with SARS-CoV-2 can cause excessive activation of the RAS system, thereby increasing the inflammatory response and triggering a cytokine storm which can then increase lung damage from COVID-19 (23).

Drug Accuracy and Dosage for COVID-19 Therapy.

Treatment for COVID-19 consists of drugs as the main therapy, therapy to treat symptoms, and additional therapy. The main therapy used is supplements/ vitamins, antibiotics, and antivirals. Therapy to treat symptoms aims to reduce the symptoms of the disease experienced by patients, such as fever, cough, sore throat, nausea, diarrhea, etc. Additional therapy aims to support the success of therapy. One of the additional therapies that are widely used in COVID-19 is anticoagulants (17). Analysis of the suitability of COVID-19 treatment is said to be appropriate, that is, patients receive main therapy (supplements/vitamins, antibiotics, and antivirals), therapy to treat symptoms, and additional therapy according to the patient's condition. Table 3 shows the results of the suitability analysis for COVID-19 treatment, 94.3% of the samples complied with the guidelines, and 5.7% of the samples did not comply with the guidelines. The samples were not suitable because 3 (three) samples did not receive antivirals and 1 (one) not get supplements/ vitamins.

Table 3. Distribution of Compliance with COVID-19 Treatment, Dosage Accuracy and Comorbid Hypertension COVID-19 Therapy Drugs

Type of Treatment Analysis	Σ (n = 70)	Percentage (%)
Suitability of COVID-19 Treatment		
Appropiate	66	94,3
No Appropiate	4	5,7
Accuracy of COVID-19 Therapy Drugs		
Appropiate	55	78,6
No Appropiate	15	21,4
Accuracy of Dosis Terapi COVID-19 Therapy Dose		
Appropiate	70	100,0
No Appropiate	0	0,0
Accuracy Antyhipertensive Therapeutic Drugs		
Appropiate	58	82,9
No Appropiate	12	17,1
Accuracy Antyhipertensive Therapeutic Drugs		
Appropiate	67	95,7
No Appropiate	3	4,3

Table 3 the results of the analysis of the accuracy of the drug therapy for COVID-19, it was found that 78.6% of the samples were correct and 21.4% of the samples were incorrect. This result is not in line with Oktarina et al's study which obtained precise drug results in 44 samples (100%) (16). Analysis of the accuracy of COVID-19 therapy drugs appropriate, patients receiving drugs included the main therapy. In this study, the severity of COVID-19 disease was only moderate and severe, based on the provisions in guidelines for patients with moderate and severe degrees as the main therapy, supplements/vitamins, antibiotics (azithromycin or levofloxacin) and antivirals (oseltamivir or favipiravir or remdesivir). Table 4 presents a sample recapitulation that is considered inappropriate.

Table 4. Recapitulation of types of drug inaccuracy in COVID-19 therapy

Inaccuracy Type	Σ (n = 15)
No obtain antibiotic*	7
No obtain antivirus**	5
No obtain supplement/vitamin dan antivirus**	1
No obtain antibiotic* dan antivirus**	2

Specific therapy that can kill the SARS-CoV-2 virus causes COVID-19 has not yet been discovered (24). Oseltamivir is a class of neuraminidase inhibitors (NAIs) with a mechanism of action that inhibits viral neuraminidase. These barriers can inhibit the release of virus particles from infected cells thereby reducing the spread of the virus in the respiratory tract. Favipiravir can be said to have potential as a broad-spectrum antiviral because it has the potential to inhibit the replication of various types of viral RNA (25). Remdesivir is a broad-spectrum antiviral that is effective against RNA viruses such as SARS-CoV and MERS. Remdesivir is the most potentially effective drug against COVID-19, but further research is still needed with wider clinical trials (26). COVID-19 is characterized by pneumonia, prevent bacterial co-infection it is necessary to use antibiotics. Levofloxacin is the antibiotic of choice in the treatment of community-acquired pneumonia (17).

