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Potential Drug Interaction on Bleeding Events in Stroke Recurrence Patients with Atrial Fibrillation

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ABSTRACT

Introduction: Stroke is a major complication of atrial fibrillation, carries a high risk of recurrence. The likelihood of adverse effects from warfarin-drug interactions increases with the number of concurrent medications. Identifying these potential interactions is crucial. This study aimed to evaluate the impact of drug interactions on bleeding events and the incidence of recurrent stroke in patients with atrial fibrillation.

Methods: This retrospective study tracked 314 stroke patients with atrial fibrillation at Dr. Sardjito and Dr. Moewardi General Hospital over one year who received warfarin at two hospitals from January 2015 to December 2019. Using purposive sampling, 50 patients were analyzed and divided into two groups, 11 with stroke recurrence and 39 without recurrence in one year of treatment. Statistical analyses, including chi-square tests and odds ratio calculations, were performed to assess factors influencing stroke recurrence.

Results: In addition, major, moderate, and minor drug interactions were not significantly different p>0,05. Meanwhile, minor drug interaction correlated with bleeding event (p<0,05) and OR 0,1. The study underscored an elevated risk of bleeding associated with combinations such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs in major interaction analysis.

Conclusion: The research highlights an increased risk of bleeding caused by interaction in combinations therapiest such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs. These findings stress the importance of careful evaluation and management of drug interactions to reduce adverse effects and enhance outcomes for patients with recurrent strokes with atrial fibrillation.

Keywords: Drug interaction; bleeding; stroke; atrial fibrillation

Introduction

Drug-drug interactions (DDIs) involve changes in a drug's pharmacokinetics or effects caused by the presence of another drug. These interactions are categorized into pharmacodynamic or pharmacokinetic types and can lead to reduced effectiveness, treatment failure, or increased medication toxicity. Preventing DDIs can be achieved by minimizing the use of multiple medications and carefully considering the benefits of drug combinations against the risks of significant DDIs. The likelihood of encountering potential DDIs (pDDIs) approaches 40% for patients on five drugs and exceeds 80% for those taking seven or more medications[1]. A prior study in 2016 involving 146 patients admitted with acute ischemic and hemorrhagic stroke identified 582 distinct potential drug-drug interactions (pDDIs), resulting in a pDDI prevalence of 61%[2]. Another study of 200 patients, in the same year, including 190 treated for ischemic stroke, found a pDDI prevalence of 89.5%[3]. The higher prevalence of multimorbidity and polypharmacy among stroke patients increases their susceptibility to experiencing pDDIs[4].

The prevalence of atrial fibrillation (AF) between 2004-2013 in acute ischemic stroke (AIS) patients increased by 22%, rising from 20% to 24%. During the same period, the prevalence of AF in patients with transient ischemic attack (TIA) increased by 38%, from 12% to 17% [5]. Stroke is one of the most feared complications of atrial fibrillation because strokes caused by atrial fibrillation have a risk of recurrence[6]. About 20–30% of all ischemic strokes are related to atrial fibrillation and these events are more disabling than most other ischemic stroke subtypes[7]. This increased in the third year of follow-up where dependency after stroke was higher than the incidence of death and recurrence. Anticoagulants according to PERKI (2014) are prescribed to reduce hypercoagulation reduce the risk of cardioembolic stroke and prevent postoperative venous thrombosis and pulmonary embolism[8]. Anticoagulation therapy, including medications like dabigatran, rivaroxaban, apixaban, and vitamin K antagonists (VKAs), is crucial for reducing stroke risk in atrial fibrillation patients. VKAs, despite their effectiveness, require careful monitoring due to interactions with food, other medications, and varying bleeding risks. Vitamin K antagonists (VKAs) have been the only oral anticoagulant drugs available for clinical use for the primary and secondary prevention of venous and arterial thromboembolic events[9].

In the management of atrial fibrillation, the use of anticoagulants is based on recommendations from national formularies Indonesia. Warfarin, despite its risks, remains the primary choice as it has long been listed in the national formulary and is effective in preventing blood clot formation in patients with this condition. On the other hand, newer anticoagulants such as dabigatran, despite being included in the national formulary, cannot yet be widely used as their current indications for use are more focused on the prevention of post-operative venous thromboembolism (VTE) in hip and knee joint replacements.

In addition, the limited selection of some DOACs in Indonesia and their relatively high price cause problems selecting for atrial fibrillation therapy[18]. Thus, the choice of warfarin as an anticoagulant therapy for atrial fibrillation is still often favored despite the availability of alternatives, given its safety and effectiveness that have been proven in extensive clinical experience.

The bleeding rates due to warfarin use vary significantly, which can be assessed through incidents of bleeding or the risk assessment of the INR (International Normalized Ratio). Consequently, determining the warfarin dosage heavily relies on evaluating the bleeding risk, represented by the INR value. Warfarin therapy for Atrial Fibrillation necessitates meticulous monitoring, particularly aiming to maintain the target INR range of 2.0-3.0 for patients with clinical atrial fibrillation. This means that if the INR value falls outside this range, the warfarin therapy is considered unsuccessful, as INR serves as a crucial parameter for assessing the efficacy of warfarin therapy. The frequency of INR tests for each patient varies based on their INR values. Typically, INR tests are conducted every 3 months once the values have stabilized, though more frequent tests may be necessary if INR values remain unstable.

Interactions that arise have the potential to harm patients and can lead to increased health therapy costs. Drug-drug interactions and bleeding risks among inpatients receiving warfarin therapy are common in the study hospital, so clinicians should be aware of potential interactions and carefully monitor the INR[10]. The results of other studies also show that close monitoring and analysis of the clinical consequences of co-prescribing drugs that interact with warfarin[11]. Another study showed that the prevalence of co-prescribing with potentially interacting drugs during warfarin therapy in outpatients is quite high, so strategies to identify and manage warfarin-drug interactions are needed to avoid potential side effects[12]. Two hospitals, a central hospital and a regional hospital were selected because stroke cases with atrial fibrillation are commonly found in referral hospitals. Identifying potential interactions involving warfarin that may cause adverse effects is necessary. The risk of adverse effects caused by warfarin-drug interactions increases with the number of drugs administered concurrently with warfarin[13]. Based on the analysis of warfarin therapy in stroke patients with atrial fibrillation, many things must be analyzed regarding the correlation between therapy and the outcome of therapy. Therefore, this study aims to evaluate potential drug interactions on bleeding events in the incidence of recurrence stroke with atrial fibrillation.

Methods

This study was conducted at Dr. Sardjito Hospital in Yogyakarta and Dr. Moewardi in Solo Central Java from August 2019 to March 2020. Patient data was obtained from secondary patient medical records and compiled into a data collection form for analysis. Ethical approval for the study was

obtained from the Faculty of Medicine Gadjah Mada University and Medical and Health Research Ethics Committee (MHREC) with the number of ethics committee approval Ref: KE/FK/002/EC/2018.

The research instruments used include, Case Report Form (CRF) for patients with nonvalvular atrial fibrillation, which contains data on demographic data (medical record number, gender, patient's date of birth, date of hospital admission) and atrial fibrillation disease (anticoagulant medication administration, anticoagulant medication admission date) and atrial fibrillation disease (anticoagulant drug administration, dose, frequency, diagnosis of other complicating diseases, other events during the hospitalization process, outpatient care to monitor anticoagulant effectiveness), medical records containing the patient's medical record data, laboratory data, medication use, drug usage, doctor's evaluation notes, drug utilization data from the Hospital Pharmacy Installation.

The study utilized an analytical observational approach with a case-control research design. Data collection was retrospective, involving a review of patient medical records. The research focused on stroke patients diagnosed with atrial fibrillation who were prescribed warfarin as part of outpatient treatment, identified through ICD codes I48 and I63 at Dr. Sardjito General Hospital (218 patients) and RSUD Dr. Moewardi (96 patients). The study encompassed a total sample size of 314 patients from January 1, 2015, to December 31, 2019, selected using a total population sampling method. Among these, 50 patients met the inclusion criteria, comprising 11 patients in the case group and 39 patients in the control group. The inclusion criteria are, Patients above 45 years of age were divided into groups of <60 years and >60 years, Outpatients, Patients diagnosed with stroke with atrial fibrillation according to ICD code 10 I63 who had been hospitalized once because of a stroke diagnosis with complete laboratory and supporting data with complete laboratory and supporting data. Patients received warfarin therapy for at least 6 months. After receiving warfarin therapy for 6 months, the patients were observed for a year after the warfarin administration related to the frequency of examination and the therapeutic value of INR on the incidence of recurrent stroke. The patient does not have a history of stage IV renal failure, pregnant or breastfeeding. The case group is a group of patients who experienced a recurrence stroke while the control case is a group of patients who do not experience a recurrence stroke event. The exclusion criteria for this study are, Patients who, during the observation period (one year), suddenly discontinued the warfarin or replaced it with another type of anticoagulant, Patients who died during the observation period so that no data on the frequency of examination and the therapeutic value of INR.

