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Adverse Drug Reactions Reporting Profile in Tertiary Referral Hospital: A Retrospective Pharmacovigilance Study in Indonesia

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Abstract

Background*: Pharmacovigilance is administered to several pharmacological classes of drugs worldwide. However, there are still insufficient data regarding the prevalence and general characteristics of drug reactions, especially in developing countries.* ***Objective****: This study aimed to determine the prevalence and characteristics of ADRs, including the pharmacological class involved, and report and classify the clinical manifestations associated with ADRs.* ***Methods****: This retrospective study was based on patient ADR reports during observation. Prevalence, patient demographics, and other data were evaluated using descriptive statistics.* ***Results:*** *Of 773 reports that met the inclusion criteria, most were doctors (80.6%), followed by pharmacists (18.7%). Of the total cases, 430 (55.6%) occurred in the women. Most suspected ADRs occurred in the 19-60 years age group (583; 75.4%). The highest incidence of ADR was observed in patients using antineoplastic agents (19.5%), systemic antibacterials (16.4%), or antihypertensives (12.5%). The majority of clinical manifestations were gastrointestinal disorders (41.7%), and approximately 309 (40%) ADR cases continued with antagonists/antidotes. Approximately 62% of the patients who experienced ADRs recovered.* ***Conclusion:*** *Antineoplastic, systemic antibacterial, and antihypertensive drugs appeared to be the most common drugs used for suspected ADR cases in this hospital. ADR reporting has been running well, but not all healthcare workers have participated actively. Hopefully, the results of this research will contribute to the upcoming strategies for pharmacovigilance activities in this hospital and other healthcare facilities to improve the quality and quantity of ADR reporting and increase the safety of medication usage.*

Keywords*: adverse drug reaction, adverse drug reaction reporting, ADR reporting, pharmacovigilance*

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INTRODUCTION

Adverse drug reactions (ADR) are drug-related problems that require special attention from health care workers. The increasing frequency and severity of ADRs are related to the worsening health status of patients, a significant increase in the healthcare burden due to prolonged hospitalization periods, and the need for additional therapy to treat the complaints and symptoms experienced by patients (Giardina et al., 2018). ADR monitoring guidelines for healthcare workers state that ADR is an undesirable response to drugs that occur at the usual doses in humans for the purpose of prevention, diagnosis, disease therapy, or to modify physiological functions (BPOM RI, 2012).

According to various studies, ADR is an important cause of morbidity and mortality in healthcare facilities. A systematic review including many studies around the world and research in other countries showed that approximately 10% of hospital admissions are related to ADRs (Yadesa et al., 2021). Moreover, ADRs are suspected to be one of the main causes of death and escalation in healthcare costs (Montastruc et al., 2021). However, the development of drugs and several new therapeutic agents makes ADR monitoring a necessity that should be considered daily to evaluate the safety of distributed drugs worldwide (Montastruc et al., 2021).

During preclinical and clinical trials in humans, selected subjects were used with certain strict criteria and limited samples in a completely different setting with daily clinical practice, so sometimes it did not adequately describe the drug's safety profile in humans because the ADRs detected in these phases were likely common ADRs with a high frequency of occurrence. Chronic toxicity, potential drug interactions, and drug safety in special groups (children, pregnant or breastfeeding women, and geriatrics) are very difficult to determine in the development and research phase before the drug receives marketing authorization (Tadge et al., 2023). Therefore, ADR reporting is a crucial tool for detecting the possibility of serious and rare ADRs associated with therapeutic agents, so that patients will receive better intervention earlier, prevent further medical injury and harm, and avoid the emergence of greater risk problems in drug use. Moreover, it can be used as a consideration for drug regulation, policies for withdrawals and distribution permits, and changes to the safety information listed on drug packaging (BPOM RI, 2019; Tadge et al., 2023).

