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RESEARCH ARTICLE

Adverse drug reactions evaluation of antimicrobials in COVID-19 inpatients using Modified Trigger Tool and Naranjo Algorithm

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Abstract

Background: The use of antimicrobials in COVID-19 treatment might increase the risk of adverse drug reactions (ADR). Therefore, the adverse effect further identification was needed to understand the safety profile of using these medicines. **Objective:** The research aims to evaluate the adverse effects of the use of COVID-19 antimicrobial agents, causality analysis, and factors related to this ADR. **Method:** Cross-sectional study using random sampling was conducted to obtain the data. The study used samples from COVID-19 adult inpatients in a hospital located in Java from July-December 2020. Adverse events (AE) were detected by a modified trigger tool using medication and laboratory result module triggers with 21 total triggers. Causality analysis of ADR was conducted using Naranjo Scale. **Result:** Of the 107 patients examined in this study, 92 patients had triggers. A total of 274 adverse events were found, where 265 adverse events were detected using the trigger tool, and 9 adverse events were detected without the trigger tool. The results of the ADR analysis using the Naranjo algorithm were obtained from as many as 126 ADRs in 60 patients with possible (94.4%) and probable (5.6%) scoring. The most common antimicrobials that cause ADR were azithromycin and oseltamivir. The most effective trigger in detecting ADR was the use of sedation with a positive predictive value of 0.67. The statistical analysis results showed no relationship between gender, age, comorbidities, severity, and body mass index on the incidence of ADR (p>0.05). **Conclusion:** Adverse drug reactions were commonly found in the use of azithromycin and oseltamivir for COVID-19 patients, so it is necessary to consider the choice of this therapy. The trigger tool and Naranjo algorithm were adequate to help the ADR monitoring process.

Introduction

Corona Virus Disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shereen *et al.,* 2020). The virus is a new type of virus from the Coronavirus family that can cause various respiratory system diseases ranging from mild to severe symptoms. Since the first case was reported, COVID-19 has spread worldwide, and in October 2020, the number of reported cases reached 39 million worldwide. COVID-19 first entered Indonesia on the 2nd of March, 2020, and has spread to all provinces in Indonesia (Satuan Tugas Penanganan COVID-19, 2021).

In 2020, there is no definite specific drug to suppress the replication of SARS-CoV-2 (Setiadi *et al.,* 2020). Many patients received off-label therapies such as azithromycin, favipiravir, and remdesivir (Kalil, 2020). At that time, COVID-19 therapy in Indonesia used antimicrobials, non-opioid analgesics, selective beta-2 adrenoreceptor agonists, benzodiazepine central nervous system drugs, mucolytic, and vitamins (PDPI, PERKI, PAPDI, PERDATIN, & IDAI, 2020). Using off-label drugs for handling COVID-19 can increase the risk of

adverse drug reactions. Therefore, monitoring ADRs is important to the patient receiving the Covid-19 treatment.

The current reporting system of adverse drug reactions (ADRs) to authority is active and voluntary. In the hospital or other healthcare facilities, the detection of ADRs can be observed from the patient's drug use history. After conducting the analysis, the ADRs can be reported to the authority using a yellow card. However, this system led to the inefficient reporting of ADRs and it also made it difficult to detect adverse reactions (Pontefract, 2016). Therefore, a simpler and more efficient method is needed to detect drug reactions. One of which is the Trigger Tool.

A trigger tool is a method developed to detect adverse events from drugs based on a retrospective or prospective study by observing a trigger that can be triggered in the occurrence of AEs. Various triggers can be observed, such as administering a medication that indicates the presence of AEs (antidote, antidiarrheal, antiallergic, or other medication), laboratory tests, or administering action to the patient (Griffin & Resar, 2009). Research conducted in an emergency unit in a hospital shows that the Trigger tool can help detect the prevalence of ADRs of 2.3% (de Almeida *et al.,* 2017). Based on one study, this method can detect up to ten times AE higher compared to other methods (Classen *et al.,* 2011).