Descriptive data analysis was conducted to examine potential interactions in medication prescriptions using the Drugs.com interaction checker tool. The analysis aimed to identify factors affecting stroke recurrence and potential bleeding events. SPSS version 22 was used for data analysis, with statistical significance set at p-value < 0.05 and a 95% confidence interval. Bivariate analysis was

performed to assess variables associated with stroke recurrence and bleeding, utilizing the Chi-Square test. Additionally, the Odds Ratio (OR) was calculated to determine whether stroke with atrial fibrillation influenced the outcome of stroke recurrence.

Results

This study is based on a retrospective study tracking the treatment of stroke patients who also suffered from atrial fibrillation which affected the incidence of bleeding in stroke during one year of treatment. In this study, researchers took a study sample of stroke patients who also suffered from atrial fibrillation and received warfarin as one of the anticoagulant drugs. The study subjects were stroke patients who suffered from atrial fibrillation and were prescribed warfarin as one of the anticoagulant drugs. An overview of patient characteristics is described in Table 1.

Table 1. Characteristics patient

	Case (Recurrence Stroke) N =11 (22%)	Control (non-Recurrence Stroke) N=39 (78%)	p
Age			
40-60	5(45,5)	9(23,1)	0,25
<40	1(9,0)	2(5,1)	
> 60 year	5(45,5)	28(71,8)	
Sex			
Male	3(27,3)	16(41,0)	0,50
Female	8(72,7)	23(59,0)	
Dose Variance			
Yes	9(81,8)	15(40,5)	**0,03**
No	2(18,2)	22(59,5)	
Health insurance			
Indonesian Social Security and Health (BPJS)	10(90,9)	33(86,8)	1,00
Non- Indonesian Social Security and Health (Non BPJS)	1(9,1)	5(13,2)	
Bleeding			
Subjects experiencing bleeding outcome	5(45.4)	3(7.7)	0,21
Subjects did not experience bleeding outcome	6(54.5)	36(92.3)	
Bleeding risk			
Subjects with bleeding risk (INR>3)	3(27.3)	6(15.4)	0,39
Subjects with no bleeding risk (INR <2 or 2.0-3.0)	8(72.7)	33(84.6)	
INR value			
INR 2.0-3.0	6(54.5)	9(23.1)	0,06
INR <2.0 or >3.0	5(45.5)	30(76.9)	
Frequency of INR examination			
Once every 8 weeks	3(27.3))	1(2.6)	0,27
Less than once every 8 weeks or more than once every 8 weeks	8(72.7)	38(97.4)	

*Chi-square test

Data analysis was conducted on 50 stroke patients with atrial fibrillation who were prescribed warfarin, focusing on the occurrence of stroke recurrence over a one-year outpatient treatment period. The sample was divided into two groups 11 patients (22%) experienced recurrence of stroke as cases group, while 39 patients (78%) as controls group. Analysis of demographic factors such as age and sex, as well as health insurance coverage, bleeding outcomes, bleeding risk (based on INR levels), INR values, and frequency of INR examinations, showed no statistically significant differences between the case and control groups ($p > 0.05$). However, significant differences were observed in dose variance ($p = 0.03$), where 81.8% of patients in the case group had dose variance compared to 40.5% in the control group.

Table 2. Mean patient drug interactions

Drug interaction	Case (Recurrence Stroke) N=11(%)	Control (non-Recurrence Stroke) N=39 (%)	p
Mayor	81	69	0,30
Moderate	91	89	0,49
Minor	72	87	0,36

Drug interactions that occur in stroke patients are classified based on their severity, namely major, moderate, and minor. Based on the results of the study, both the re-stroke group and the non-re-stroke group both had a risk of major interactions (81% Vs 69%), moderate interactions (91% Vs 89%) and minor interactions (72% Vs 87%). So it can be seen that in the case group and control group, the incidence of moderate interactions was found to be higher, namely 91% and 89% of patients experiencing moderate interaction events as a result of drug prescribing. The existence of interactions must be considered by various parties because it will affect the clinical output of the patient.

Table 3. Relationship between drug interactions and the incidence of bleeding

Variable	Bleeding N=8(%)	No bleeding N=42(%)	OR (95% CI)	p
Mayor Interaction				
Yes	4(50,0)	29(69,0)	0,4(0,09-2,1)	0,42
No	4(50,0)	13(31,0)		
Moderate Interaction				
Yes	8(100)	38(90,5)	0,8(0,7-0,9)	1,00
No	0(0)	4(9,5)		
Minor Interaction				
Yes	4(50,0)	36(85,7)	0,1(0,03-0,8)	**0,04**
No	4(50,0)	6(14,3)		

Based on the analysis, drugs with minor interaction potential still pose a risk of bleeding. The list of

drugs that are included in minor interactions are the combination of warfarin-spironolactone, warfarin-simvastatin, warfarin-atorvastatin, warfarin-acarbose, warfarin-allopurinol, warfarin-telmisartan, digoxin-spironolactone, bisoprolol-antaside, sucralfate-bisoprolol, nifedipine-omeprazole, aspirin-bisoprolol, furosemide-aspirin, aspirin-spironolactone, aspirin-bisoprolol, ranitidine-paracetamol, and ranitidine-mefenamic acid.

Table 4. Minor interaction on bleeding outcome

Minor case-control interactions	Effects
Aspirin+Bisoprolol	High dose aspirin use interferes with the effect of beta blockers in hypertension by inhibiting prostaglandin synthesis. In addition, metoprolol, one of the beta blockers, increases the absorption of aspirin, which has no significant clinical effect.
Aspirin+Spironolakton	Aspirin interferes with the secretion of canrenone, a major metabolite of spironolactone, reducing its natriuretic effects. If a diuretic is insufficient, reducing salicylate administration or increasing the diuretic dose is recommended, while monitoring the patient's potassium levels.
Bisoprolol+Antacid	Antacids decrease beta blocker bioavailability, likely due to receptor binding or reduced gastric dissolution. Separate the administration of these drugs.
Digoxin+Spironolakton	Spironolactone may reduce tubular secretion of digoxin. As a result, digoxin plasma clearance falls and blood plasma levels rise. Some data suggest that spironolactone has inotropic side effects.
Furosemide+Aspirin	Aspirin may interfere with the diuretic and natriuretic effects of loop diuretics by inhibiting their prostaglandin-mediated renal action.
Ranitidine+Paracetamol	Ranitidine may have potential hepatotoxic effects when used together with paracetamol.
Ranitidine+Mefenamat acid	H2 antagonists interfere with NSAIDs by altering blood plasma levels, decreasing absorption, and reducing urinary elimination through inhibited metabolism and changed gastric pH.
Sucralfat+Bisoprolol	Antacids reduce the bioavailability of beta blockers, likely due to receptor binding or decreased gastric dissolution. Administer these drugs at different times.
Warfarin+Acarbosa	The anticoagulant effect of warfarin may be increased in patients receiving akarbosa although the mechanism is unknown.
Warfarin+Allopurinol	Allopurinol may inhibit warfarin metabolism, affecting its anticoagulant effect, so further monitoring is needed.
*Warfarin+Atorvastatin	The clinical effects of combining lovastatin and warfarin are not fully evaluated, but lovastatin may reduce prothrombin levels. There is no significant effect of atorvastatin on anticoagulants.
Warfarin+Simvastatin	Simvastatin may enhance the anticoagulant effect of warfarin by the mechanism of altering protein binding. Clinical effects have not been widely studied but should be monitored.
*Warfarin+Spironolakton	Spironolactone causes diuresis and haemoconcentration of clotting factors resulting in decreased anticoagulant effect.
Warfarin+Telmisartan	Telmisartan causes a slight decrease in steady-state plasma concentrations of warfarin although it cannot be proven to be significant.

*Effect refers to the risk of bleeding caused by drug interactions.

Table 5. Major drug-drug interaction of the recurrence stroke group

Major interaction in the case group (recurrence stroke)	Effect
Amiodaron+Azitromisin	ined increases the risk of potentially life-threatening heart rhythm irregularities leading to death. Levels of amiodarone increase with concomitant use, increasing the risk of side effects such as pneumonitis, neurological damage, liver damage, thyroid abnormalities and visual disturbances.
Amiodaron+Furosemid	ine increases the risk of heart rhythm irregularities and requires monitoring of electrolyte levels (magnesium and potassium).
*Amiodaron+Warfarin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
Amlodipin+Simvastatin	ine increases the blood levels of simvastatin, which may increase the risk of simvastatin side effects such as liver damage and rabdomyolysis.
Ciprofloxacin+Warfarin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
Spironolakton+Candesartan	ine increases the level of potassium in the blood. Increases the risk of hyperkalaemia which can lead to kidney damage, muscle paralysis, irregular heart rhythms and heart attack
Spironolakton+Irbesartan	ine increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, irregular heart rhythm and heart attack.
Spironolakton+Ramipril	ine increases the level of potassium in the blood (hyperkalaemia)
*Warfarin+Aspirin	ine leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Clopidogrel	ine increases the risk of bleeding complications
*Warfarin+Meloxicam	ine leads to a risk of faster bleeding

*Effect refers to the risk of bleeding caused by drug interactions.