Based on Indonesia's National Pharmacovigilance Data Center, from January to early December 2023, 11,084 ADR reports were received from various healthcare facilities and pharmaceutical industries in Indonesia, but it was thought that there are still many more underreported ADRs (BPOM RI, 2023). In contrast, approximately 21, 336 drugs have been registered over the last five years in Indonesia (BPOM RI, 2022). Ideally, ADR reporting should be performed for all drugs distributed and circulating in Indonesia. However, ADR reporting was not mandatory for healthcare workers because a voluntary reporting system was adopted, which was manually sent using an ADR reporting form or digitally entered on the E-MESO website. Therefore, the number of reports is still quite small compared to the total number of distributed drugs. In line with this, a systematic review analyzed 37 studies conducted in different countries and found that the rate of underreporting of ADRs exceeded 90% in many cases, showing that widespread and significant underreporting of ADRs is a global problem and affects all types of ADRs (Al Meslamani, 2023).

In a study on ADR prevalence worldwide, 85% of reports came from developed countries such as the United States, England, France, Germany, Canada, and Australia (Aagaard et al., 2012). In developing countries, including Indonesia, various studies have been conducted on the ADR of several pharmacological classes, such as chemotherapeutic agents (Melani, Darmawan and Raharjo, 2019), anti-diabetic (Yosmar, Inanta and Sari, 2018), anti-hypertensive (Indriani, Rokhmah and Shania, 2022), anti-tuberculosis (Rini, Ikawati and Perwitasari, 2014), anti-retroviral (Pertiwi, Wardani and Wedayani, 2021), analgesic-anti-inflammatories (Permata and Azmi, 2024), and cardiovascular drugs (Almasdy et al., 2018). However, there is insufficient information available regarding ADR prevalence and characteristics in healthcare facilities, particularly tertiary referral hospitals that manage complex multidisciplinary cases involving polypharmacy with diverse therapeutic classes and high-risk medications. Therefore, a retrospective pharmacovigilance study was conducted using ADR reports. This study aimed to ascertain the prevalence and characteristics of ADRs in hospitalized and ambulatory patients, including the pharmacological classes involved, and document and categorize the clinical manifestations associated with ADRs.

MATERIALS AND METHODS

Study design

This retrospective study was based on ADR reports at 2 years and 10 months from January 2021 to October

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2023 at the Saiful Anwar General Hospital, Malang, East Java, Indonesia.

Instrument and data analysis

Data were obtained from inpatient ADR reports during the observational period. ADR reports were collected manually in yellow and digitally using an internal ADR reporting link. The inclusion criteria were completeness of ADR reports, including patient demographics, manifestations of ADR, suspected drugs, chronology of events, and outcome of ADR.

The data obtained included the number of reports per month, reporters, demographic characteristics of the patient (age, sex), history of disease and comorbidities (if any), history of previous drug allergies (if any), main diagnosis, number of drugs received when experiencing ADR, drugs suspected, ADR clinical manifestations, patient follow-up, and outcome. Other medications used by patients (if any) were also included in the report. The actions taken to treat ADR are grouped into four categories: continuing the drug with an antagonist/antidote, continuing the drug without the antagonist/antidote, stopping the drug with the antagonist/antidote, and stopping the drug without the antagonist/antidote.

The main diagnoses and clinical manifestations of ADRs were grouped using the Medical Dictionary for Regulatory Activities (MedDRA)® system and classified according to System Organ Class (SOC). Drugs suspected to cause ADR are categorized using the Anatomical Therapeutic and Chemical (ATC) group (2^{nd} level) (Giardina et al., 2018). Patient demographics and ADR reporting data were evaluated using descriptive statistics.

