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Identification of Drug Related Problems (DRPs) in Rheumatoid Arthritis Patients at Palembang City Hospital

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Abstract

Background: *Rheumatoid arthritis is a chronic systemic inflammatory arthritis disease that affects mainly synovial joints. The incident of RA can lead to the emergence of complications or comorbidities, which then allows patients to receive a variety of therapies that can trigger the incidence of DRPs during the treatment. The prevalence of RA in Indonesia itself in 2018 has reached 7.30%, with the highest percentage occurring in the elderly age group and more prevalent in women.* ***Objective****: This study aimed to determine the incidence of DRPs in RA patients in Palembang city hospitals based on the category of DRPs identified as related to drug selection and dose selection problems, as the relationship between demographic factors and the incidence of DRPs.* ***Methods****: This research is non-experimental study conducted with a retrospective cross-sectional survey. Data collection was carried out by looking at patient medical record data at X and Y Hospital in Palembang from January 2021 to March 2023.* ***Results****: The results showed that the most frequent drps in the drug selection category were drug interactions (72.03%), while in the dose selection category were insufficient dosage regimens (60.74%). The results of bivariate analysis between the incidence of DRPs and gender (p=0.809), age (p=0.879), the number of drugs used (p=0.001), and comorbidities (p=0.089).* ***Conclusion****: There is no relationship between demographic factors and comorbidities with the incidence of DRPs, and there is a relationship between the number of drugs and the incidence of DRPs.*

Keywords*: drugs, drug-related problems, drug selection, dose selection, Rheumatoid arthritis*

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INTRODUCTION

The immune system is the body's ability to fight organisms or toxicants that tend to damage tissues or organs. When the immune response attacks antigens in the body's own tissues, which are found inside or on the surface of cells, autoimmunity will occur [1]. Apart from osteoarthritis, one of the most common autoimmune diseases in Indonesia is rheumatoid arthritis (RA), osteoarthritis, is rheumatoid arthritis. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that can damage the bones and cartilage of the joints (Prihanto *et al.*, 2022).

The prevalence of RA in Indonesia itself in 2018 has reached 7.30% especially in South Sumatra at 6.48%, with the highest percentage occurring in the elderly age group and more prevalent in women than men (Kemenkes RI, 2018). The increasing incidence of RA can cause various complications, such as osteoporosis, infection, coronary artery disease, atherosclerosis, and other diseases. One study in Korea mentioned that RA patients are more at risk of having comorbidities, such as hypertension, dyslipidemia, and myocardial infarction or angina (Jeong *et al.*, 2017). This allows patients with a diagnosis of RA to get a variety of drug therapies that can trigger drug-related problems (DRPs) during their treatment.

Research conducted by Hasan and Mumtazah (2016) showed that RA patients had the most comorbidities, namely osteoarthritis, and the most patients experienced DRPs in the category of inappropriate drug combinations at 54.2%. Ma *et al*. (2019) in their research found that 78.5% of 289 patients had DRP problems, namely side effects, drug interactions, and drug selection problems. The research of Sah *et al*. (2022) explained that 88.4% of patients experienced DRPs in the form of medication safety, advanced age, polypharmacy, and other related factors.

This study aims to determine the incidence of DRPs in RA patients in Palembang city hospitals based on drug and dose selection categories. It also aims to determine the correlation between demographic factors, the number of drugs, and comorbidities and the incidence of DRPs in RA patients in Palembang city hospitals.

MATERIALS AND METHODS

Study design and setting

This study was a non-experimental study conducted with a retrospective cross-sectional survey. The study was conducted at X Hospital and Y Hospital in Palembang City from May to June 2023.

Sampling technique

The population of this study included patients diagnosed with rheumatoid arthritis at X Hospital and Y Hospital in Palembang City. The sampling technique was carried out in taking research subjects using purposive sampling. The inclusion criteria included patients with or without comorbidities and patients aged 20 to 65 years. The exclusion criteria included patients with incomplete and/or illegible medical records and patients who were pregnant and/or breastfeeding. The study subjects who met the inclusion criteria were 112 patients.

Data collection

Data collection was carried out retrospectively in the form of secondary data taken from medical record data and the status of patients with a diagnosis of rheumatoid arthritis who met the inclusion and exclusion criteria.

Data analysis

The obtained data were then grouped and analyzed using the Statistical Package for the Social Sciences (SPSS) Version 25.0 for Windows with the Chi-Square test. If the expectation value results in the Chi-Square test were more than 20%, Fisher's exact test was continued.

Ethical approval

This study was approved by the Health Research Ethics Committee of the Health Polytechnic of the Ministry of Health Palembang (Number 0697/KEPK/Adm2/VII/2023).