Therefore, this study was conducted using modified trigger tools relevant to available data in the study centre and Naranjo Algorithm. This study aims to analyse the adverse event (AE) from the use of antimicrobials in the COVID-19 treatment, analysis of their causality to define ADR and influencing factors of the ADR occurrence.

Methods

Design

This study was conducted retrospectively with a cross-sectional study design. Random sampling was applied for inpatient Covid-19 at a hospital in Java, Indonesia, from July to December 2020. The data source was secondary data from medical records, prescriptions, treatment records, nurse records, and patient laboratory results.

Criteria inclusion for the sample in this study were: (1) inpatients with Covid-19 from July to December 2020; (2) duration of hospitalisation of more than 24 hours (3) age ≥18 years; (4) The patient's medical record has been completed. However, patients referred to the intensive care unit (ICU) and patients receiving psychiatric treatment or rehabilitation were excluded from this study.

Ethical approval for this study was obtained from Universitas Indonesia Hospital Nomor: 0011/SKPE/KKO/2021/00

Assessment

The modified Institute for Healthcare Improvement (IHI) trigger tool was used to detect the AEs from the data source. The research team modified the global trigger tool to make the trigger apply to the hospital's available data. Finally, two modules (treatment and outcomes laboratory) with 21 total triggers were used for this study. The modified triggers already got approval from IHI but have not been tested yet by IHI. After the AEs were identified, the analysis was continued with the Naranjo algorithm to define the causality analysis of ADRs.

Naranjo's algorithm classifies the possibility of ADR occurring related to the drugs used by various factors such as drug administration with the incidence of ADR, other causes for the occurrence of ADR, drug levels, and patient history with the drugs used (Belhekar, Taur, & Munshi, 2014). The ADR classification based on the scores obtained was divided into four: definite, probable, possible, and doubtful (Naranjo *et al.,* 1981).

The univariate analysis was conducted to determine the distribution and frequency of patients' sociodemographics, patient treatment characteristics, and adverse drug reactions from the data collected. The relationship between patient characteristics and the incidence of ADR was analysed using chi-square analysis. These data were analysed using IBM SPSS Statistics Premium Version 24.

Results

A total of 107 patient data were collected in this study, with most of the patients female 46 (43.5%), aged <60 years old 90 (84.1%), having comorbidities (82.2%) with mild severity 60 (56.1%). Statistical analysis results showed no relationship between gender, age, comorbidities, severity, and body mass index on the incidence of ADR ($p > 0.05$). The sociodemographic and clinical characteristics of the patients can be seen in Table I.

Among 107 patients, 92 patients (86%) were found to have adverse events (AE) that were detected by using trigger tools (Figure 1). A total of 274 adverse events were found, where 265 adverse events were detected using the trigger tool, and 9 adverse events were detected without the trigger tool. The non-trigger adverse effect was found based on medical record including pain (2), headache (2), sleep (1), fatigue (1),

diarrhoea (1), nausea (1), and dizziness (1). All of the adverse events were further analysed using the Naranjo algorithm, and it was found that 60 patients were having 126 events of adverse drug reactions (ADR). The event found was classified with Naranjo probability index as possible (94.4%) and probable (5.6%) (Figure 2a) and 93% found using a trigger and 7% found without a trigger module (Figure 2b).

Table I: Characteristics and demographics of patient

Characteristic	N (%), n=107	Number patients with ADR	Number of patients without ADR	*p*-value†
Gender				
Male	61 (56.5)	32 (52.5%)	29 (47.5%)	0.502
Female	46 (43.5)	28 (60.9%)	18 (39.1%)	
Age (years)				
18-59	90 (84.1)	51 (56.7%)	39 (43.3%)	0.986
≥60	17 (15.9)	9 (52.9%)	8 (47.1%)	
Body Mass Index				
Normal	33 (30.8)	19 (57.6%)	14 (42.4%)	1.000
Below/Above Normal	74 (69.2)	41 (55.4%)	33 (44.6%)	
Severity Grade				
Mild	60 (56.1)	36 (60.0%)	24 (40.0%)	1.000
Moderate-Severe	34 (31.7)	20 (58.8%)	14 (41.1%)	
Unknown	13 (12.1)			-
Comorbidity				
No comorbidity	19 (17.8)	9 (47.4%)	10 (52.6%)	0.556
With comorbidity	88 (82.2)	51 (58.0%)	37 (42.0%)	
Hypertension	26 (24.2)			
Dyspepsia	24 (22.4)			
Diabetes	15 (14.0)			
Anxiety disorder	13 (12.1)			
CAD*	8 (7.4)			