RESULTS AND DISCUSSION

During the observation period, there were 773 cases reported as ADRs, 178 (0.68%) in 2021, 301 (0.95%) in 2022, and 294 (0.92%) in 2023. The number of reports was still small compared to the total number of patients, whereas previous research stated that out of 3695 episodes of hospital stay, approximately 15% of inpatients experienced at least one ADR during their inpatient period (Davies et al., 2009). This is in line with the relatively low number of ADR reports in Indonesia, as in other developing countries (Al-Worafi et al., 2017). However, the total number of reports received by the Indonesian National Pharmacovigilance Center has significantly increased. In 2022, the number of national ADR reports reached more than 10,000 from healthcare facilities all over Indonesia, an increase of 53% compared to the average number of reports for the past five years (BPOM RI, 2023). This is probably a positive sign of underreporting, which was a limitation of the spontaneous ADR reporting system implemented in Indonesia because it was estimated that only 6-10% of ADRs were reported from the actual number. A systematic review examined factors that influence ADR reporting among healthcare workers. The results showed that the socio-demographic characteristics of healthcare workers did not significantly influence ADR underreporting, but several other factors that mattered were the wrong assumption (only serious ADRs need to be reported), apathy (delayed reporting, lack of interest in reporting), complacency (the assumption that all drugs must be safe and well-tolerated), fear of being thought strange if reporting a predictable ADR, and feelings of insecurity (feeling that it is almost impossible to determine whether a drug is the suspected cause of a specific ADR). In addition, the absence of reporting obligations and confidentiality is another reason for low ADR reporting rates (García-Abeijon et al., 2023).

In this study, the largest number of ADR reporters was dominated by residents and physicians (80.6%), followed by pharmacists (18.7%) and other healthcare workers, such as nurses and midwives (0.7%). According to the ADR Reporting Guidelines in Indonesia, all healthcare workers are allowed to report ADR (BPOM RI, 2012). Residents and doctors were the most frequently reported ADRs. This is probably because of the obligation to report ADRs as academic assignments in some medical residency programs. The second most frequent reporters were pharmacists, especially ward pharmacists and ambulatory pharmacists. This is in line with their competence in monitoring the safety and efficacy of patients' medications, but more reports should be collected due to the availability of clinical pharmacists in each hospital ward. The nurses and midwives were the least frequently reported. According to previous research, barriers for nurses to report ADRs include lack of time and heavy workload, unawareness of the reporting procedure, insecurity to make the wrong report, and fear of being accused (Adu-Gyamfi et al., 2022). Furthermore, it has been found that the knowledge and implementation of pharmacovigilance among healthcare workers is quite low; therefore, continuous socialization regarding this matter is urgently needed (Wangge and Akbar, 2016).

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Table 1. Characteristics of study subjects

Characteristics	Number of Cases (n=773)	% Percentage
Age Group (years)		
0-18	31	4.0
19-60	583	75.4
> 60	159	20.6
Sex		
Males	343	44.4
Females	430	55.6
Main Disease Categories[a]		
Infections and infestations	181	23.4
Benign, malignant and unspecified neoplasms	179	23.2
Renal and urinary disorders	102	13.2
Blood and lymphatic system disorders	87	11.3
Immune system disorders	62	8.0
Gastrointestinal disorders	24	3.1
Hepatobiliary disorders	24	3.1
Psychiatric disorders	22	2.8
Hypertensive	16	2.1
Endocrine disorders	14	1.8
Cardiac disorders	13	1.7
Vascular disorders	13	1.7
Musculoskeletal	12	1.6
Nervous system disorders	6	0.8
Respiratory, thoracic and mediastinal disorders	6	0.8
Reproductive system and breast disorders	6	0.8
Eye disorders	2	0.3
Skin and subcutaneous tissue disorders	2	0.3
Metabolism and nutritional disorders	1	0.1
Dental Impaction	1	0.1
Comorbidities[b]		
Geriatric	159	25.7
Hypertension	109	17.6
Infection	79	12.8
Renal impairment	72	11.6
Cardiovascular disorders	52	8.4
Diabetes mellitus	47	7.6
Myelosuppression	20	3,2
Hypoalbumin	16	2.6
Electrolyte imbalance	16	2.6
Malignancy	12	1.9
Autoimmune	10	1.6
Previous history of drug/food allergies	8	1.3
Hepatic impairment	7	1.1
Blood disorders	6	1.0
Underweight	5	0.8
Hyperthyroid	1	0.2
Total	**619**	**100%**
Number of Drugs Taken		
≤ 4	722	93.4
5-9	51	6.6
≥ 10	0	0
Total ADR Reports obtained	**773**	