Azithromycin is a macrolide class of antibiotics. Infection due to the corona virus causes inflammation and tissue damage, especially in the lungs. Azithromycin can provide an immunomodulating effect (stimulating the body's defense system) (16). Supplements/vitamins recommended for patients with moderate and severe degrees of COVID-19 are vitamin C, vitamin D and vitamin E (18). Vitamin C, used orally and intravenously, is effective in reducing the risk of complications, reducing the severity of the disease, treating symptoms, and improving the prognosis of COVID-19 patients. Vitamin D deficiency can increase the risk of occurrence and severity of COVID-19 and can also increase the risk of thrombosis. The use of vitamin D3 can increase anti-inflammatory cytokines and reduce the production of pro-inflammatory cytokines (17). Giving vitamin E has been shown to improve the function of the body's immune system and reduce the risk of respiratory tract

infections and several viral and bacterial infections, especially in the elderly. However, there is no significant evidence regarding the efficacy of Vitamin E supplements in patients with SARS-Cov-2 infection (27).

Table 3. shows the results of the analysis of the accuracy of the dose of COVID-19 therapy, 100% of the samples were dosed correctly. This result in line with Oktarina et al's study which obtained 100% correctly of dose results (16). The dosage of the drug includes the dose and frequency of administration of the drug. Analysis of the accuracy of the dose in patients was assessed as correct, namely the dose of anitvirus and/or antibiotics obtained was correct. The therapy obtained was compared with the daily dose and frequency with the guidelines, then the correct dose is stated, the therapy given falls within the set dose range and frequency.

Drug Accuracy and Dosage of Antihypertension Therapy

Analysis of drug accuracy in antihypertension therapy is the selection of type drugs given in therapy based on the 2019 Hypertension Management Consensus. The selection of drugs in therapy is based on an algorithm based on the degree of severity of hypertension (20). Table 3 shows the results of the analysis of the accuracy of antihypertension therapy drugs, it was found that 82.9% of the samples were correct and 17.1% of the samples were incorrect. This result is in line with the research of Tyashapsari and Zulkarnain who obtained 81% correct drug results and 19% incorrect drug results (28). This result is also in line with Untari et al's study which obtained 70.65% of the correct drug and 29.35% of the wrong drug (29). This result is also in line with the research of Astuti and Endang who obtained 78.5% of correct drug results and 21.5% of incorrect drugs (30).

The results analysis of samples that were considered inappropriate for the drug were 12 samples, there were 11 samples of stage 2 hypertension and there was 1 sample of stage 1 hypertension. The inaccuracy of drugs in 10 samples of stage 2 hypertension was due to receiving one type of drug therapy. According to the guidelines, it is recommended that stage 2 hypertension is initially treated with combination therapy of 2 drugs, ACEi or ARB with CCB or diuretics (20). Combination therapy reduces blood pressure to a greater extent with minimal side effects. Combination therapy for antihypertension drugs should ideally use a diuretic group, such as the thiazide diuretic group. The combination of diuretics with several other antihypertension such as ACEi, ARB, or β-blockers is an additive effect of these antihypertension is avoiding fluid loss. Low doses of antihypertension combinations are more effective in reducing side effects than high doses of antihypertensive monotherapy (29). The inaccuracy of medication in 1 sample of stage 2 hypertension inappropriate combination therapy, which is the combination of an aldosterone antagonist diuretic (spironolactone) with a loop diuretic (furosemide). Use of diuretic combinations to increase effectiveness and prevent resistance. Loop diuretics and spironolactone diuretics act on the kidney at different sites so their combinations can be synergistic. Prolonged administration of loop diuretics single therapy induces hypertrophy in the distal tubules resulting in increased sodium reabsorption. This can be prevented by co-administering loop diuretics with the diuretic spironolactone (31).

The inaccuracy of medication in 1 sample of stage 1 hypertension inappropriate combination therapy, is a combination of a calcium channel blocker (amlodipine) with a loop diuretic (furosemide). According to the guidelines, it is recommended stage 1 hypertension with initially treated with single therapy with ACEi, ARB, CCB, or diuretics or combination therapy of 2 drugs namely ACEi or ARB with CCB or diuretics (20).