Certain drug combinations pose a significant bleeding risk, which necessitates careful management. Specifically, combining amiodarone with warfarin substantially increases the risk of bleeding, making it essential to adjust doses and monitor prothrombin time or INR values closely. Similarly, the use of ciprofloxacin with warfarin also heightens bleeding risk, requiring meticulous dose adjustments to prevent complications. The combination of warfarin with aspirin further escalates the risk of bleeding, demanding dose modifications based on prothrombin time or INR values to ensure safety. Additionally, the concurrent use of warfarin with clopidogrel or meloxicam significantly raises the potential for bleeding complications. Therefore, careful monitoring and precise dose adjustments are critical when managing these drug combinations to effectively mitigate the increased bleeding risk and prevent adverse outcomes. Effective management of these interactions is vital for maintaining patient safety and minimizing the risk of serious bleeding events.

Table 6. Major drug-drug interaction in the non-recurrence stroke group

Major interaction in control group (non-recurrence stroke)	Effect
Amlodipin+Simvastatin	Combined increases the blood levels of simvastatin which may increase the risk of side effects of simvastatin use such as liver damage and rhabdomyolysis.
Bisoprolol+Tizanidine	Combined causes a decrease in blood pressure.
Ramipril+Valsartan	Combined increases the risk of side effects such as decreased blood pressure, decreased kidney function and hyperkalaemia conditions.
Spironolakton+Candesartan	Combined increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, heart rhythm irregularities and heart attack.
Spironolakton+Irbesartan	Combined increases the level of potassium in the blood. Increases the risk of hyperkalaemia which will result in kidney damage, muscle paralysis, heart rhythm irregularities and heart attack.
Spironolakton+Ramipril	Combined increases the level of potassium in the blood (hyperkalaemia)
Spironolakton+Valsartan	Combined increases the level of potassium in the blood which can lead to hyperkalaemia in cases of severe hyperkalaemia can lead to kidney damage, muscle paralysis, heart rhythm disturbances and heart attack.
Warfarin+Aspirin	Combined leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Clopidogrel	Combined increases the risk of bleeding complications.
*Warfarin+Ibuprofen	Combined leads to a risk of faster bleeding. Dose adjustment may be required based on prothrombine time or INR values.
*Warfarin+Mefenamic Acid	Combined leads to a risk of faster bleeding
*Warfarin+Meloxicam	Combined leads to a risk of more rapid bleeding

*Effect refers to the risk of bleeding caused by drug interactions.

Discussion

Based on the results of the study in the recurrence stroke group, patients tended to experience drug-drug interaction in the form of 81% major interactions, 91% moderate interactions, and 72% minor interactions. While the drug prescription of the non-reccurence stroke group obtained that 69% of patients had major interactions, 89% had moderate interactions and 87% had minor interactions. The results of this study are similar to research reports that a higher percentage of patients were exposed to at least one serious drug-drug interaction among acute stroke with recurrent ischaemic events compared to first-time ischaemic patients (74% vs 50%; p<0.01). Other research showed serious DDIs potentially associated with an increased risk of a cerebral event were identified in 19 (17%) patients with ischemic stroke, and in 7 (19%) patients with hemorrhagic stroke[2].

An increased risk of bleeding occurs in the outcome of recurrence stroke both group case group (recurrence stroke) and control group (non recurrence stroke) showed that there were several combinations of therapies that gave bleeding effects including with the prescriptions warfarin-amiodarone, warfarin-clopidogrel, warfarin-diclofenac sodium, warfarin-aspirin, warfarin-meloxicam,

warfarin-ibuprofen and warfarin-mefenamic acid drug interactions. The results of this study align with findings that commonly co-prescribed drugs interacting with warfarin include antibiotics, anticoagulants, diuretics, and NSAIDs[10]. Diclofenac sodium, aspirin, meloxicam, ibuprofen and mefenamic acid are a class of nonsteroidal anti-inflammatory drugs (NSAIDs) that have potential effects of hypoprothrombin events and bleeding risk when associated with oral anticoagulants. This is supported by studies showing that NSAID use is associated with an increased risk of bleeding, stroke or systemic embolism, and hospitalization[14]. Pharmacological effects of NSAIDs related to warfarin-NSAID drug interactions include gastrointestinal irritation, prolongation of prothombin time and inhibition of platelet adhesion-aggregation[15]. Patients taking warfarin had an increased risk of major bleeding and gastrointestinal bleeding with NSAID use[16]. NSAIDs also alter the pharmacokinetics of warfarin resulting in increased INR or prothrombin time (PT) so frequent INR checks and dose adjustments of oral anticoagulants are required while the warfarin-NSAID combination is prescribed. However, a cautious approach is needed for the interpretation of the NSAID results for the following reasons.

The chi-square results of each drug interaction category showed that major, and moderate interactions (OR = 0.4; 0.8;) had no significant difference $p > 0.05$ on the incidence of bleeding. The results of chi-square on drug interactions and their effect on the incidence of bleeding outcomes showed that drugs that have a risk of minor interactions have a significant effect in bleeding events with a value of $p = 0.04$ compared to drug interactions that have a risk of major and minor interactions ($p = 0.42$; $p = 1.00$). This suggests that minor interactions should be closely monitored and managed to minimize the risk of bleeding complications. Minor interaction can accumulate and have a significant impact on patient health[17]. It addressing minor interactions can prevent them from escalating into more serious issues and improve treatment outcomes. Ensuring comprehensive patient care involves monitoring and managing all potential risks, including minor ones, to maintain patient safety and quality of life.

The limitation of this study was no further discussion on patient medication adherence or assessment of patient knowledge of the risks and benefits of warfarin therapy. Therefore, further observational research to understand patient understanding of side effects and medication adherence is needed. A study in 2020 indicated that patients in that study understood they were using warfarin for their atrial fibrillation; however, most patients were unable to assess the risk of stroke when using or not using warfarin, as well as the risk of bleeding when using warfarin[19].

Future research should explore strategies to mitigate the risks posed by drug interactions in stroke patients, particularly focusing on medications like NSAIDs (no steroidal anti-inflammatory drugs) that have been identified as high-risk for bleeding events when combined with warfarin. This includes

evaluating the feasibility and efficacy of alternative drug combinations or intermittent dosing schedules to minimize adverse effects without compromising therapeutic outcomes. Additionally, prospective studies with larger and more diverse patient cohorts could provide clearer insights into the clinical implications of drug interactions in stroke management. Enhanced pharmacovigilance and systematic monitoring protocols should be implemented to detect and manage drug interactions promptly, thereby improving patient safety and optimizing treatment efficacy in stroke care settings.

Conclusion

The study highlighted that both recurrence stroke and non-recurrence stroke groups exhibited similar risks of drug interactions, encompassing major, moderate, and minor severities. Interactions posing minor risks correlated with bleeding events. The study underscored an elevated risk of bleeding associated with combinations such as warfarin-amiodarone, warfarin-clopidogrel, and various NSAIDs including diclofenac sodium, aspirin, meloxicam, ibuprofen, and mefenamic acid. It necessitates vigilant monitoring and frequent INR checks when warfarin is administered with interacting drugs.

Conflicts of Interest

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Original Article   **Open Access**

Legal Protection for Health Workers against Occupational Safety and Health Standards in Hospital

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ABSTRACT

Introduction: The implementation of Occupational Safety and Health (OHS) is a form of effort to make a workplace that is safe, healthy, free from environmental pollution, so that it is free from work accidents and occupational diseases that can increase work efficiency and productivity. This study aims to analyze how legal protection for health workers against occupational safety and health standards in hospitals and how obstacles and solutions for legal protection for health workers against occupational safety and health standards at RSJ Grhasia Yogyakarta, RS JIH Yogyakarta, and RS Paru Respira Yogyakarta.
Methods: The approach of this research is empirical juridical, the research specification is descriptive-analytical with qualitative data analysis.
Results: Legal protection for health workers against occupational safety and health standards in hospitals has been implemented by the Law and Regulation of the Minister of Health. The obstacle faced by the hospital is the lack of hospital human resources whose duties are still concurrent so the OHS program is not optimal. The solution to these obstacles is that every month monitoring is always carried out for work programs and work reports even though human resources are limited but the occupational safety and health program continues to run optimally.
Conclusion: The hospital can add human resources so that the OHS program in the hospital runs perfectly, giving sanctions to health workers who do not use PPE, making the OHS program in the hospital as a separate agency.