[a] Main disease: a diagnostic which caused a patient received medication suspected for ADR

[b] Comorbidities: any medical condition other than the main disease

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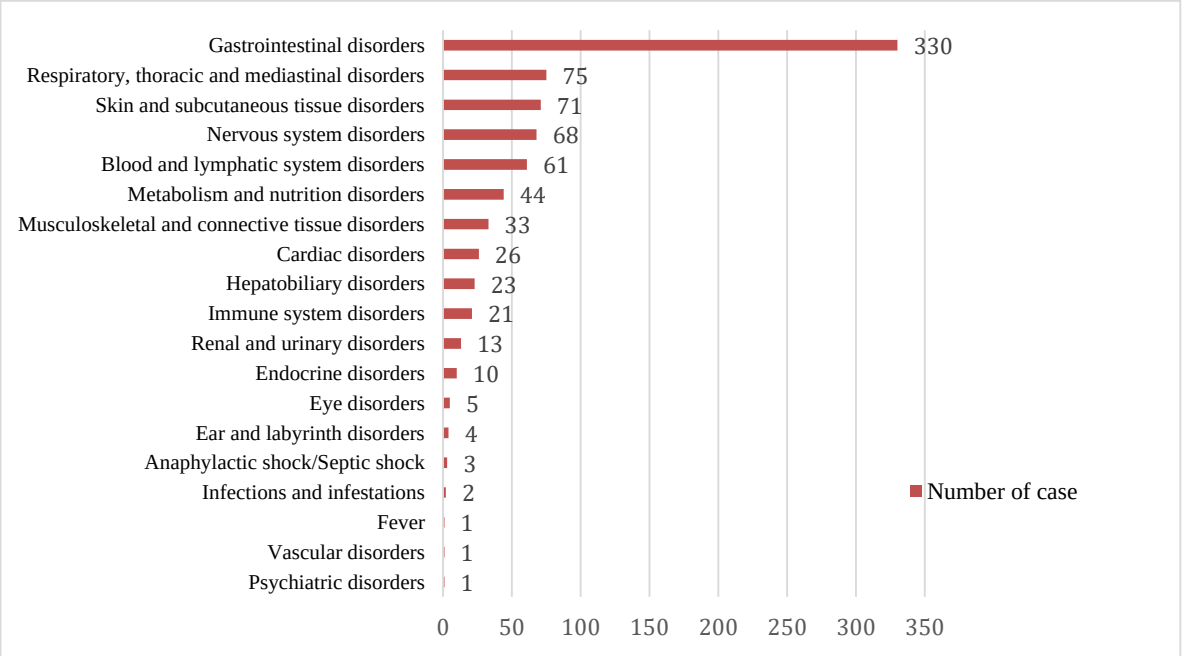

Figure 1. Clinical Manifestation of Suspected ADRs classified by SOC according to MedDRA®

Patient demographic characteristics are presented in Table 1. Of all cases, 430 cases of ADR were experienced by women, and the rest were men (343); therefore, women tended to experience more ADRs than men (55,6% vs 44.4%). This is in line with global post-marketing surveillance data on spontaneous reports, which indicates that women, especially in their reproductive years, have more ADRs than men (Watson et al., 2019). Previous studies have also stated that women have an approximately two-fold higher risk of ADRs than men. Several studies have also reported the existence of a specific pattern and relationship between sex, pharmacokinetic-pharmacodynamic parameters, and ADR incidence. In general, women have a lower body weight and organ size but a higher percentage of body fat, which affects the absorption and distribution of drugs. The larger the volume of distribution (Vd), the more likely it is that the drug will be found in body tissue. Research has shown that 86 types of FDA-approved drugs result in increased drug levels and longer drug elimination times in women than in men, making them a greater potential for ADR incidence (Zucker and Prendergast, 2020). Another study in Indonesia found that female patients were more likely to experience ADR to oral hypoglycemic drugs than were male patients (Yosmar et al., 2018).

