Severity and Risk Rating of Drug-Drug Interaction Potency in Chronic Kidney Disease in Public Health Hospital

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Abstract

Background: Chronic kidney disease has emerged as a prominent cause of mortality worldwide in the last two decades. Drug interactions are a significant problem in individuals with chronic kidney disease, as they often receive numerous concurrent treatments. The aim is to examine the frequency of drug-drug interactions in outpatient treatment for chronic renal disease, classified according to their severity and risk level. Furthermore, the study aims to demonstrate the combined effect of the most common drug-drug interactions potency and associated risk factors.

Methods: This study is a retrospective cross-sectional analysis of outpatients diagnosed with chronic kidney disease at Ansari Saleh Public Hospital in Banjarmasin, Indonesia. Medical records from 2022 were obtained retrospectively from computerised sources. The evaluation of potential interactions between drugs was conducted using Lexicomp®. The categorical data were displayed as percentages, and the continuous variables were depicted as means.

Results: The study found that most drug interactions fell into the moderate severity (77.1%) and category C (75.5%) for the risk assessment. The prevalence of drug-drug interactions was 83.6% and the average number of potential drug interactions per patient was 3.34 ± 3.481. The concurrent use of candesartan and furosemide was the most prevalent drug-drug interaction (5.1%). The number of prescribed medications was a notable determinant for probable drug-drug interactions ($p < 0.05$).

Conclusion: Identifying and averting potential drug-drug interactions is crucial to guarantee patient safety.

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Keywords: Adverse Effect; Medication Error; Polypharmacy

Introduction

Drug-drug interactions potency refers to the potential for drug interactions to occur when two or more medications are used together, regardless of whether harm actually arises (1). Meta-analysis studies indicated that the prevalence of drug-drug interactions in hospital settings was 72.2% (2). Furthermore, drug-drug interaction has the potential to cause adverse drug effects (1). Significant drug-drug interaction can increase the likelihood of treatment failure or even mortality (1,3). It was shown that drug-drug interaction were responsible for around 28% of drug and adverse drug reaction (4). As a result, recognizing and managing drug-drug interactions potency is crucial for patients.

Potential drug interactions are of particular concern in chronic kidney disease, who are frequently treated with multiple concomitant medications. Chronic kidney disease is characterized by a diminished estimated glomerular filtration rate or enhanced urine albumin detectable for at least 90 days, as well as irreversibility and progression (5,6). Chronic kidney disease is a progressive ailment that impacts over 10% of the worldwide populace, which amounts to over 800 million individuals. Chronic kidney disease has become a leading cause of death globally over the past twenty years. Chronic kidney disease poses a substantial burden in countries with low and intermediate economic levels (6). In Indonesia, the prevalence of chronic kidney failure was 3.8% in 2018, an increase from 2.0% in 2013 (7). Pharmacotherapy is one of the strategies used to reduce the progression of chronic kidney disease in patients (5). Research has demonstrated that individuals with chronic kidney disease are prescribed a range of six to

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ten drugs, which is indicative of polypharmacy (4,8–10). The utilization of polypharmacy result in medication-related problems due to drug interactions (11–13).

Multiple investigations have found that drug-drug interactions potency are widespread in chronic kidney disease, with prevalence ranging from 61.9% to 92.5% in various studies (3,8,9,14,15). Prior research in Indonesia, Iran and Spanyol has determined the occurrence rate of probable drug-drug interactions by categorizing them according to their severity. The prevalence of minor interactions ranged from 9.1% to 33.84%, moderate interactions ranged from 64.65% to 77.3%, and serious interactions ranged from 2% to 11.4% in patients chronic kidney disease (9,14–16). Furthermore, potential drug interactions can be categorized according to the risk rating. The risk rating is classified as A, B, C, D, or X. The transition from A to X is accompanied by a heightened sense of urgency over the necessary course of action (17). Studies in Spain and Turkey examined the risk of probable drug-drug interactions in chronic kidney disease. Both studies found that the prevalence of risk category A drug interactions was 0.8 to 1.2%, category B was 9.1 to 10.5%, category C was 77.3 to 78.9%, category D was 7.9 to 11.4%, and category X was 1.1 to 1.9% (9,18).