Keywords: Legal protection; health workers; occupational health and safety; hospital

Introduction

Implementing occupational safety and health is a form of effort to make the workplace safe, healthy, and free from environmental pollution so it is free from work accidents and occupational diseases, which can increase work efficiency and productivity. In addition to causing casualties and material losses for workers and entrepreneurs, work accidents also disrupt the production system in detail, namely resulting in environmental damage that will pose a risk to the wider community.[1,2]

Occupational safety and health also have an important position in health services, as stated in Law Number 17 of 2023 concerning Health Article 99 paragraph 1, along with the issuance of the Minister of Health Regulation No. 66/2016 on hospital occupational safety and health. Through this Decree, standards for the implementation of occupational health and safety for hospitals have been established. The background of the preparation of this standard is an effort to protect the possibility of negative impacts caused by the health service process, as well as the existence of facilities, infrastructure, medicines and other logistics in the hospital environment so as not to cause work accidents, occupational diseases and emergencies including fires and disasters that affect hospital workers, patients, visitors and the surrounding community. [3,4]

The legal basis for sanctions in Occupational Safety and Health is contained in the Regulation of the Minister of Health Republic of Indonesia Number 66 of 2016 concerning Hospital Occupational Safety and Health Article 29 paragraph 4 "In the context of guidance and supervision of Hospital Occupational Safety and Health, the minister, head of the provincial health office, head of the district/city health office may impose administrative sanctions in the form of a verbal warning or written warning to Hospitals that do not organize Hospital Occupational Safety and Health".[5]

Now hospital occupational safety and health has become mandatory in hospitals as a condition for obtaining legal recognition and also the quality of the services provided, namely hospital occupational safety and health which is one of the requirements that must be met if the hospital wants to be accredited by the National Accreditation Committee. In addition, occupational safety and health in hospitals carried out by hospitals is a form of compliance with applicable laws in Indonesia, where Occupational Safety and Health has now also been regulated in Law PP 50 of 2012 concerning the implementation of occupational safety and health. The use of personal protective equipment in the hospital occupational safety and health program at a hospital is often associated with infection prevention for health workers, especially nurses. The use of Personal Protective Equipment by nurses is used to prevent infection for nurses when starting action on patients. [5–7]

The implementation of OHS in hospitals has a very important role in protecting the health and safety of health workers. Fitriani et al. (2021) identified that the factors influencing the implementation of OSH

in the Padang City Regional General Hospital are complex, including policies, human resources, and adequate facilities and infrastructure. This study highlights the urgent need for better OHS implementation and adequate legal protection for health workers. In addition, Yuniarti et al. (2020) examined the effect of OHS implementation on the occupational safety and health of health workers at the Padang City Hospital, which showed that effective OHS implementation can significantly reduce the risk of accidents and occupational diseases. These results emphasize that good OHS implementation and strong legal protection for health workers are crucial elements to ensure a safe and healthy working environment in hospitals.

The research conducted by the author to be more focused and better directed, it is necessary to limit the problem, namely the study of the very complex tasks of Health Workers including preventive, curative, promotive, and rehabilitative. So that this thesis is limited to legal protection for health workers on safety and health standards in hospitals, especially nurses because the duties of nurses are closely related to the incidence of workplace accidents.[8,9]

Based on the criteria for occupational safety and health workers in hospitals, hospitals are divided into 3 classes, namely classes A, B and C, so that this research place is focused and more directed research is carried out in 3 classes of hospitals with class A, B and C criteria. In the city of Yogyakarta, class A hospitals are RSJ Grhasia Yogyakarta, class B hospitals are RS JIH Yogyakarta and class C hospitals are RS Paru Respira Yogyakarta.

Methods

This research uses empirical juridical research methods, which combine legal materials (secondary data) with primary data obtained from the field. The aims is to analyze a legal issues in the actual social and cultural context. This research begins by collecting relevant data from real situations in society, then identifying problems and finding solutions based on these data. This research used qualitative methods with descriptive-analytical, describing legal symptoms systematically, factually, and accurately and assessing the results of the description without making general conclusions. [10,11]

Primary data was obtained through interviews with facilitators and persons in charge of the OHS program in several hospitals in Yogyakarta (RSJ Grhasia Yogyakarta, RS JIH Yogyakarta, and RS Paru Respira Yogyakarta). Meanwhile, secondary data consists of primary legal materials such as laws related to occupational health and safety, secondary legal materials such as books and research results, and tertiary legal materials such as legal dictionaries and encyclopedias. This research has been approved by the Ethics Committee issued by the DIY National Unity and Political Agency and complies with the stipulated requirements with number: 074/2823/Kesbangpol/2018.

Result

Legal Protection for Health Workers against Occupational Safety and Health in Hospitals.

RSJ Grhasia Yogyakarta, RS JIH Yogyakarta, and RS Paru Respira Yogyakarta have implemented Occupational Safety and Health (OSH) programs in accordance with the laws and regulations. Health workers in the three hospitals receive legal protection for their occupational safety and health. In addition, the hospitals still have obstacles in a legal protection for health workers, such as a lack of human resources and supervision.

This is evidenced by the following findings that all three hospitals have accredited OSH policies and work programs. RSJ Grhasia was fully accredited in 2015, JIH Hospital was fully accredited in 2017, and Respira Lung Hospital was 4-star accredited in 2017. All three hospitals conducted OSH socialization to all levels of the hospital. RSJ Grhasia conducts training on the 5 OSH obligations every year, RS JIH conducts OSH orientation and fire prevention training every year, and RS Paru Respira Yogyakarta conducts OSH technical guidance and fire prevention training every year. All three hospitals provide personal protective equipment (PPE) for health workers. The PPE provided is in accordance with the type of work and risks faced by health workers. All three hospitals conduct occupational health checks to all levels of the hospital. These examinations include initial examinations before work, periodic examinations, and special examinations.

Each hospital has a Standard Operating Procedure (SOP) for the use of personal protective equipment (PPE). The PPE used must be in accordance with the type of work and risks faced by health workers. Based on the data obtained, the number of occupational accidents in the three hospitals varies. RSJ Grhasia Yogyakarta had 2 cases of occupational accidents out of a total of 11 cases in the last 2 years, RS JIH Yogyakarta had 20 cases of occupational accidents in the last 3 years, and RS Paru Respira Yogyakarta had no cases of occupational accidents in the last 3 years.

All three hospitals provide health insurance for occupational safety and health for health workers. This health insurance includes, occupational health checks: This examination aims to detect early diseases and health problems that can be caused by work. Treatment: Treatment is provided to health workers who experience occupational accidents or occupational diseases. Recovery: Recovery is provided health workers who have suffered occupational accidents or occupational diseases in order to return to normal work.

Obstacles and Solutions to Legal Protection for Health Workers against Occupational Safety and Health in Hospitals

Barriers to legal protection for health workers against occupational safety and health standards in hospitals. This study found several obstacles in legal protection for health workers against OSH standards

in hospitals, a lack of human resources for the OSH program. This causes the OSH program to not run optimally and also lack of supervision of the implementation of the OSH program. This means there are still health workers who do not use PPE properly or do not follow the established OSH procedures.

Solutions for legal protection for health workers against occupational safety and health standards in hospitals that can be done to overcome these obstacles are increase human resources for the OSH program. This can be done by increasing the number of health workers in charge of OSH or by providing OSH training to existing health workers. Strengthening supervision of the implementation of the OSH program. This can be done by conducting regular OSH inspections and imposing sanctions on health workers who do not comply with OSH regulations.

Discussion

Legal Protection for Health Workers against Occupational Safety and Health in Hospitals

This study reveals that the three hospitals studied RSJ Grhasia Yogyakarta, RS JIH Yogyakarta, and RS Paru Respira Yogyakarta have implemented occupational safety and health (OSH) programs and provided legal protection for health workers. However, there are still some obstacles in the legal protection, such as a lack of human resources and supervision.