RESULTS AND DISCUSSION

Demographic data

Based on the results of the study, it is known that the female sex dominates rheumatoid arthritis patients in Palembang city hospitals by 74%, which is in line with research conducted by Wahid et al., (2021) which states that the majority of rheumatoid arthritis patients are female by 70%. This happens because women have the hormone estrogen, which can affect the immune system. In addition, the hormone estrogen also functions to help maintain bone density, but if the levels are excessive, it will cause autoimmune diseases (Susarti and Romadhon, 2019).

The age of rheumatoid arthritis patients in Palembang city hospitals is mainly in the 46-55 year age group at 32.14%. This is almost similar to research conducted by Sah *et al*., (2022) which states that the majority of rheumatoid arthritis patients are aged 41-60 years and research by Wahid *et al*., (2021) that the majority of rheumatoid arthritis patients range from 45-

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55 years. This is due to increasing age, which causes decreased body function, so that the protective layer of the joint, which functions as a barrier to bone friction, will begin to thin out, and the bone fluid that functions as a lubricant will begin to thicken, so that it will cause pain when moved (Elsi, 2018).

The number of drugs used by rheumatoid arthritis patients in Palembang city hospitals is not only given for indications of rheumatoid arthritis disease but also given to treat comorbidities. Based on the results of the study, rheumatoid arthritis patients in Palembang city hospitals are known to consume the majority of the number of drugs <5 by 58.93%, so it can be said that the majority of patients do not experience polypharmacy. This indicates that this study is not in line with research conducted by Sah et al. (2022) and Ma et al. (2019), which state that rheumatoid arthritis patients experience polypharmacy.

The results showed that the majority of rheumatoid arthritis patients in Palembang City hospitals had comorbidities, and the most common comorbidity was osteoarthritis. This is in line with research conducted by Hasan and Mumtazah (2016) , which states that osteoarthritis is the most common comorbidity in rheumatoid arthritis patients.

Table 1. Demographic data of rheumatoid arthritis patients

Characteristics	Frequency	Percentage
Aged		
≤ 25	11	10
26-25	8	7
36-45	26	23
46-55	36	32
56-65	31	28
Gender		
Male	29	26
Female	83	74
Number of drugs used		
< 5	66	59
≥5	46	41
Comorbidities		
Comorbidities present	67	60
No comorbidities	45	40

In this study, it was also known that rheumatoid arthritis patients in Palembang City Hospital were given csDMARD monotherapy, corticosteroids, NSAIDs, and vitamins or supplements. The administration of csDMARD monotherapy is carried out by giving Methotrexate drugs, which dihydrofolate reductase inhibitors will inhibit chemotaxis, thus providing anti-inflammatory effects through induction of adenosine release. Research conducted Savitri *et al.*, (2019) showed the use of Methotrexate monotherapy by 3%. While the most corticosteroid administration is Methylprednisolone, where this drug will affect the decrease in Disease Activity Score-28 (DAS28) value compared to other drugs because of its role as an anti-inflammatory and pain reliever. Furthermore, the administration of NSAIDs in patients is most common in diclofenac sodium, which works as a cyclooxygenase enzyme inhibitor that reduces the production of prostaglandins that cause inflammation, fever, and pain.

DRPs in the drug selection category

The identification of drug-related problems was carried out based on PCNE V9.01. The results showed that DRPs in the drug selection category mostly occurred in drug interactions at 72.03%. This is in line with previous research conducted , which showed that the largest percentage of DRPs occurred in drug interactions at 54.2%. Potential drug interactions in patients mostly happen in the use of Diclofenac and Meloxicam, where the use of Diclofenac will increase anticoagulants and serum potassium. In this co-use, Diclofenac will increase Meloxicam levels through anionic drug competition for renal tubular clearance. The increase in anticoagulant will result in an increased risk of bleeding, while the rise in serum potassium will increase the risk of hyperkalemia.

The percentage of drugs without indications of 16.09% occurred in the administration of diclofenac sodium together with other NSAID drugs. Based on the literature, diclofenac sodium has contraindications when used together with other NSAIDs and will increase side effects in the form of stomach ulcers. Meanwhile, the percentage of too many drugs for the same indication was 6.33%, the majority of which occurred in the use of diclofenac sodium and Meloxicam, both of which are NSAIDs to treat pain and inflammation. Based on the literature, the use of NSAIDs should be given in low doses, even if the dose will be reduced or stopped if the DMARD is effective. Too many drugs for the same indication can lead to drug interactions and several side effects.

Drug administration according to guidelines but with contraindications occurred at 2.90% in rheumatoid arthritis patients who were given diclofenac sodium together with other NSAIDs. The literature states that diclofenac sodium has contraindications when used together with other NSAIDs, which Diclofenac will

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increase side effects in the form of stomach ulcers in patients.