Adverse drug reactions can arise due to drug-drug interactions, and clinicians may not be aware of the clinical hazards associated with certain combinations of drugs. Drug-drug interactions are a major factor leading to hospital visits, resulting in a substantial cost burden. Acquiring additional knowledge about drug-drug interactions to diminish the occurrence of undesirable effects related drug-drug interactions. Also assist in the management of drug-drug interactions, thus enhance clinical pharmaceutical safety (1,17).

Although numerous studies have carefully assessed the risk of drug-drug interactions in chronic kidney disease, there is a lack of research that specifically examines the risk rating, the management and the correlated risk of drug-drug interactions among patients with chronic kidney disease in Indonesia. Hence, the objective of this research was to investigate the prevalence of drug-drug interactions categorized by severity and risk rating in prescriptions among individuals receiving outpatient care for chronic kidney disease. Additionally, the study aimed to present the combination of the most common drug-drug interactions potency and correlated risk factors.

Methods

A retrospective cross-sectional study conducted on outpatients with chronic kidney disease at Ansari Saleh Public Hospital in Banjarmasin, Indonesia. Research was conducted from August to September 2023. Data were retrospectively acquired from computerized medical records for the year 2022. The individuals included in the study were over 18 years of age and received treatment that involved the administration of two or more drugs. Excluded from the study were medical records with incomplete data, including age, gender, and comorbidities. The current study protocol has been registered with and granted approval by the Ethics Committee for Health Research, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin (No. 061/FK ULM/EC/IV/2023).

Assessment and categorized of potential drug-drug interactions was performed using Lexicomp®. The most popular program for analyzing medication interactions was Lexicomp® (19). The efficacy of Lexi-interact as a drug-drug interactions screening tool has been assessed, and it is largely regarded as one of the most efficient options currently available. Research has determined that Lexi-interact exhibits a high level of sensitivity (96%), specificity (80%), and overall performance (89%). In addition, it provides suggestions on how to avert and manage drug– drug interactions in case they arise. (20).

The Lexicomp® software is classified into drug-drug interactions according to their severity and risk rating. Severity and risk rating categorization refers to the Lexicomp® software (21).

The severity category is divided into three levels (22):

a. Minor, which refers to mild effects that can be easily overcome;

b. Moderate, which indicates moderate effects that can result in organ damage; and

c. Major, which signifies fatal effects that can lead to death.

The risk rating category is divided into (16):

a. Category “A”: No known interaction

b. Category “B”: The absence of necessary intervention to manage drug interactions;

c. Category “C”: Monitoring is necessary to detect potential harmful outcomes resulting from drug interactions;

d. Category “D”: The occurrence of undesirable consequences is quite likely in cases of drug interaction; hence it is advisable to investigate alternate treatments that are safer;

e. Category ‘X’: The medicine combination is not recommended and must be averted due to its clinically substantial side effects.

The open epi calculator was utilized to determine the sample size in the research, using a confidence level of 80%, a precision of 5%, and a population of 123 patients with chronic kidney disease medical records in 2022. The calculation yields a study sample of at least 71 medical record patients. Researchers retrieved information from medical records, including age, gender, diagnosis, comorbidities, disease's stage, laboratory results (creatinine), and patient therapy and dialysis status. The laboratory results (creatinine) were solely used to confirm the disease's stage. This study included no participants on dialysis.

The categories of variables were shown as percentages, and the continuous variables were displayed as means together with their respective standard deviations. Statistical approaches were used to assess the patients' age, gender, number of prescriptions, and potential drug-drug interactions. Subsequently, a test known as the Chi-square was used to investigate the variables associated (age, gender of the patients and number of prescriptions) with potential drug-drug interactions. Statistical significance was defined as a p-value of less than 0.05. Statistical analyses were performed using IBM SPSS statistical software (version 25).

Results

Finally, in this study, 73 patients with chronic kidney disease with medical records were included. Potential drug interactions were discovered in 61 (83.6%) of the medical records reviewed. The average number of potential drug interactions per patient was 3.34 ± 3.481. The prevalence of probable drug interactions was 72.1% in men and 27.9% in women; the age group 25-64 years was 55.7% and the number of prescribed medicine 6 or more (59%), (Table 1). The medications with the highest prescription rates were candesartan, bisoprolol, paracetamol, diltiazem, furosemide, folic acid, and clopidogrel. The study found that patient with chronic kidney disease had comorbidities such as hypertension (34.2%), diabetes mellitus (31.5%), hypertension-diabetes mellitus (9.6%), and other conditions. In the present investigation, most of the patients were classified as stage 4 of chronic renal disease.