*Coronary Artery Disease; †*p*-value were analysed using Chi-Square Analysis

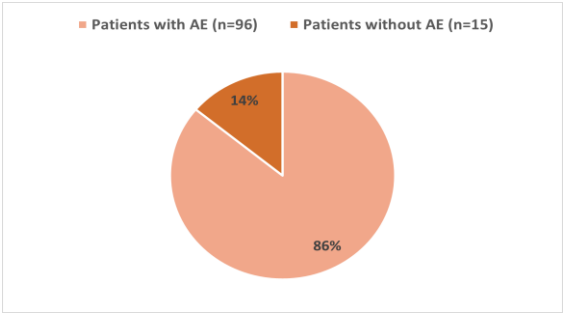
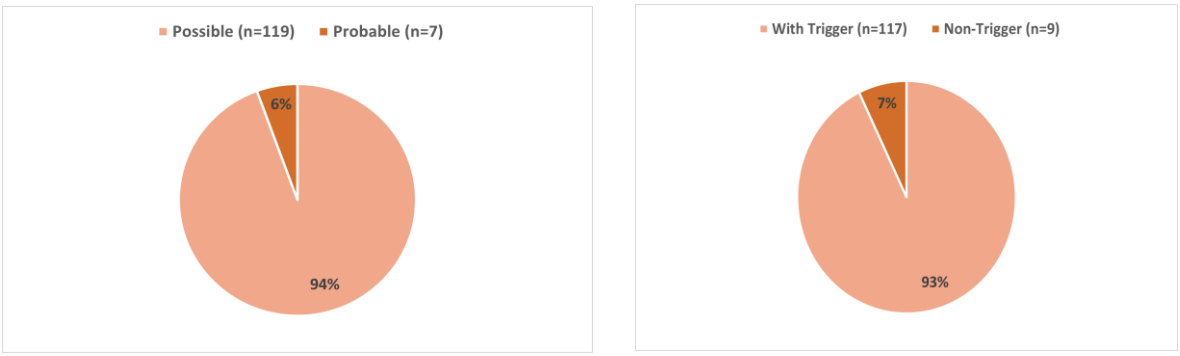


Figure 1: Distribution of patients with AEs positive Modified Trigger Tools



(a) (b)

Figure 2: Distribution of Detected ADRs Found (N=126) based on (a) Naranjo Probability Index and (b) Trigger/Non-Trigger

Most ADRs found to occur were nausea, insomnia, and an ulcer (Figure 3). Using the Naranjo algorithm, drugs that cause ADR can be identified. It was found that the most common drugs that cause ADR were azithromycin and oseltamivir (Table II). Both of these antimicrobial agents possibly caused ADR related to mild gastrointestinal disturbance, neurologic disorder, hypersensitivity reactions, or even changes in laboratory results. Azithromycin is the most common cause of ADR in digestive disorders, elevated transaminase enzymes, headaches, and dizziness. Some antimicrobial agents such as chloroquine, levofloxacin, favipiravir, and ceftriaxone were also identified to cause ADR in COVID-19 patients (Table II).