Indications without drugs in patients amounted to 2.11%, the majority of which occurred in patients with indications of Hypothyroid. Hypothyroidism occurs when thyroid hormone levels are less than optimal in the body due to congenital abnormalities of inflammation or inflammation in the thyroid gland or iodine deficiency (Ningsih, 2023). Based on research conducted Yi-jing *et al.,* (2022) concluded that rheumatoid arthritis patients have a high risk of experiencing thyroid dysfunction, especially Hypothyroid. Cross-sectional research conducted [illegible] mentioned that some of the things that are mentioned as potential links between rheumatoid arthritis and hypothyroidism are autoimmuneidism are autoimmune, syndromes and genetic factors, treatment factors, environmental triggers, and inflammation.

Drug administration not according to guidelines of 0.26% occurred in the administration of xanthine-oxidase in rheumatoid arthritis patients. According to the literature, patients with rheumatoid arthritis are given pharmacological therapy in the form of DMARDs, folic acid supplementation, corticosteroids, and NSAIDs. Meanwhile, inappropriate duplication of active ingredients occurred at 0.26% in the administration of diclofenac sodium. Duplication of treatment occurs when the use of two or more drugs that have the same active substance and for the same indication. According to Cipolle *et al.,* (1998), duplication of drug therapy can provide potential toxic effects of drugs and have little or no positive impact on patient outcomes.

DRPs in the dose selection category

DRPs in the dose selection category occurred most in the insufficient dose regimen of 60.74%, which is not in line with research conducted by Ma *et al.,* (2019) which states that dosing problems in rheumatoid arthritis patients are mostly caused by drug doses that are too high or dosing regimens that are too frequent. Drug administration with an insufficient dosage regimen occurred in the administration of Aspirin, Furosemide, Glucosamine, Ibuprofen, Mecobalamine, and Diclofenac sodium.

Too frequent dosing regimen occurred at 18.52% in the administration of Meloxicam. Meloxicam administration in rheumatoid arthritis patients was given at a frequency of three times a day, while in the literature, rheumatoid arthritis patients were given Meloxicam at a frequency of once a day at a dose of 15 mg. The administration of too-low drug doses of 17.04% also happened in the administration of Meloxicam, which aims to treat pain and inflammation. The literature shows that the use of Meloxicam for rheumatoid arthritis is 15 mg once a day, but rheumatoid arthritis patients are given at a dose of 7.5 mg once a day.

Incorrect/unclear / non-existent dosing time instructions occurred in 2.22% of rheumatoid arthritis patients, which in the administration of Ceftazidime, Diclofenac Sodium, and Eperisone, did not explain the dose of drugs to be used by patients. Meanwhile, too high drug doses of 1.48% occurred in the administration of Simvastatin, which is a Statin class drug that reduces LDL and triglyceride levels and increases HDL levels in the blood. Based on the literature, Simvastatin has a dosage of 5-10 mg once a day for patients with dyslipidemia, while it is known that patients with comorbid dyslipidemia are given the drug at a dose of 20 mg once a day.

Table 2. DRPs in the drug selection category

DRPs Category	Number of patients	Percentage	Frequency	Percentage
Drug selection				
-Drugs not in accordance with guidelines	1	0.57	1	0.26
- Medication as per guidelines, but there are contraindications	11	6.29	11	2.90
-Drug without indication	50	28.57	61	16.09
-Drug interactions	80	45.71	273	72.03
-Inappropriate duplication of active ingredients	1	0.57	1	0.26
-Indication without drug	8	4.57	8	2.11
-Too many drugs for the same indication	24	13.71	24	6.33

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Table 3. Distribution of DRPs on drug selection category

DRPs Category	Frequency
Drugs not in accordance with guidelines	
Allopurinol	1
Total	**1**
Medication as per guidelines, but there are contraindications	
Diclofenac sodium	11
Total	**11**
Drug without indication	
Amlodipine	7
Atorvastatin	5
Azithromycin	1
Candesartan	2
Cefadril	1
Cetirizine	2
Eperisone	1
Fenofibrate	2
Flunarizine HCl	1
Furosemide	2
Gabapentin	1
N(2)-L-Alanyl-L-Glutamine	1
Lansoprazole	11
N-Acetylcysteine	1
Omeprazole	20
Simvastatin	1
Doripenem	1
Betahistine mesylate	1
Total	**61**
Inappropriate duplication of active ingredients	
Diclofenac sodium	1
Total	**1**
Indication without drug	
Amyotrophic Lateral Sclerosis (ALS)	1
Diabetes mellitus	1
Dsypnea	1
Hypothyroidism	2
Hypertensive Heart Disease (HHD)	1
Osteoarthritis	1
Vertigo	1