Table 1. Characteristics and Factor Associated with potential drug-drug interactions

Characteristics		Drug-drug interaction potency		P-value	Odds ratio (95% CI)
		Yes (%)	No (%)		
Age	25-64 years old	34 (55.7)	8 (66.7)	0.484	0.630 (0.171-2.315)
	≥ 65 years old	27 (44.3)	5 (33.3)		
Gender	Man	44 (72.1)	9 (75)	1.000	0.863 (0.208-3.575)
	Women	17 (27.9)	3 (25)		
Number of prescribed medications	2-5	25 (41)	10 (83.3)	0.007*	0.139 (0.028-0.689)
	≥ 6	36 (59)	2 (16.7)		
Total		61 (100)	12 (100)	-	-

Uji Chi-square (*); CI: Confidence interval

The chi-square statistic revealed that the prevalence of drug-drug interactions potency varied significantly depending on the number of concurrent drugs in the group ($p < 0.05$). Nevertheless, there were no significant differences in the prevalence of drug interaction potency between the gender ($p = 1.000$) and age ($p = 0.191$) groups. Patients who were prescribed more than six drugs had a higher risk of drug interaction potency (OR: 0.139, CI: 0.028-0.689) (Table 1).

Severity categorization refers to the Lexicomp® software. The severity of drug-drug interactions potency was classified as minor, moderate, and major, with proportions of 13.4%, 77.1%, and 4.7%, respectively (Table 2). Most of the risk of drug interaction potential was classified as C: monitor therapy (75.5%), followed by B: no action needed (10.7%), D: consider therapy modification (8.3%), and X: avoid combination (0.8%) (Table 3). Candesartan/Furosemide was the most common interaction among all potencies of drug interactions (n = 13), followed by Bisoprolol/Furosemide (n = 12) and Bisoprolol/Diltiazem (n = 10) (Table 4). In category X (avoid combination) were found Silodosin / Tamsulosin and Domperidone / Diltiazem were found (Table 5).

Table 2. Severity of drug-drug interaction potential

Severity of drug-drug interaction potential	Frequency (%)	Combination of drug-drug interaction potency (top 3)
Minor	34 (13.4)	Clopidogrel/ Atorvastatin
		Parasetamol/ Tramadol
		Gliquidone / Calcium Carbonate
Moderate	195 (77.1)	Candesartan/ Furosemide
		Bisoprolol/ Furosemide
		Bisoprolol/ Diltiazem
Major	12 (4.7)	Codeine / Cetirizine
		Spironolactone / Candesartan
		Clopidogrel / Lansoprazole
Total	253 (100)	-

Table 3. Risk of drug-drug interaction potency

Risk of drug-drug interaction potency	Frequency (%)	Combination of drug-drug interaction potency (top 3)
A: No action needed	0 (0)	-
B: No action needed	27 (10.7)	Clopidogrel/ Atorvastatin
		Parasetamol/ Tramadol
		Gliquidone / Calcium Carbonate
C: monitoring therapy	191 (75.5)	Candesartan/ Furosemide
		Bisoprolol/ Furosemide
		Bisoprolol/ Diltiazem
D: consider therapy modification	21 (8.3)	Bisoprolol / CloNIDine
		Ferrous Fumarate / Calcium Carbonate
		Gliquidone / Acarbose
X: avoid combination	2 (0.8)	Silodosin / Tamsulosin
		Domperidone / Diltiazem
Total	253 (100)	-

Table 4. Type X potential drug-drug interactions found

Combination of drug-drug interaction potency	Potential clinical outcome	Mechanism of drug-drug interaction potency
Silodosin / Tamsulosin	Alpha1-Blockers can intensify the blood pressure-lowering impact of additional Alpha1-Blockers.	additive pharmacologic impact such as low blood pressure and fainting.
Domperidone / Diltiazem	Diltiazem can elevate the levels of Domperidone in the bloodstream.	inhibition of CYP3A4, an enzyme responsible for domperidone metabolism