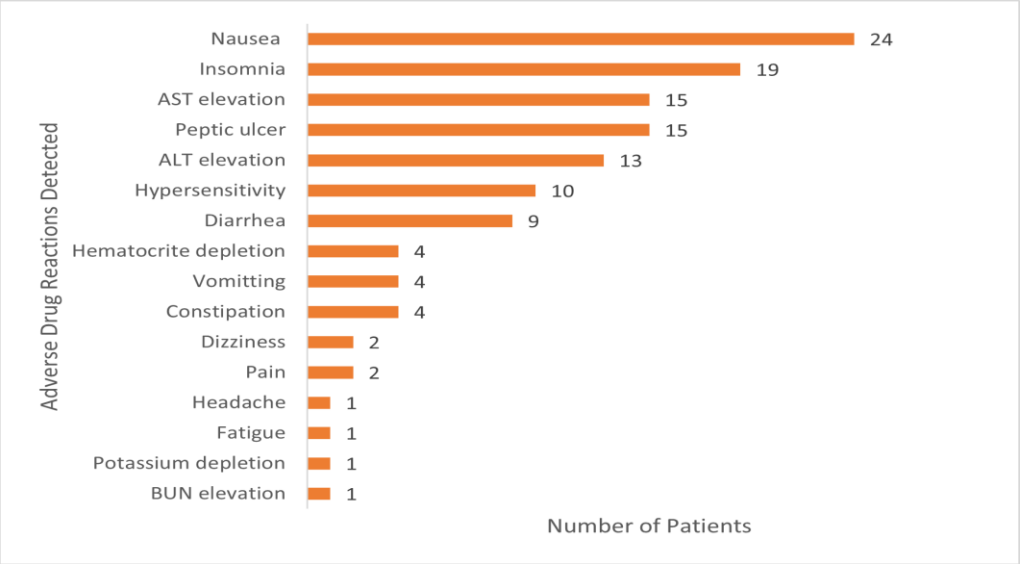


Figure 3: Adverse Drug Reactions occurred in COVID-19 inpatients

Table II: Adverse drug reactions and number of events caused by the antimicrobial agent

Adverse drug reactions	Number of events found						
	Azithromycin	Oseltamivir	Chloroquine	Levofloxacin	Favipiravir	Ceftriaxone	Remdesivir
Gastrointestinal							
Nausea	18	9	9	2	2	1	-
Peptic Ulcer	8	8	3	4	1	-	
Diarrhoea	6	4	1	3	1	-	1
Constipation	3	2	3	1	-	-	-
Vomiting	4	-	2	1	-	-	-
Neurological							
Insomnia	6	12	5	5	1	-	-
Pain	1	-	-	-	-	-	-
Dizziness	-	1	-	2	-	-	1
Headache	1	-	-	-	-	-	-
Fatigue	1	-	-	-	-	-	-
Immunologic							
Hypersensitive	6	4	5	4	-	-	-
Laboratory changes							
↑ AST	9	7	6	4	3	1	-
↑ ALT	8	5	5	4	3	1	1
↓ Haematocrit	1	1	-	3	1	-	-
↑ BUN	1	-	-	-	-	-	-
↓ Potassium	-	-	-	-	1	-	-
Total events	73	53	39	33	13	3	3

↑ = elevation; ↓ = depletion; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransaminase; BUN= Blood Urea Nitrogen

The ADRs that were detected in this study were more frequently using medication triggers with antiulcer as the highest positive triggers. Some patients detected a trigger, but no ADR was detected as in the trigger of a decrease in haemoglobin and an increase in serum creatinine. A positive predictive value is the ratio of the ADR that occurs to the number of positive triggers. This score could be used to evaluate the sensitivity of triggers used to detect ADR. The most effective trigger in detecting ADR was the use of sedation with a positive predictive value of 0.67, followed by an antiemetic agent (0.53) and ALT elevation (0.52). Table III shows the positive predictive value of the trigger and Naranjo algorithm to detect ADR in COVID-19 patients.