Dose analysis comparing the daily dose and frequency obtained with the 2019 Hypertension Management Consensus (20). Table 3 shows the results analysis of the correct dose of antihypertensive therapy in this study, it was found 95.7% of the samples were dosed correctly and 4.3% of the samples were dosed incorrectly. This result is in line with the research of Tyashapsari and Zulkarnain who obtained 95% correct dose and 5% incorrect dosage (28). This result is also in line with Untari et al's study which obtained 98.91% correct dose and 1.09% incorrect dosage (29). This result is also in line with the research of Astuti and Endang, obtained 98.5% of the correct dose and 1.5% of the incorrect dosage (30). The results of the analysis of samples inappropriate were the doses of 3 (three) samples, is dose of lisinopril. The inaccuracy of the doses in 3 (three) samples obtained lisinopril the fact lisinopril obtained lower dose is 5 mg/day with a frequency of once a day. The recommended dosage range for lisinopril in the guidelines is 10-40 mg/day with a frequency of once a day (20).

Potential Drug Interaction Events

Analysis of potential drug interactions in this study using the sites drugs.com, medscape and covid19-druginteractions.org. All drugs recorded in the patient's medical record during hospitalization were sought for interactions between drugs and drugs. The results of examining drug-drug interactions in this study are potential for drug interactions because not consider the time of taking the drugs received by the patient, whether the drugs are used or used together with or not.

Table 5. Prevalence and Number of Potential Drug Interaction

Potential Drug Interaction Events	**Σ (n = 70)**	**Percentage (%)**
Prevalence of Potential Drug Interactions		
Samples with potential drug interactions	68	97,1
Samples without potential drug interactions	2	2,9
Number of Potential Drug Interactions		
0	2	2,9
1 - 5	37	52,9
6 – 10	14	20,0
>10	17	24,3

The results in table 5, samples with potential drug interactions at 97.1% and samples without potential drug interactions at 2.9%. This result same with Maulidia et al's study is samples have the potential to experience drug interactions at 93.33% and samples did not have the potential to experience drug interactions at 6.67% (32). The results showed that in the range of 1 to 5 potential drug interaction events 52.9% of the sample, 6 to 10 potential drug interaction events 20.0% of the sample, and more than 10 potential drug interaction events 24.3% of the sample. This potential for drug interactions is due to the use of drugs in large quantities in COVID-19 patients or polypharmacy. Polypharmacy can increase the risk of drug interactions in COVID-19 patients. Adverse drug reactions (ADRs), medication errors, and an increased risk of hospitalization are also with polypharmacy treatment (32).

Table 6. Distribution of Potensial Drugs Interaction Based on Level of Severity and Mechanism

Potensial Drugs Interaction	**Σ (n = 477)**	**Percentage (%)**
Level Severity		
Unknown	31	6,5
Minor	96	20,1
Moderate	287	60,2
Major	63	13,2
Mechanism		
Unknown	125	26,2
Pharmacokinetics	248	52,0
Pharmacodynamics	104	21,8

Based on the severity of the interaction, drugs are considered minor, moderator, major and unknown. The results of the study in table 6 showed that the most severe drug interactions were in the moderate category with 60.2% of events, in the minor category with 20.1% of events, in the major category is 13.2% of events, and finally unknown is 6.5% of events. These results are in line with the study by Yuniar et al which found the potential for drug interactions based on the severity at most in the moderate category of 74%, minor of 21%, and major of at least 5% (33). The results of other studies that are in line are those by Maulidia et al who got the most severe in the moderate category with 74.62% of events, minor with 16.15% of events, and mayor with at least 9.23% of events (32).

Based on the mechanism of drug interaction is listed as pharmacokinetic, pharmacodynamic, and unknown. The results of the study in table 6 showed that the mechanism of drug interactions was mostly in the pharmacokinetic category with 52.0% of the events, the unknown category with 26.2% of the events, and the pharmacodynamic category with 21.8% of the events. This result is not in line with the research by Yuniar et al the most interaction potential in the pharmacodynamic category is 69% and in the pharmacokinetic category

is 31% (33). The ten highest potential events for drug-to-drug interactions in this study could be seen in table 7.