The largest age group exposed to ADR was adults (19-60 years), which is in line with previous studies (Gupta et al., 2017; Keche et al., 2021). Geriatrics aged > 60 years were in the second position with 159 cases (20.6%), followed by pediatrics with 31 cases (4%), as shown in Table 1. Approximately a quarter of the geriatric patient population admitted to the hospital experienced at least one type of ADR during their period of hospitalization (Yadesa et al., 2021). Various physiological changes occur in geriatrics, including changes in the pharmacokinetic and pharmacodynamic responses to drugs inside the body, making them more susceptible to ADR (Yadesa et al., 2021). Reduced organ perfusion also implies deprivation of liver function, causing a decline in the hepatic clearance of certain drugs. In addition, along with the aging process, kidney function and muscle mass decrease, so the glomerular filtration rate decreases even though serum creatinine levels are within the normal range (Corsonello, Pedone, and Incalzi, 2010). Apart from physiological changes, various degenerative diseases in geriatric patients could trigger polypharmacy in their therapeutic management, which was also associated with a higher risk of ADR in this age group. On the other hand, the occurrence of ADR in geriatric patients could reduce patient compliance and detain the expected therapeutic outcomes, resulting in a higher burden and cost in healthcare services (Yadesa et al., 2021).

The top five main diagnoses were infectious diseases (23.4%), malignancies (23.2%), kidney and urinary tract disorders (13.2%), blood and lymphatic system disorders (11.3%), and immune system disorders (8%). Approximately 23.4% of patients presented with hypertension as a comorbidity, 17% had infections, 15.5% had kidney impairment, 11.2% had other cardiovascular disorders, and 10.1% had diabetes mellitus. Ferner and Aronson (2019) stated that diseases can affect the absorption, distribution, metabolism, and

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elimination of drugs, particularly those related to kidney and hepatic impairment. Higher drug concentrations can occur due to reduced hepatic metabolism and renal elimination, leading to a higher chance of ADR manifestation (Ferner and Aronson, 2019). Furthermore, the influence of other diseases and conditions remains poorly explored. Of all the patients, 93.4% received 1–4 medications during the hospitalization period. The concurrent use of medication and drug–drug interactions is well established and is an important cause of avoidable ADRs (Ferner and Aronson, 2019). Therefore, it is highly recommended that healthcare providers monitor any potential or major drug-drug interactions.

Most ADR were gastrointestinal disorders (330, 41.7%), followed by respiratory tract disorders (75, 9.5%), skin and subcutaneous tissue disorders (71, 9%), neurological disorders (68, 8.6%), and blood and lymphatic system disorders (61, 7.7%) (Figure 1). Among all ADR reports, antineoplastic agents (19.5%) were in the first rank of suspected drugs, followed by systemic antibacterials (16.4%), antihypertensives (12.5%), analgesics/anti-inflammatory drugs (9.6%), and antituberculosis drugs (8.9%) (Figure 2). The top five classes of suspected drugs for ADR were in line with the pharmacovigilance data of 2022 in Indonesia, which mentioned the top 10 suspected drugs for ADR, namely antituberculosis, systemic antibacterial, and antineoplastic drugs (BPOM RI, 2023). Aagaard et al. (2012), who examined ADR patterns reported worldwide over the last 10 years (2000-2009), also found that in developed countries, the highest prevalence of ADR was found in antineoplastic and immune system-related drugs, whereas in developing countries, the highest prevalence of ADR was found in systemic antibacterials (Aagaard et al., 2012). Other studies have reported that antibacterials contribute to 33-68% of ADR incidents (Keche et al., 2021). However, chemotherapeutic agents are known to cause potentially serious ADR. For example, in a study conducted on more than thousand chemotherapy patients in France, almost half experienced ADR (Ingrand et al., 2020).