Table III: Trigger tools' effectivity to detect ADR

Trigger	Positive (A), N (%)	ADR Detected (B)	Positive predictive value (B/A)
Laboratory triggers			
↑ AST	31 (11.3%)	15	0.45
↑ ALT	25 (9.1%)	13	0.52
↓ Haematocrit	9 (3.2%)	4	0.22
↓ Potassium	4 (1.4%)	1	0.25
↓Haemoglobin	4 (1.4%)	0	0
↑ Increasing BUN	2 (0.7%)	1	0.5
↑Creatinine serum	2 (0.7%)	0	0
Total	**77**	**34**	**Average = 0.277**
Medication triggers			
Antiulcer administration	75 (27.3%)	15	0.17
Antiemetic administration	40 (14.5%)	27	0.53
Sedative agent administration	30 (10.9%)	19	0.67
Antihistamine administration	20 (7.2%)	10	0.5
Laxative administration	13 (4.7%)	4	0.38
Antidiarrhea administration	13 (4.7%)	8	0.46
Medication stops	4 (1.4%)	0	0
Vitamin K administration	2 (0.7%)	0	0
Total	**197**	**83**	**Average = 0.338**

↑ = elevation; ↓ = depletion; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransaminase ; BUN= Blood Urea Nitrogen

Discussion

In this study, patient characteristics (gender, age, BMI, severity index, and comorbid) did not have an association with the risk of ADR occurred. Based on research by Gor & Desai (2008), gender did not affect ADRs incidence. Geriatric patients may be more susceptible to ADR due to homeostatic disorders, polypharmacy, comorbidities, and impaired organ function (Schnader, *et al*., 2004). However, in another study, it was known that COVID-19 patients with high BMI (Body Mass Index) have a high risk of disease complications, so comorbidities such as hypertension and diabetes must be considered (Malik *et al.,* 2020). Patients with an obese BMI have a higher chance of suffering from a more severe degree of COVID-19 (Cai *et al.,* 2020). This is probably due to chronic inflammation and suppression of the immune response. The mechanism of inflammation caused by obesity is still poorly understood. There is evidence that hypoxia occurs as adipose tissue increases in size. Hypoxia can initiate inflammation by inducing the HIF1 gene programme (Saltiel & Olefsky, 2017).

In a study conducted by Guo and authors (2020), patients with comorbidities had a higher risk of developing tissue damage, excessive inflammatory response, and hypercoagulable conditions. This proves that comorbidities play a role in the development of COVID-19 infection (Guo, *et al*., 2020). Metabolic conditions become chronic when viral infections increase the severity and mortality rate of COVID-19 patients. Changes in the metabolic environment and disorders of the immune system caused by hypertension, obesity, and diabetes can increase the severity of the patient (Shah *et al.,* 2020).

The relationship between hypertension and COVID-19 can be explained by using ACE2 (angiotensin-converting enzyme 2) as a receptor for Sars-CoV-2 entry. ACE2 is one of the enzymes that regulate vasodilation and vasoconstriction. The entry of the SARS-CoV-2 virus into the body is influenced by the ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) (Mukherjee & Pahan, 2021). Patients with comorbid hypertension have high angiotensin II levels, which correlate with diastolic blood pressure. Angiotensin II is an inflammatory tissue mediator that

increases vascular permeability and recruits inflammatory cells. During the COVID-19 infection, there is a downregulation of ACE2 and an increase in angiotensin II and tissue inflammation (Shah *et al.,* 2020).

In this study, the number of COVID-19 patients with ADR was higher in the patients with comorbidities than those without comorbidity but not statistically significant. Similarly, in another study on patients with malaria, patient with comorbidity were three times more likely to have ADR than patients without comorbidity (Bassi *et al.,* 2017). ADRs also increase in patients with COVID-19 with comorbidity of hypertension, diabetes mellitus, and ischemic heart disease due to drug-drug interactions (Yadav, Rohane & Velhal, 2021).

The most ADRs found to have occurred in this study were nausea, insomnia, and peptic ulcer. This is not too different from the previous research conducted by Sun and authors (2020), regarding the incidence of ADR in COVID-19 patients in China which found that the most common ADRs were gastrointestinal disorders (23%), liver injury (13.8%), rash (4.15%) and hyperlipidaemia (1.3%). Besides that, in the study conducted, azithromycin and oseltamivir were the two types of antimicrobials that caused the most ADR.