Table 5. Potential clinical outcome, mechanism, severity, risk, and management of potential drug-drug interaction for the top 10 combination drugs found mostly

Combination of drug-drug interaction potency	N (%)	Potential clinical outcome	Mechanism	Severity	Risk	Management
Candesartan/ Furosemide	13 (5.1)	Furosemide may enhance the hypotensive effect of angiotensin II receptor blockers	The state of reduced volume caused by the use of loop diuretics, along with the widening of blood vessels in the periphery and the first decrease in blood flow to the kidneys caused by the angiotensin receptor blocker (ARB).	Moderate	Category C	Changes in blood pressure and renal function should be monitored, due to the risk of severe hypotension and decreased renal function. Temporary discontinuation or reduction in loop diuretic or ARB dosage may be required.
Bisoprolol/ Furosemide	12 (4.7)	Furosemide may enhance the hypotensive effect of bisoprolol	The mechanism of this interaction is the additive hypotensive effects due to the depletion of the volume associated with the loop diuretic and the therapeutic actions of antihypertensives.	Moderate	Category C	Close monitoring of blood pressure is recommended, and antihypertensive dosages should be adjusted accordingly if needed.
Bisoprolol/ Diltiazem	10 (4)	potential to cause bradycardia	Bradycardia-causing agents can potentiate the bradycardic impact of additional Bradycardia-causing agents.	Moderate	Category C	Monitor therapy
Clopidogrel/ Atorvastatin	7 (2.8)	Atorvastatin may diminish the antiplatelet impact of Clopidogrel.	The conversion of clopidogrel to its active metabolite is hindered by atorvastatin, which acts as a substrate for the enzyme CYP3A4.	Minor	Category B	No action needed
Clopidogrel/ Diltiazem	7 (2.8)	Calcium channel blockers may diminish the therapeutic effect of clopidogrel.	Diltiazem mediated inhibition of the metabolic activation of clopidogrel considering that most diltiazem are substrates for and/or known inhibitors of CYP3A4, one of the enzymes believed responsible for the activation of clopidogrel	Moderate	Category C	Monitor therapy
Furosemid/ Aspirin	6 (2.4)	Aspirin can reduce the effectiveness of Furosemide. Furosemide has the potential to elevate the levels of aspirin in the blood.	Competition between furosemid and aspirin for the transport of organic acids in the renal proximal tubule, resulting in impaired renal elimination. Aspirin alteration of renal prostaglandins may also be involved.	Moderate	Category C	Monitor therapy
Parasetamol/ Tramadol	5 (2)	Opioid agonists may decrease the absorption of Acetaminophen	Opioid-induced dysfunction in stomach motility and emptying of the gastric can cause a delay in the absorption of acetaminophen, potentially leading to decreased absorption.	Minor	Category B	No action needed
Clonidin/ Diltiazem	5 (2)	potential to cause bradycardia	Bradycardia-causing agents can potentiate the bradycardic impact of other Bradycardia-causing agents.	Moderate	Category C	Monitor therapy
Aspirin/ Diltiazem	5 (2)	Diltiazem may increase the antiplatelet impact of Aspirin	The mechanism of these interactions is unknown, although it has been hypothesised that calcium channel blockers inhibit thromboxane B2 production and/or interfere with platelet calcium metabolism.	Moderate	Category C	Monitor therapy
Amlodipin/ Furosemid	5 (2)	Furosemid may enhance the hypotensive effect of amlodipin	Additive hypotensive effects due to furosemide-associated volume depletion and the therapeutic actions of amlodipin	Moderate	Category C	Monitor therapy

Discussion

According to current studies, drug-drug interactions are widespread among chronic kidney disease. Several factors can contribute to the presence of drug-drug interactions in hospitalized patients with chronic kidney disease. The prevalence of potential drug interactions in patients with chronic kidney disease in this study is consistent with previous studies. The results of previous studies in Indonesia showed a prevalence of potential drug interactions of 61.9%–85.7% (14,15). According to the results of research in Saudi Arabia and Spain, Saudi Arabia obtained a prevalence of 85.3%–92.5% (3,8,9,23). Some of these studies used the Lexicomp application to assess drug interactions, but others also used other applications such as Micromedex, Medscape, and Drugs.com. Each patient in this study had the potential to experience three drug interactions. Previous research obtained similar results, where 36% of patients with chronic kidney diseases had the potential to experience up to 1-5 drug interactions (9). The number of drugs received by chronic kidney disease patients in the study was at least two and at most twelve drugs.