In 40% (309) of ADR cases, the suspected drugs were continued with antagonists/antidotes, such as urticaria and diarrhea manifestation due to afatinib. Afatinib was continued with antihistamines and supportive therapy for diarrhea. In 246 (31.8%) cases, the drugs were stopped without antagonists/antidotes, for example, in toxic optic neuropathy due to linezolid toxicity in drug-resistant tuberculosis patients. In another case, prolonged QT interval was suspected due to Levofloxacin, Bedaquiline and Clofazimin. The drugs were discontinued, the patient's heart rhythm was monitored periodically, and the anti-tuberculosis regimen was changed without any addition of antagonists/antidotes. Furthermore, in 143 (18.5%) cases, the suspected drugs were stopped with antagonists/antidotes, such as in bleeding manifestations due to Warfarin and Clopidogrel, the drugs were stopped, and the patients were given Vitamin K injection as a warfarin antagonist and Tranexamic Acid as an antifibrinolytic. However, in 75 (9.7%) patients, the drugs were continued without antagonists/antidotes. In these cases, patients generally showed improvement without specific antagonist/antidote or the symptoms improved with dose reduction, so the drug could be continued with consideration of greater benefits, for example, in constipation cases due to bortezomib injection in multiple myeloma patients and hypokalemia due to furosemide. actions taken during the follow-up of ADRs are shown in Figure 3.

Regarding ADR outcomes, most patients (482; 62%) recovered, while the remaining patients (163; 21.1%) recovered with residual symptoms, had not recovered yet (131; 13.1%), or had unknown outcomes (15; 1.9%) because the patients were moved to another ward or the data were incomplete. Unfortunately, 1.5% (12 cases) of patients died due to progression of the main disease and poor prognosis (Figure 4).

This study was conducted retrospectively using ADR report data history; therefore, the limitation of this study was that only the available data archives with all of their limitations could be analyzed. Most ADR reports collected lacked details describing the chronology of ADR occurrence, making causality analysis difficult. In fact, some improvements and adjustments were required for the internal reporting links so that the ADR reports collected would be more complete and reliable; thus, they could be analyzed comprehensively in the future. We hope this article adds to the information on pharmacovigilance data in Indonesia, particularly data from tertiary hospitals. In addition, it is hoped that healthcare workers as professional care providers will take an active role in detecting and reporting ADR incidence to collect more drug post-marketing surveillance data and to enhance drug safety monitoring in Indonesia.

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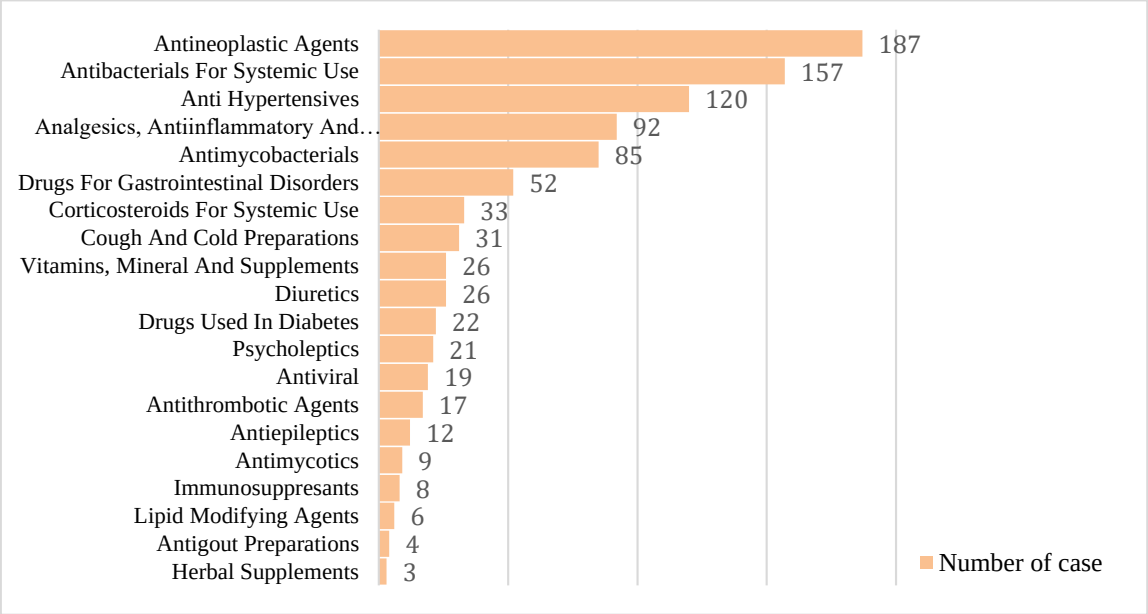