Table 7. Highest Potensial InteractionOccurence

Potensial Drugs Interaction	Σ Cases	Level Severity	Mechanism Interaction Type
Omeprazole - Cyanokobalamin (B12)	30	Minor	Pharmacokinetics
Favipiravir - Paracetamol	29	Unknown	Pharmacokinetics
Amlodipine - Dexamethasone	28	Moderate	Pharmacokinetics
Levofloxacin - Dexamethasone	20	Major	Unknown
Dexamethasone - Vitamin E	14	Minor	Pharmacodynamics
Omeprazol - Warfarin	13	Moderate	Unknown
Asam Askorbat - Warfarin	13	Minor	Pharmacokinetics
Amlodipine - Metilprednisolon	12	Moderate	Pharmacokinetics
Remdesivir - Levofloxacin	12	Moderate	Unknown
Zink Sulfat - Levofloxacin	11	Moderate	Unknown

The potential drug interactions at minor severity levels with the most frequent pharmacokinetic mechanisms, between omeprazole and vitamin B12 (cyanocobalamin) were found in as many as 30 samples. Omeprazole can reduce vitamin B12 levels inhibiting absorption in the digestive tract. Potential drug interactions at moderate severity with pharmacokinetic mechanisms most commonly found, between amlodipine and dexamethasone were found in 28 samples. Simultaneous use of amlodipine with dexamethasone can cause an increase in amlodipine metabolism so that it can reduce the antihypertension effect. The anticipation increases the dose of amlodipine (calcium channel blockers) when used with dexamethasone (34).

The most common potential for drug interactions at major severity with an unknown mechanism between levofloxacin and dexamethasone which were found in as many as 20 samples. Concomitant administration of dexamethasone with levofloxacin antibiotics can cause an increase in the side effects of tendinitis and tendon rupture. Tendon rupture may occur during or up to several months after levofloxacin therapy is completed (19). The potential for drug interactions at an unknown severity level with the most common pharmacokinetic mechanism is between favipiravir and paracetamol which was found in 29 samples. Co-administration of paracetamol (650 mg once daily) and favipiravir (1200 mg twice daily or 800 mg twice daily) increased paracetamol levels by 3% and 16% (1200 mg dose) and by 8% and 14% (800 mg dose). The daily dose of paracetamol in adults should not be more than 3000 mg/day.

Analysis was implement out to find out whether there is a significant relationship between the length of stay and the potential for drug interactions. The data obtained and categorized then tested for data normality. Based on the results of the data normality test, it is known that the data is not normally distributed and therefore the correlation test is continued with Spearman's rho correlation test. The Spearman's rho correlation test results can be observed in table 8.

Table 8. Correlation test Length of Stay between Potential Drugs Interaction

Effect Influence	Analysis Correlation	
	Correlation Coefficient (r)	Sig. (P-*value*)
Length of Stay	0,143	0,237

The results of Spearman's rho correlation test show that the sig P-*value* is 0.237. Sig. P Value 0.237 > 0.05, is no significant relationship between the length of stay and the potential for drug interactions. The correlation coefficient between the length of stay and the potential for drug interactions showed positive results with a weak correlation level.

Conclusions

Demographic characteristics by category gender are female and the age category is 46-59 years. The most clinical degrees of severity of COVID-19 disease is moderate degrees, the most severe degrees of hypertension

are stage 1, and the longest length of stay is >14 days. There are drug accuracy, drug inaccuracy, and dosage accuracy in COVID-19 therapy and dosage accuracy and inaccuracy in antihypertension therapy. There is the most potential for drug interactions in the range of 1-5 events, the most moderate category of drug interactions and there is no relationship between the length of stay and potential drug interactions.

Ethics approval and consent to participate
Research permits and ethical clearance number 055/Etik-Crssp/I/2022 from dr. Soehadi Prijonegoro Sragen January, 2022.

Conflicts of Interest
This study no confict of interest.

Funding Statement
This study full funding by Puskamutu Health Ministry of Health Indonesia

Acknowledgments
Thank you to all crew hospital dr. Soehadi Prijonegoro.

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