In another study, azithromycin also found an increase in the enzyme transaminase in 1.5% of patients and cardiotoxicity, especially if combined with hydroxychloroquine (Eftekhar *et al.,* 2021). Azithromycin has antiviral and immunomodulatory properties that may play a role in the treatment of COVID-19. The immunomodulating properties of azithromycin that can downregulate cytokines, maintain epithelial cell integrity, and prevent lung fibrosis may play a role in the inflammatory stage of COVID-19 (Esnal, *et al.*, 2020). Azithromycin enhances the immune response to viruses by increasing the production of interferon types I and III and genes involved in virus recognition, such as MDA5 and RIG-I. These mechanisms are universally involved in the body's response to infectious agents and potentially against SARS-CoV-2. (Bleyzac *et al*., 2020). Currently, the use of azithromycin is often an option if a COVID-19 patient is suspected of having bacterial co-infection or is accompanied by atypical pneumonia but must still be considered due to the risk of bacterial resistance (Gysenlinck, 2021), and guideline recommendations in each country (Gbinigie & Frie, 2020). Due to the high risk of side effects associated with the use of azithromycin in this study, this agent should be reconsidered for its use in COVID-19 patients.

Oseltamivir has also been found to be at risk for side effects in other previous studies. Influenza patients taking oseltamivir experienced the most ADR nausea, vomiting, abdominal pain, and headaches (Strong *et al*., 2009). The most common ADRs in other previous studies from the use of favipiravir were gastrointestinal disorder, increased uric acid, decreased neutrophil count, increased AST, increased ALT, and increased triglycerides (Joshi, *et al*., 2021). However, in this study, it was found out four events of ADRs are caused by favipiravir. The difference that occurred in this study could be due to the small number of samples using favipiravir (12.1%).

The medication trigger in this study was proven to produce a higher amount of ADR than laboratory results. The results of this study contradict the research conducted by Gadde, Dhanenkula, & Kammila (2018), which also uses the trigger tool and the Naranjo algorithm. In that study, it was found that ADR was detected more with laboratory triggers than with drug use triggers. This difference may occur due to differences in research methods and the different triggers used (13 triggers with 6 triggers for drug use). Trigger tool modifications carried out in this study can help better ADR detection.

The results of this study indicate that the most common triggers found are the use of antiulcer and antiemetic. A large number of patients with comorbid dyspepsia may be the cause of the large use of antiulcer drugs in COVID-19 patients at this hospital. The PPV value for an antiulcer is 0.17, which is due to a large number of antiulcer uses, but few of the patients taking antiulcer have ulcerative ADR. The widespread use of antiulcer can be attributed to the large use of antimicrobials for COVID-19 patients. The antimicrobials used include azithromycin, oseltamivir, chloroquine, and levofloxacin. The most common ADR reported from these antimicrobials is gastrointestinal disorder so an anti-ulcer is prescribed to prevent the ADR. The use of sedation has a PPV of 0.67 this may be due to the administration of sedation used as a response to the occurrence of insomnia side effects after antimicrobial administration. Another study conducted by previous researchers also showed that the increase in BUN (Blood Urea Nitrogen), the use of antiemetics (Naessens, *et al*., 2010) and antihistamines (Pandya *et al*., 2020) were also sensitive enough to detect ADR.

This study shows that combining a modified trigger tool (medication and laboratory results) and the Naranjo Algorithm has excellent potential for detecting side effects, especially in COVID-19 patients. The application of this tool has the potential to be developed in studies to detect other infectious diseases. However, the choice of trigger tools to be used could be chosen by considering the ADR potential for each therapy, the nature of the diseases, and the patient's condition.

This study had shortcomings where the data taken were retrospective data obtained from secondary data (medical records and other sources). This causes the data collected to have some shortcomings if there are events that are not written in the medical record. In addition, the use of the Naranjo algorithm in COVID-19 patients in Indonesia also has limitations because it is not common to do challenges, placebos, dose increases and decreases, and drug levels in body fluids.

Conclusion

Adverse drug reactions were commonly found in the use azithromycin and oseltamivir for COVID-19 patients so it is necessary to consider the choice of this therapy. The combination between the modified trigger tool and the Naranjo scale was found to be adequate to help the ADR monitoring process.

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