The results of the current study show that patients who can experience drug interactions with patients who receive drug prescriptions for six drugs (5.92 ± 2.35). In line with previous studies (8,9,15). The use of more than five drugs by patients at one time is called polypharmacy (10). The study of polypharmacy in the treatment of patients with chronic kidney disease is important due to the presence of comorbidities (hypertension, diabetes mellitus, and cardiovascular disease) (24). Patients with chronic kidney disease who have the potential to experience drug interactions are mainly in the age group of 25 to 64 years (62.93 ± 11.28) and are men. The results of this study are similar to those of previous studies (14,25,26). Based on data from Indonesian Basic Health Research (2018), chronic kidney disease sufferers are higher than women (7). Kidney disease develops faster in men than in women, so the prevalence of the disease increases (15). Chronic kidney disease patients are patients of adult age because the glomerular filtration rate decreases by approximately 1% per year (14). The prevalence of diabetes mellitus and cardiovascular disease that progresses to chronic kidney disease leads to an increase in the prevalence of chronic kidney disease at the age of less than 60 years (15).

Many studies have been conducted to identify factors associated with potential drug interactions. The current study shows that a significant factor associated with the potential for drug interactions in patients with chronic kidney disease is the number of drugs prescribed. The greater the number of drugs prescribed, the greater the potential for drug interactions (27). Factors that were not significantly associated with the potential for drug interactions were age and gender. The results of previous studies similarly show that gender is not associated with the potential for drug interactions in patients with chronic kidney disease (3,9). However, previous studies have shown that age is one of the factors associated with potential drug interactions (3,9). The difference in results may be due to differences in age grouping or country of study.

The potential drug interactions in patients with chronic kidney disease were based on severity, risk, and drug combinations with the highest potential drug interactions. Based on the combination of drugs with the most potential drug interactions, the top five include candesartan/furosemide, bisoprolol/furosemide, bisoprolol/diltiazem, clopidogrel/atorvastatin, and clopidogrel/diltiazem. The results of this study agree with those of previous studies conducted in Indonesia (14,22,28).

Candesartan / furosemide was the first drug combination with potential interaction in the current study (14). However, a study in Nigeria showed different results. Calcium carbonate/oral ferrous sulphate is the most common drug combination with potential interactions in patients with chronic kidney disease (24). The cause of the difference may be that in the study of potential drug interactions with the Lexicomp application, researchers considered the frequency of administration and the route of drug preparation, whereas previous studies did not consider these factors. The candesartan/furosemide drug combination is a combination of antihypertensive drugs recommended for patients with chronic kidney disease. Candesartan belongs to the class of angiotensin II receptor blockers. Angiotensin II receptor blockers are indicated as antihypertensives in patients with chronic kidney disease, with or without diabetes. Therapy with angiotensin II receptor blockers is recommended for all patients with chronic kidney disease, especially those with albuminuria (10). The combination of furosemide and candesartan has a synergistic effect on blood pressure reduction. The combination of furosemide and candesartan can reduce intravascular volume, prevent hypokalemia, and reduce the activation of the renin–angiotensin–aldosterone system (RAAS), which causes vasoconstriction (29). The candesartan/Furosemide combination is a potential drug interaction of moderate severity with risk category C. However, candesartan/furosemide is indicated in combination therapy in patients with chronic kidney disease (30). The handling that can

be done in the implementation of pharmaceutical services involves monitoring the patient's blood pressure during treatment (21).