The implementation of OSH standards in the three hospitals is in line with other studies which show that hospitals in Indonesia have implemented OSH standards, although there are still shortcomings in their implementation (Fitriani et al., 2021). This is reinforced by the research findings of Yuniarti et al. (2020) show the implementation of OSH in hospitals can improve the occupational safety and health of health workers.[12,13]

The three hospitals in this study have Standard Operating Procedures (SOPs) for the use of personal protective equipment (PPE) and provide PPE that is appropriate to the type of work and risks faced by health workers. This finding is in line with other studies which show that PPE is one of the important tools to protect health workers from the risk of work accidents.[14]

The three hospitals in this study provide health insurance for occupational safety and health for health workers, including occupational health checks, treatment, and recovery. The applicable laws and regulations, such as Law Number 36 of 2009 concerning Health and Regulation of the Minister of Health of the Republic of Indonesia Number 66 of 2016 concerning Occupational Safety and Health in Hospitals. [15]

Legal protection for health workers is a critical aspect of ensuring their safety and well-being in the workplace. In many countries, comprehensive laws and regulations have been established to safeguard health workers from occupational hazards. For instance, the Occupational Safety and Health

Administration (OSHA) in the United States sets and enforces standards to ensure safe and healthful working conditions. These regulations include mandatory training on safety protocols, the provision of personal protective equipment (PPE), and the implementation of emergency preparedness plans. Such legal frameworks not only protect health workers from immediate physical harm but also provide them with the necessary resources and support to manage work-related stress and psychological challenges[16]

In Indonesia, the legal protection for health workers is still evolving. The implementation of K3 (Kesehatan dan Keselamatan Kerja) laws aims to address the unique challenges faced by health workers in hospitals. However, there are gaps in enforcement and compliance that need to be addressed to ensure these laws are effective. Strengthening legal protections involves not only creating robust regulations but also ensuring their implementation through regular monitoring and audits. Moreover, health workers must be educated about their rights and the legal provisions available to them. This empowerment can lead to better compliance with safety protocols and an overall safer work environment. Studies have shown that when health workers feel legally protected and supported, their job satisfaction and performance improve significantly, leading to better patient outcome.[17,18]

Barriers and Solutions to Legal Protection for Health Workers against Occupational Safety and Health in Hospitals

This study found several obstacles to legal protection for health workers, namely the lack of human resources and supervision. This finding is in line with other studies which show that the lack of human resources and supervision is one of the factors that can hinder the effectiveness of OSH programs.

Based on the findings of this study and other studies, the following are some efforts that can be made to improve legal protection for health workers is increase human resources for the OSH program. This can be done by increasing the number of health workers in charge of OSH or by providing OSH training to existing health workers. Strengthen supervision of the implementation of the OSH program. This can be done by conducting regular OSH inspections and imposing sanctions on health workers who do not comply with OSH regulations. [19,20]

Increase socialization and education about OSH to health workers. This can be done by conducting training, seminars, and workshops on OSH. Strengthen regulations and law enforcement related to OSH. This can be done by revising applicable laws and regulations and increasing law enforcement against OSH violations. [13,19,21]

Based on observations that distinguish between the author and researcher lies in the title of the research and the focus of the study. Arif Wahyu Dwinata's research title is Legal Protection of Occupational Safety and Health for Dentists at Primary Clinics in Sleman Regency, where a very clear problem restriction lies in health workers, namely dentists and the focus of the study raised by Arif is legal

protection for dentists and factors that affect occupational safety and health.

In Fhelis Subiyadevi's research, the title of her research is the Implementation of the Hospital Occupational Health and Safety Management System to Fulfill the Rights of Health Workers at Roemani Semarang General Hospital, where very clear problem restrictions lie in the Hospital Occupational Health and Safety Management System and what are the supporting factors and inhibiting factors in the implementation of Hospital Occupational Health and Safety.

Whereas in the author's research the title of this research is legal protection for health workers against occupational safety and health standards in hospitals, where the restrictions of this research lie on health workers, especially nurses.

The implementation of Occupational Health and Safety (OHS) in hospitals is not only a concern in Indonesia, but also a major focus in many countries. A study conducted by Kirch et al. (2020) in Germany showed that effective OHS implementation in hospitals can reduce the risk of nosocomial infections and improve the welfare of health workers. The study found that hospitals with comprehensive OHS programs experienced a significant reduction in the incidence of occupational accidents and work-related diseases. This finding reinforces that investment in OHS programs not only protects healthcare workers but also improves hospital operational efficiency.[22]

In addition, research by Smith et al. (2019) in the United States showed that good OHS training and adequate legal protection for health workers can increase compliance with safety protocols and reduce work stress. The study revealed that health workers who feel safe and protected tend to have higher productivity and better quality of care. Strong legal protection also serves as an incentive for health workers to follow recommended safety practices, ultimately contributing to a safer and healthier work environment in hospitals.[16]

Conclusion

Not only does it organize occupational health but these three hospitals also provide legal protection for health workers against occupational safety and health in accordance with Law No. 36 of 2014 concerning Health Workers Article 57 letter d. In addition, the hospital has also organized occupational safety and health in the hospital in accordance with the Regulation of the Minister of Health of the Republic of Indonesia Number 66 of 2016 concerning Occupational Safety and Health of Hospitals.

The occupational safety and health program holders in the three hospitals admitted to experiencing obstacles in terms of human resources, especially for the occupational safety and health program in each hospital is still lacking. For example, 1 work unit has not only 1 workload but several workloads. It can be seen that occupational safety and health in hospitals has not stood alone as an agency but is still in the work program contained in facility and safety management.

From these three hospitals, the solutions to the obstacles faced are the same, namely with limited human resources, hospital occupational safety and health programs must continue to run with routine monitoring every month to monitor and assess how the progress and development of occupational safety and health programs in hospitals. So it is hoped that from this solution, health workers, especially nurses, can minimize the incidence of occupational accidents in hospitals. The provision of Personal Protective Equipment in each hospital is as needed, where every health worker who needs Personal Protective Equipment will easily get it at the hospital as needed without limitations.

Conflicts of Interest

Funding sources

Acknowledgments

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Original Article   **Open Access**

Factors Associated with Anxiety Level of Resident Doctors during The COVID-19 Pandemic

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ABSTRACT

Introduction: COVID-19 is an infectious disease that first appeared in Wuhan in December 2019. Indonesia as of January 2021 has reached more than one million cases, with more than 300 doctors dying. Resident doctors of Universitas Hasanuddin continue to provide services during the pandemic so that it is vulnerable to infection and anxiety. However, there is no clear data regarding this.

Methods: Comparative research with a quantitative approach, conducted in October-December 2020 on resident doctors of Universitas Hasanuddin. A total of 399 residents filled out an anonymous questionnaire online, consisting of general data, PSS-10, and GAD-7. Data processing used Microsoft Excel and SPSS 24.0 to obtain the expected statistical results. Analysis used the chi-square test.

Results: Almost 50% of resident doctors of Universitas Hasanuddin experienced anxiety (GAD-7: 49.6% mild-severe anxiety; PSS-10: 48.4% moderate-severe stress). Psychiatric history and COVID-19 confirmed history were associated with anxiety ($p < 0.05$). Study period level and working hours also affected stress levels. Availability of personal protective equipment was associated with anxiety. Age, gender, marital status, financing, number of children, number of households, infectious work area and contact history had no effect on anxiety.

Sources of anxiety included fear of infection, availability of PPE, transmission to family, continuity of study, continuity of incentives, and uncertainty of the end of the pandemic.

Conclusion: Psychiatric history and COVID-19 diagnosis are factors associated with MPPDS anxiety during the COVID-19 pandemic.

Keywords: COVID-19; stress; anxiety; resident doctors; psychiatric history; confirmed COVID-19

Introduction

COVID-19 is an infectious disease caused by the coronavirus. The virus first emerged as an outbreak in Wuhan, China in December 2019. COVID-19 is currently a pandemic affecting various countries globally.[1] Since the announcement of the first confirmed positive case on March 2, 2020, the number of cases in Indonesia has jumped quite quickly. After experiencing a decline, as of June 2021, the growth in the number of positive COVID-19 infections has increased again.[2]

Since the determination of COVID-19 as a global pandemic by the World Health Organization (WHO) on March 11, 2020, Universitas Hasanuddin has issued a circular on Preparedness and Efforts to Prevent the Spread of COVID-19 Infection at Universitas Hasanuddin with a policy that face-to-face lectures are conducted with online learning.[3] Meanwhile, the resident doctors continue to provide services as usual at the hospital, but academic activities that involve many people are temporarily suspended.[4]

Various studies have been conducted to look at the impact of chronic illness on mental health. Studies related to the SARS pandemic found a tendency for widespread fear to cause behavioral changes in the community. During COVID-19, due to the lack of information about the disease and the need to stay at home, people may experience boredom, disappointment and irritability. The COVID-19 pandemic can also lead to social rejection, economic problems, discrimination and stigmatization.[5,6]

A cross-sectional study of 994 medical and nursing staff in Wuhan using the Patient Health Questionnaire (PHQ)-9, Generalized Anxiety Disorders (GAD)-7, the 7-item Insomnia Severity Index (ISI) and the 22-item Impact of Event Scale-Revised (IESR) found that 36.9% experienced sub-threshold symptoms of distress, 34.4% mild symptoms, 22.4% moderate symptoms, and 6.2% severe symptoms at the beginning of the pandemic. This study also found that people with mild symptoms were more likely to seek psychological support for patients and through social media while those with severe symptoms tended to seek professional help for self-support.[7]

Various stressors have been reported by health workers. Direct exposure in hospitals, death or confirmation of a relative or close person, and personal perception of the dangers of COVID-19 can affect the mental state of health workers. In areas with high exposure levels, were experiencing pressure due to excessive workload, lack of personal protective equipment (PPE), frustration at not being able to provide maximum health services and isolation. Another finding was that women were more prone to psychological disorders. [7,8,9,10]

An Italian study found that besides gender, another sociodemographic factor that can affect stress levels and psychological state is the presence of children. Health workers with children tended to have lower stress levels. Marital status had no significant effect. Meanwhile, another study found that having a cohabiting couple increased the fear of COVID-19. Economic status also had no effect, this could be due

to the perception of health workers who work without expecting rewards.[8,11]

Residents as one of the health workers who provide health services in hospitals during the COVID-19 pandemic is one of the populations that are vulnerable to stress and psychological problems. However, there is no clear data on what can cause this. There is also no monitoring system for psychological conditions or counseling for residents. Based on this, this study aims to determine the factors associated with anxiety levels in resident doctors of the Faculty of Medicine Universitas Hasanuddin during the COVID-19 pandemic.