Figure 2. Drug Classes Suspected for ADRs classified by ATC code 2nd level

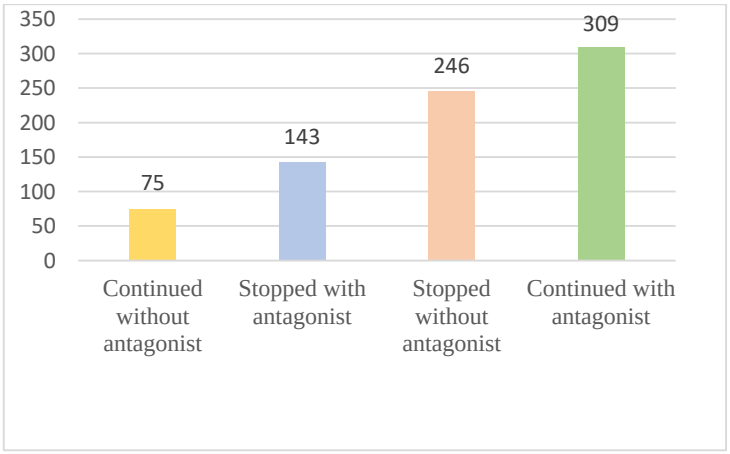

Figure 3. Follow up to suspected ADRs

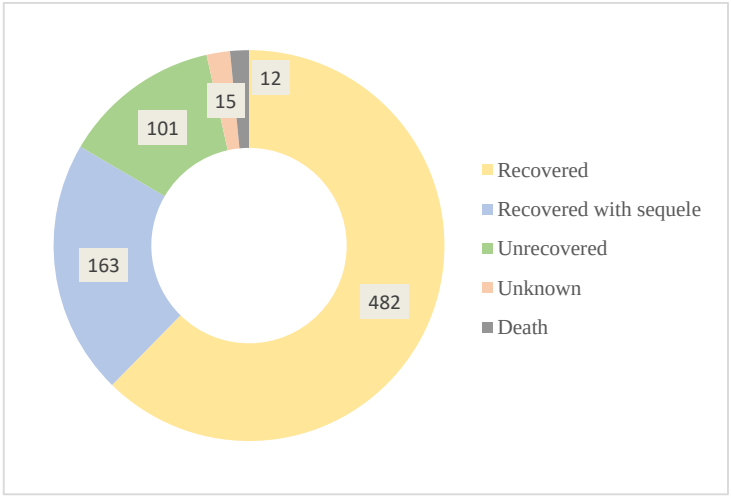

Figure 4. Output of Suspected ADRs

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CONCLUSION

Antineoplastic, systemic antibacterial, and antihypertensive drugs appeared to be the most common drugs for suspected ADR in this hospital. ADR reporting has been running well, but not all healthcare workers have participated actively. Most ADRs manifest as gastrointestinal, respiratory, or subcutaneous skin disorders. Hopefully, the results of this research will contribute to upcoming strategies for pharmacovigilance activities in this hospital and other healthcare facilities to improve the quality and quantity of ADR reporting, especially in Indonesia, to increase the safety of medication usage.

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AUTHOR CONTRIBUTIONS

Conceptualization, C.M.S., B.S.; Methodology, C.M.S.; Software, C.M.S.; Validation, B.S.; Formal Analysis, C.M.S.; Investigation, C.M.S.; Resources, B.S.; Data Curration; B.S.; Writing - Original Draft, C.M.S.; Writing - Review & Editing, B.S.; Visualization, C.M.S.; Supervision, B.S.; Project Administration, C.M.S., B.S.; Funding Acquisition, C.M.S., B.S.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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