Bisoprolol/furosemide and bisoprolol/diltiazem combinations were ranked second and third, respectively, in potential drug interactions. According to the results of previous studies in Indonesia (22,28). However, the difference was in the severity category, where bisoprolol/furosemide was in the serious severity category and bisoprolol/diltiazem was in the significant severity category. The difference in severity category with the results of the current study is due to drug interaction analysis using a different application (Medscape®). Diltiazem is a calcium channel blocker (CCB) indicated in antihypertensive therapy. Diltiazem is a line of drug combination therapy for hypertension in patients with chronic kidney disease (30). Bisoprolol is a class of antihypertensive beta-blockers (31). Bisoprolol is an additional line of therapy for hypertension in patients with chronic kidney disease (32). The additive effects of bisoprolol and diltiazem on heart rate and atrioventricular conduction may result in severe bradycardia or heart block (33). The treatment that can be performed in the implementation of pharmaceutical services is monitoring patient therapy during treatment (21).

Furthermore, the combination of clopidogrel and atorvastatin ranked fourth in potential interactions. Similar results were reported in a previous study in the country of Oman, where the combination of clopidogrel and atorvastatin was the main potential drug interaction (34). However, the severity category of the potential drug interaction between clopidogrel and atorvastatin in that study was moderate. The difference in severity category results was due to the drug interaction analysis using a different application (Micromedex®). Regarding the results of the analysis in the current study (Lexicomp®), the combination of clopidogrel and atorvastatin included minor severity and did not require any action. Clopidogrel is an antiplatelet drug, and atorvastatin is a statin drug (35). Based on research by Zhang et al., clopidogrel or atorvastatin did not diminish the antiplatelet efficacy of clopidogrel or increase adverse event frequency over six months (35).

The fifth place for potential drug interactions was the clopidogrel/diltiazem combination. However, there are limited studies that mention the prevalence of potential drug interactions between clopidogrel and diltiazem. Based on a review of patients who received clopidogrel and calcium channel blockers for at least two months, when calcium channel blockers were discontinued, the value of P2Y12 reaction units decreased significantly. This indicates that calcium channel blockers can inhibit the antiplatelet activity of clopidogrel (36).

The potential drug interactions using Lexicomp® software were the majority of moderate severity and risk category C (monitor therapy) in this study. The results of studies in Iran, India and Spain obtained similar results (8,9,16,18). Research evaluating potential drug interactions in patients with chronic kidney disease using Lexicomp® software is still limited in Indonesia. One of the studies in Indonesia obtained the results of potential drug interactions in heart failure patients with comorbid chronic kidney disease based on Lexicomp® software, mainly of moderate severity and risk category C (22). Research in Indonesia has examined the potential for drug interactions in patients with chronic kidney disease using Mixromedex®, Medscape®, and Drugs.com® applications (4,14,15).

The current study obtained the results of drug combinations with the risk category of potential drug interactions X (avoid combination). The prevalence of potential drug interactions in category X in the current study was higher than in previous studies in Indonesia (22). This difference in results may be due to the previous study on the main diagnosis of heart failure and chronic kidney disease as comorbid, while compared to research in Spain, it is smaller (9). In addition to differences in country, the difference in results is likely due to differences in comorbidities experienced by patients, so the therapy regimens received are different.

Based on the results of the current study, patients may experience drug interactions with chronic kidney disease. The list of potential drug interactions can be a record for healthcare professionals in the selection of therapeutic regimens for chronic kidney disease. Potential drug interactions in risk category X were found in the current study; therefore, drug combinations that should be avoided need attention so that they can be prevented in practice in hospitals and other health facilities. Data analysis of potential drug interactions was conducted using medical record data from the patient's last visit to the hospital outpatient department. After the search, there are many patients with chronic kidney disease who receive the same prescription every month. In the last two months of visits, potential drug interactions were repeated in the patients, with a prevalence of 52.1%. The current study is expected to serve as a reference for hospitals and health facilities to prevent drug interactions, especially in patients with chronic kidney disease.

The limitation of the study is that the data are taken from medical records; therefore, in analysing the factors related to the potential for drug interactions, it is limited to those available in medical records. This study offers the advantage of evaluating the potential of drug-drug interactions based on the risk rating of patients with chronic kidney disease in outpatient care at the South Kalimantan Hospital in Banjarmasin, Indonesia.

The research revealed that most drug interactions were in the moderate severity and category C for the risk rating, necessitating the requirement for monitored therapy. The combination of candesartan and furosemide was the most common drug-drug interactions. The number of concurrent medications was a significant risk factor for potential drug-drug interactions. Detecting and preventing potential drug-drug interactions is crucial to ensure patient safety.

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