P-ISSN: 2406-9388
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DRPs Category	Frequency
Total	**8**
Too many drugs for the same indication	
Amlodipine and Candesartan	1
Amlodipine and Ramipril	1
Aspirin and Meloxicam	2
Aspirin and Spironolactone	1
Glucosamine and Acetaminophen	1
Lansoprazole and Antacids	1
Lansoprazole and Sucralfate	1
Meloxicam and Mefenamic acid	1
Metformin, Glimepiride, and Vildagliptin	1
Methylprednisolone and Dexamethasone	2
Diclofenac sodium and Aspirin	1
Diclofenac sodium and Meloxicam	9
Omeprazole and Lansoprazole	2
Total	**24**

Table 4. DRPs in the dose selection category

DRPs Category	Number of patients	Percentage	Frequency	Percentage
Dose selection				
-Too low drug doses	21	19.44	23	17.04
-Drug doses too high	2	1.85	2	1.48
-Insufficient dose regimen	59	54.63	82	60.74
-Dosing regimen are too frequent	23	21.30	25	18.52
-Incorrect / unclear / non-existent dosing time instructions	3	2.78	3	2.22

Table 5. Distribution of DRPs on dose selection category

DRPs Category	Frequency	Information
Too low drug doses		
Meloxicam	23	The patient was given a dose of 7.5mg/day; literature 15 mg/day
Total	**23**	
Drug doses too high		
Simvastatin	2	The patient was given a dose of 20mg/day; literature 5-10mg/day
Total	**2**	
Insufficient dose regimen		
Aspirin	6	Patients are given once a day, whereas in literature, every 3-4 hours
Furosemide	5	Patients are given two times a day; whereas in literature every 6-8 hours
Glucosamine	17	Patients are given once a day, while in literature three times a day
Ibuprofen	4	Patients are given once a day, whereas in literature, every 4-6 hours
Mecobalamin	16	Patients are given once a day, while in literature three times a day

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Diclofenac sodium	34	Patients are given two times a day, whereas in literature, every 8 hours
Total	**82**	
Dosing regiment are too frequent		
Meloxicam	25	Patients are given three times a day; while in literature, once a day
Total	**25**	
Incorrect/unclear/non-existent dosing time instructions		
Ceftazidime	1	No instructions
Eperisone	1	
Diclofenac sodium	1	
Total	**3**	

Table 6. Results of bivariate analysis between factors and the incidence of DRPs in RA patients

No	Factor	P value		Interpretation
		Drug selection	Dose selection	
1	Gender	0.809	0.901	No relationship
2	Aged	0.879	0.832	No relationship
3	The number of drugs used	0.001	0.000	There is a relationship
4	Comorbidities	0.089	0.086	No relationship

Bivariate analysis

Based on the results of bivariate analysis between demographic factors and the incidence of DRPs, it can be seen that there is no relationship between gender and age with the incidence of DRPs in both drug selection and dose selection categories. In addition, there was also no relationship between comorbidities and the incidence of DRPs in rheumatoid arthritis patients in Palembang city hospitals, both in the drug selection category and the dose selection category. Meanwhile, this study found that there was a relationship between the number of drugs and the incidence of DRPs in the drug selection category (P = 0.001) and the dose selection category (P = 0.000). Which, this result is in line with the findings of Hasan and Mumtazah (2016) that there is a relationship between the number of drugs and the incidence of DRPs.

CONCLUSION

Based on the results of the research that has been done, it can be concluded that there are drug-related problems in rheumatoid arthritis patients in Palembang City hospitals. Drug related problems in the drug selection category occurred in drug interactions (72.03%), drugs without indications (16.09%), too many drugs for the same indication (6.33%), drugs according to guidelines but there are contraindications (2.90%), indications without drugs (2.11%), drugs not according to guidelines (0.26%), and inappropriate duplication of active ingredients (0.26%). Drug-related problems in the category of dose selection occurred in insufficient dose regimen (60.74%), too frequent dose regimen (18.52%), too low drug dose (17.04%), wrong/unclear/no dosing time instruction (2.22%) and too high drug dose (1.48%). There was no relationship between demographic factors and the incidence of DRPs. There was a relationship between the number of drugs and the incidence of DRPs. There was no relationship between comorbidities and the incident of DRPs. Future research is expected to explore more deeply and in detail related to the incidence of DRPs itself, both in rheumatoid arthritis patients and in patients with other diseases. It is suggested that related professionals implement strategies that can minimise the possibility of DRPs in patients, such as making SOPs on how to manage RA therapy or other diseases.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.M., H.N.; Methodology, S.M., H.N.; Software, S.M.; Validation, S.M., H.N., S.H.A.; Formal Analysis, S.M.; Investigation, S.M.; Resources, S.M.; Data Curation, S.M.; Writing - Original Draft, S.M.; Writing - Review & Editing, S.M., H.N., S.H.A.; Visualization, S.M.; Supervision, H.N., S.H.A.; Project Administration, S.M., H.N., S.H.A.; Funding Acquisition, S.M.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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