Methods

This study is a comparative study with a quantitative approach, conducted in October-December 2020 on resident doctors of the medical faculty of Universitas Hasanuddin. 399 residents filled out an anonymous questionnaire online, consisting of general data, PSS-10 to assess stress levels, and GAD-7 to assess anxiety levels. Data processing used Microsoft Excel and SPSS 24.0 to obtain the expected statistical results. The chi-square test was used for analysis. This study has been approved for ethical clearance by the ethical committee of the Medical Faculty of Universitas Hasanuddin.

Result

Demographic Information

Table 1. Characteristic of Respondents

Characteristic	Number (N)	Percentage (%)
Age (Years)		
21-25	1	0.3
26-30	165	41.4
31-35	174	43.6
35-40	47	11.8
41-45	7	1.8
46-50	5	1.3
Sex		
Male	185	46.4
Female	214	53.6
Marital Status		
Married	266	66.7
Not Married	129	32.3
Divorced	4	1.0
Psychiatric History		
None	356	89.2
History of Access of Psychological Information/Aid	27	6.8
History of Disease or Medication	16	4.0

Characteristic	Number (N)	Percentage (%)
Number of Children		
0	167	41.9
1	108	27.1
2	81	20.3
3	38	9.5
4	4	1.0
5	1	0.3
Number of Families		
(median, SD)	3	2.6
Program Grade		
Junior	148	37.1
Intermediate	143	35.8
Senior	108	27.1
Place of Assignment		
Infection room	58	14.5
Non infection room	341	85.5
Working hours		
≤ 40 hours/weeks	160	40.1
> 40 hours/weeks	239	59.9
financing		
Independent	310	77.7
scholarship	89	22.3
Contact History		
None	44	11.0
Without PPE	21	5.3
PPE Level 1-2	216	54.1
PPE Level 3	118	29.6
Diagnosis History		
Yes	119	30.5
None	271	69.5
PPE perception		
Proper	216	54.1
Improper	183	45.9

Anxiety Levels of Resident Doctors of Universitas Hasanuddin

Table 2. Stress Levels

Stress Levels	N	%
Mild	206	51.6
Moderate	188	47.1
Severe	5	1.3

Table 3. Anxiety Levels

Anxiety Levels	N	%
Minimum/No anxiety	201	50.4
Mild	151	37.8
Moderate	29	7.3
Severe	18	4.5

In Tables 1 and 2, it can be seen that almost 50% of resident doctors of Universitas Hasanuddin experience stress and anxiety. This shows that quite a lot of residents experience stress and anxiety during the COVID-19 pandemic.

Factors Associated with Residents' Anxiety during the COVID-19 Pandemic

Table 4. Factors Associated with Residents' Anxiety during the COVID-19 Pandemic

Variables	Stress Levels (N (%))		p-value*	Anxiety Levels (N (%))			p-value*
	Mild	Moderate-Severe		Minimum/No Anxiety	Mild	Moderate-Severe	
Age (years)							
21-30	73 (44.0%)	93 (56.0%)		71 (42.8%)	74 (44.6%)	21 (12.7%)	
31-35	96 (55.2%)	78 (44.8%)	0.051	95 (54.6%)	58 (33.3%)	21 (12.1%)	0.160
35-40	29 (61.7%)	18 (38.3%)		26 (55.3%)	17 (36.2%)	4 (8.5%)	
> 40	8 (66.7%)	4 (33.3%)		9 (75.0%)	2 (16.7%)	1 (8.3%)	
Sex							
Male	100 (54.1%)	85 (45.9%)	0.367	100 (54.1%)	69 (37.3%)	16 (8.6%)	0.148
Females	106 (49.5%)	108 (50.5%)		101 (47.2%)	82 (38.3%)	31 (14.5%)	
Psychiatric History							
None	195 (54.8%)	161 (45.2%)		189 (53.1%)	130 (36.5%)	37 (10.4%)	
History of Access of Psychological Information/Aid	9 (33.3%)	18 (66.7%)	**0.001**	7 (25.9%)	17 (63.0%)	3 (11.1%)	**0.003**
History of Disease or Medication	2 (12.5%)	14 (87.5%)		5 (31.3%)	4 (25.0%)	7 (43.8%)	
Number of Children							
0	80 (47.9%)	87 (52.1%)		81 (48.5%)	69 (41.3%)	17 (10.2%)	
1	56 (51.9%)	52 (48.1%)	0.474	55 (50.9%)	36 (33.3%)	17 (15.7%)	0.455
2	44 (54.3%)	37 (45.7%)		39 (48.1%)	34 (42.0%)	8 (9.9%)	
> 2	26 (60.5%)	17 (39.5%)		26 (60.5%)	12 (27.9%)	5 (11.6%)	
Number of Families							
0	37 (50.0%)	37 (50.0%)		37 (50.0%)	27 (36.5%)	10 (13.5%)	
1-3	70 (52.2%)	64 (47.8%)	0.982	74 (55.2%)	47 (35.1%)	13 (9.7%)	0.815
3-6	78 (52.3%)	71 (47.7%)		69 (46.3%)	62 (41.6%)	18 (12.1%)	
>6	21 (50.0%)	21 (50.0%)		21 (50.0%)	15 (35.7%)	6 (14.3%)	

*Chi-square test

Various factors associated with residents' anxiety during the COVID-19 pandemic were analyzed. These factors are age, gender, psychiatric history, number of children, and number of families in the house.

In addition, factors related to studies and duties in the hospital were also assessed, namely the program stage, duty area, working hours, financing, contact history, diagnosis history, and perceptions of PPE. The results of the analysis are listed in Table 4.

| Variables | Stress Levels (N (%)) | | p-Value* | Anxiety Levels (N (%)) | | | p-value* |
	Mild	Moderate-severe		Minimum/No Anxiety	Mild	Moderate-severe	
Program Grade							
Junior	59 (39.9%)	89 (60.1%)	**0.001**	68 (45.9%)	62 (41.9%)	18 (12.2%)	0.675
Intermediate	83 (58.0%)	60 (42.0%)		74 (51.7%)	53 (37.1%)	16 (11.2%)	
Senior	64 (59.3%)	44 (40.7%)		59 (54.6%)	36 (33.3%)	13 (12.0%)	
Duty Area							
Infectious	25 (43.1%)	33 (56.9%)	0.160	27 (46.6%)	24 (41.4%)	7 (12.1%)	0.808
Non-Infectious	181 (53.1%)	160 (46.9%)		174 (51.0%)	127 (37.2%)	40 (11.7%)	
Working Hours							
≤ 40 hours/week	96 (60.0%)	64 (40.0%)	**0.006**	89 (55.6%)	55 (34.4%)	16 (10.0%)	0.220
> 40 hours/week	110 (46.0%)	129 (54.0%)		112 (46.9%)	96 (40.2%)	31 (13.0%)	
Financing							
Private	154 (49.7%)	156 (50.3%)	0.145	157 (50.6%)	118 (38.1%)	35 (11.3%)	0.852
Scholarship	52 (58.4%)	37 (41.6%)		44 (49.4%)	33 (37.1%)	12 (13.5%)	
Contact History							
None	25 (56.8%)	19 (43.2%)		27 (61.4%)	14 (31.8%)	3 (6.8%)	
Without PPE	12 (57.1%)	9 (42.9%)	0.696	8 (38.1%)	11 (52.4%)	2 (9.5%)	0.385
PPE Level 1-2	106 (49.1%)	110 (50.9%)		100 (46.3%)	85 (39.4%)	31 (14.4%)	
PPE Level 3	63 (53.4%)	55 (46.6%)		66 (55.9%)	41 (34.7%)	11 (9.3%)	
Diagnosis History							
Yes	52 (43.7%)	67 (56.3%)	**0.034**	53 (44.5%)	44 (37.0%)	22 (18.5%)	**0.030**
None	150 (55.4%)	121 (44.6%)		143 (52.8%)	103 (38.0%)	25 (9.2%)	
PPE perception							
Proper	112 (51.9%)	104 (48.1%)	0.923	116 (53.7%)	84 (38.9%)	16 (7.4%)	**0.012**
Improper	94 (51.4%)	89 (48.6%)		85 (46.4%)	67 (36.6%)	31 (16.9%)	

Junior-grade residents tended to experience more stress and anxiety than the seniors. Residents with working hours > 40 hours/week tended to experience moderate-severe stress (p=0.006) and had anxiety (53.2%) compared to residents with working hours ≤ 40 hours/week. Another factor that also has a statistically significant relationship is the residents' perception of the availability of PPE in the hospital (p=0.012).

Discussion

Our study found that almost 50% of residents experienced anxiety (GAD-7: 49.6% mild-severe anxiety; PSS-10: 48.4% moderate-severe stress). Various studies have shown the proportion of anxiety in

health workers in the COVID-19 pandemic era. Jianbo et.al. found 44.6% of health workers experiencing anxiety in facing the COVID-19 pandemic.[9] Meanwhile, Korkmaz et al. found a prevalence of 71% anxiety (mild-severe), with 33% having clinical significance.[12]

Psychiatric history and COVID-19 diagnosis history are two factors that have a statistically significant relationship with anxiety (stress level and anxiety level). Asmundson et al, mentioned that people with a history of anxiety disorders and affective disorders showed higher symptoms of COVID-19-related stress and fear compared to those without a history. Specifically, people with a history of anxiety disorders were most vulnerable to experiencing COVID-19-related stress and anxiety.[13] Several studies examined the impact of coronavirus infection on mental health. A meta-analysis study found that there was an increased incidence of depression, anxiety, PTSD, and other mental disorders following SARS, MERS, and SARS-COV2 infections.[14]

In our study, it was found that junior residents tended to experience more stress than senior. There were also more junior residents (54.1%) who experienced anxiety compared to intermediate (48.3%) and senior residents (45.3%) although not statistically significant. This is in line with research on medical students in Saudi Arabia and Ethiopia, where stress levels were higher in the early years of study. This is said to be related to students in the early years facing something new, separating from family, and over time developing adaptation skills.[15,16] Different things were found in the study of Collins et.al. where senior residents in the surgical department were more likely to have higher GAD-7 scores than juniors.[17]

Working hours and availability of personal protective equipment also affect stress and anxiety levels. High workload has been known to be one of the stressors for health workers.[7,9,10,18] China focuses on one of the concerns for health workers to provide personal protective equipment, separate living quarters.[7] This is also true in studies in India, and specifically in studies of residents from various departments/sections in the world.[17,18]

Age, gender, financing, number of children, and number of families living in the same house did not significantly affect anxiety. Working in an infectious area and having a history of contact with confirmed/suspected COVID-19 patients also had no effect on anxiety. Various studies have reported mixed results on these factors. The different results in this study can be concluded that although the presence of children and cohabiting families is an influential factor in anxiety, the number of children and the number of families living in the same house is not a significant influential factor. It is necessary to elaborate further on the social support of the family, as well as the presence of risk factors in the family living in the same house. This may also be related to the results of a study of residents working with COVID-19 patients in the United States where residents also tended to find it difficult to engage with the care of their children, and difficult to balance work and personal life.[19] In this study, we also asked about

other sources of anxiety for residents. These sources of anxiety included concerns about being infected, availability of Personal Protective Equipment (PPE), sick family, transmission to family, concerns about the continuation of the study, continuity of incentives, and uncertainty about the end of the pandemic. We suggest this finding be considered in placement and rotation of the resident doctors also to be noted by each resident on their own that many factors can be related to their stress and anxiety.

Conclusion

This study provides an overview of anxiety in resident doctors of Universitas Hasanuddin and the factors that influence it. Anxiety was measured using stress level (PSS-10) and anxiety level (GAD-7). Overall, 48.4% of respondents experienced moderate-severe stress, and 49.6% experienced anxiety with levels varying from mild-severe.

Factors that influence stress levels and anxiety levels are psychiatric history and confirmed diagnosis history of COVID-19. Other factors that also influence stress levels are the program grade and working hours. Meanwhile, the availability of PPE also affects the residents' anxiety level.

Age, gender, financing, number of children, and number of family living in the same house did not significantly affect anxiety. Working in infectious areas and a history of contact with confirmed/suspected COVID-19 patients also had no effect on anxiety. Although there was a trend towards reduced or increased anxiety in some factors, no significance was found in this study.

The sources of anxiety included concerns about being infected, availability of Personal Protective Equipment (PPE), sick family, transmission to families, concerns about the smooth running of the study, continuity of incentives, and uncertainty about the end of the pandemic.

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The Impact of Protein Intake on Stunting in Toddlers: A Lapai Health Center Study

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ABSTRACT

Introduction: Stunting is a short stature caused by chronic malnutrition based on weight-for-age, height-for-age, and chronological age that greatly impacts child growth and development. According to SSGI 2021, Southeast Sulawesi is ranked fifth in Indonesia with the highest stunting rate at 30.2% and North Kolaka Regency has a stunting rate of 29.1%. The causes of stunting are quite diverse, one of which is the lack of protein food consumption. The purpose of this study was to determine the relationship between protein intake and the incidence of stunting in toddlers.

Methods: This study was an observational analytic study. This study was participated by 18 children who were registered at the Lapai Health Centre. Using the cross-sectional method and chi-square test, 18 children will be analyzed to determine the relationship of protein intake to stunting.

Results: The results showed that the percentage of toddlers with less protein intake was 72.2% and only 27.8% were in the sufficient category. Toddlers with the stunting category were 77.8% and toddlers with the normal category were only 22.2%. With data analysis using the chi-square test, the P-value <0.05 (P-value 0.04) was obtained.

Conclusion: This study focuses on the increasing incidence of stunting in toddlers caused by a lack of protein intake. The results of this study emphasize to that parents and local governments to pay more attention to children's protein intake during toddlerhood by providing varied protein intake.

Keywords: Stunting; protein intake; toddler

Introduction

Indonesia, as a developing nation, primarily focuses on matters related to nutrition. The nutritional problem is the increasing prevalence of stunting toddlers. Stunting is short stature due to chronic malnutrition characterized by weight age, below height age and below chronological age. Several factors cause stunting, one of which is due to inadequate consumption of protein foods. Based on the latest publication of the WHO shows the number of children under five with short stature worldwide is 154.8 million toddlers. Data from WHO on stunting rates published in 2018 revealed that Indonesia became the third highest stunting rate in the Southeast Asia region with a percentage of 36.4% [1].

Indonesia is a nation grappling with a triple burden of malnutrition, characterized by issues of under nutrition, overweight, and deficiencies in micronutrients [2]. According to data from the R&D of the Indonesian Ministry of Health, the Study of the Nutritional Status of Toddlers in Indonesia in 2021 is quite high with a stunting prevalence of 24.4%. Southeast Sulawesi Province occupies the 5th position with the highest stunting rate in Indonesia amounting to 30.2% with North Kolaka district having a stunting rate of around 29.1% [3].

Stunting has adverse effects on growth and development. The short-term effects of stunting, namely impaired brain development and intelligence, disruption of body metabolism, disruption of physical growth, and increased medical costs. The long-term impact of stunting, namely cognitive function and physical development that is less than optimal, weakening of the immune system that can lead to mild diseases and the development of degenerative diseases, such as diabetes, obesity, cancer, cardiovascular disease, and disability in old age .[4]The purpose of this study is to determine the relationship between protein intake and the incidence of stunting in toddlers in the work area of the Lapai Health Center, North Kolaka Regency.

Methods

This study was conducted at Puskesmas Lapai, North Kolaka Regency, South-east Sulawesi in August 2023. Patient data was obtained directly through primary data whereas theprimary data was obtained from the FFQ Food Record form semi-quantitative anthropometric examination. Ethical approval for this study was obtained from the Faculty of Medicine, Muslim Indonesia University and the Health Research Ethics Committee of Muslim Indonesia University with the ethics committee approval number Ref: 377/A.1/KEPK-UMI/VII/2023.

This study used an observational analytic method using a cross-sectional approach, where variables were measured simultaneously. The sample calculation used the Slovin formula. Data collection methods in this study using primary data. Primary data were obtained from parents of toddlers who directly filled

in the semi-quantitative FFQ Food Record form to determine the daily protein intake of toddlers and to determine the incidence of stunting by anthropometric examination using a microtoise, baby scale, digital scales, and infantometer. Measurements were taken directly by the researcher. Data were obtained during visits to the health center and home visits.

Result

In this study, the researcher took the research samples by taking anthropometric measurements on toddlers who visited the Lapai Health Centre. In addition, researchers made visits to the homes of toddlers recorded at the Lapai Health Centre. After taking anthropometric measurements, interviews were conducted with parents regarding the condition and food intake of toddlers and filling out semi-quantitative FFQ Food Record forms to determine the protein intake of toddlers daily, weekly, and monthly. The data was collected and analyzed further.

The data were obtained on the distribution of sex, age, height/length, weight, and distribution of protein intake.

Univariate Results

Table 1. Gender Distribution of Toddlers

Gender	n	%
Woman	4	22.2
Man	14	77.8
Total	18	100.0

Source: Primary Data, 2023

Table 1 illustrates the gender distribution of toddlers with men dominating the percentage of 77.8% with 14 people, while women only 22.2% with 4 people.

Table 2. Description of Age, Weight, Height and Protein Consumption/Day

Characteristic	N	Minimum	Maximum	Average	Standard Deviation
Age (Months)	18	13	37	24.17	7.88
Weight (kg)	18	6.10	13.50	9.46	2.04
Height (cm)	18	63.50	92.70	78.48	7.63
Protein Consumption/Day (g)	18	11.04	15.04	13.41	1.24

Source: Primary Data, 2023

Table 2 shows descriptions of the frequency of age, weight, height, and protein consumption/day of toddlers. The average age of toddlers is 24.17 months with the smallest age of 13 months and the largest age of 37 months. The average weight of toddlersis 9.46 kg with the smallest body weight of 6.1 kg and the largest weight of 13.5 kg. The average height of toddlers is 78.48 cm with the smallest height of 63.50 cm and the largest height of 92.70 cm. The average consumption of protein/day is 13.41 grams.

Table 3. Distribution of Adequacy of Toddler Protein Consumption

Protein Adequacy	n	%
Enough	5	27.8
Less	13	72.2
Total	18	100.0

Source: Primary Data, 2023

Table 3 illustrates the distribution of the adequacy category of protein consumption/day toddlers with the percentage of toddlers in the category of protein intake less by 72.2% and the category of sufficient only 27.8%.

Table 4. Distribution of Stunting Incidence in Toddlers

Stunting Category	n	%
Stunting	14	77.8
No *Stunting*	4	22.2
Total	18	100.0

Source: Primary Data, 2023

Table 4 illustrates the spread of stunting in toddlers. Stunting toddlers have a percentage of 77.8% with 14 people and normal toddlers only 22.2% with 4 people.

Bivariate Analysis

Table 5. Analysis of the Relationship between Protein Consumption Adequacy and the Incidence of Stunting in Toddlers

			Stunting Category		Total	P-value
			Stunting	Normal		
Protein Adequacy Category	Less	n	12	1	13	0.04
		%	92.3	7.7	100.0	
	Enough	n	2	3	5	
		%	40.0	60.0	100.0	
Total		n	14	4	18	

	%	77.8	22.2	100.0

Source: Primary Data, 2023

Table 5 shows the results of the chi-square test with a p-value obtained of 0.04 (<0.05) which indicates that there is a significant relationship between protein intake and the incidence of stunting in toddlers.

Discussion

The results describe the prevalence of male toddlers dominating when compared to the number of female toddlers. This is in line with the 2021 Health Statistics Profile data which explains that the percentage of children aged 0-4 years who have health complaints according to sex is dominated by men with 18.34% and for women with 15.68% [5]. In addition, the results of research from Anggi Tria Abimayu and Nurul Dina Rahmawati in 2023 show that the percentage of male toddlers is very dominating with 52.1% more than female toddlers with 47.9% [6]. A different investigation by Dian Kholika Hamal et al in 2021 proposed that male infants face a 1.15 times higher risk of stunting compared to their female counterparts [7].

The age of the respondents selected was 6-60 months because according to the results of the SSGI 2022 stated that stunting has increased specifically in the age range starting from 6 months [8]. In addition, the fulfillment of child nutrition, especially in toddlers (0-5 years) must be a big concern because the growth rate at this age is quite rapid (Golden Age) [9]. The results of research on protein consumption / day showed a decrease in protein consumption with an average intake per day of 13.41 grams. This information is derived from the Minister of Health Regulation of the Republic of Indonesia Number 28 of 2019, elucidating the recommended protein intake for infants/children aged 6-72 months to be within the range of 15-25 grams [10].

The results of research on protein adequacy explain that protein consumption intake tends to be less. This is in line with the 2014 individual food consumption survey data which describes a decrease in animal protein consumption in toddlers, which is <5% for children aged 6 months and over [11]. In addition, Susenas 2022 data reveals an average daily protein food intake per capita of 62.21 grams (higher than 57 grams), but animal protein intake, such as meat 4.79 grams, eggs and milk 3.37 grams, and fish/shrimp/squid/shellfish 9.58 [12].

The findings indicated a significantly elevated percentage of toddlers classified as stunted, reaching 77.8%. This substantial prevalence of stunting among children under five aligns with the data reported by the SSGI 2022, which records a stunting rate of 21.6% in Indonesia. This prevalence is fairly high because

the achievement of the stunting rate in 2024 is 14% and the achievement of the WHO is less than 20%. Southeast Sulawesi in the SSGI 2022 ranks 9th with the highest stunting rate in Indonesia with 27.7% [8].

The chi-square test results delineate a distinct correlation between the sufficiency of protein intake and stunting in toddlers, evidenced by a p-value of 0.04 (less than 0.05). Several studies identify stunted children as having low serum amino acid levels compared to normal children given that amino acids, particularly essential types of proteins such as lysine, leucine, and tryptophan, are necessary for cognitive growth and development [13].

The research conducted by Annisa Rizky Maulidiana et al regarding Low Intake of Essential Amino Acids in Toddlers in Malang City suggests that the intake of nine EAA in toddlers who are stunted tends to decrease when compared to children who are not stunted. EAA intake should be obtained from food, especially a combination of different types of protein source foods [14]. Other studies have suggested that children lack EAA intake from animal protein foods, especially isoleucine ((OR (95%Cl) 2.58 (1.09 – 6.09, p = 0.00)) [15].

According to a study conducted by Satriani et al in 2019, it was elucidated that there exists a distinct correlation between protein consumption and stunting. The intake of protein-rich foods among stunted toddlers is comparatively lower in comparison to their normal counterparts [16]. Furthermore, based on the study conducted by Iseu Siti Aisyah and Andi Eka Yunianto in 2021, it reveals a distinct connection between the consumption of protein-rich foods and the prevalence of stunting. Insufficient consumption of protein foods has a 5,160 times risk of stunting [17]

Conclusion

Based on the results of the research analysis, there were 13 toddlers with less protein intake category and 5 toddlers with sufficient protein intake category with 14 toddlers belonging to stunting category and 4 toddlers with normal category. From the results of the analysis, it can be concluded that there is a significant relationship between protein intake and the incidence of stunting in toddlers aged 6-60 months in the Working Area of the Lapai Health Center, North Kolaka Regency. After the study, further research is needed by paying attention to other stunting risk factors, such as intake of other nutrients, diet, family social and economic factors, history of chronic diseases, and maternal factors. In addition, people are advised to pay more attention to children's protein intake during toddlerhood in the form of varied protein intake and increase the frequency of protein intake because protein intake will support children's growth and development.

Conflicts of Interest

There is no conflict of interest.

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81

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Original Article　　　　　　　　　　　　　　　　　　　**Open Access**

Physical Activity, Sleep Quality and Academic Performance among Physiotherapy Students: A Cross-Sectional Study

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ABSTRACT

Introduction: The lockdown due to the COVID-19 leads to changes in health behaviors, including physical activity and sleep quality. The consequence of insufficient sleep among most university students is a decline in their learning ability. Furthermore, insufficient sleep and lack of physical activity can have detrimental impacts on students' physical well-being, such as increased risk of chronic diseases. This study aimed to explore the association between physical activity, sleep quality, and academic performance in Indonesian undergraduate physiotherapy students.

Methods: This study used a cross-sectional design. One hundred and thirty-four students (Female, aged 18-25) were recruited from the Bachelor Program in Physiotherapy at a university in South Sulawesi, Indonesia. The Pittsburgh Sleep Quality Index was used to assess sleep quality. To assess physical activity level, The International Physical Activity Questionnaire-Short Form (IPAQ-SF) was used. Students' academic performance was evaluated based on the final grades of the selected course.

Results: The majority (63%) of physiotherapy students had low physical activity levels. Almost all students (95.5%) suffered from poor quality of sleep. Sleep quality and academic performance were found to be positively correlated, indicating that students with good sleep quality performed better in school. It is noted that 64% of physiotherapy students with A and B grades had low physical activity.

Conclusion: Academic performance is negatively correlated with poor sleep quality. High-achievement students typically have lower levels of physical activity. This study highlights the issue of insufficient sleep quality and the need for promotion of sleep hygiene.

Keywords: Sleep quality; students; universities; academic performance; health behavior

Introduction

The lockdown due to the COVID-19 causes changes in health-related behaviors, such as physical activity and sleeping habits. Numerous studies have documented how the COVID-19 pandemic affected sleep and physical activity patterns. A study conducted on university students in Spain found that among physically active students, the COVID-19 confinement resulted in a decrease in their level of physical activity and sleep quality.[1] Meanwhile, no significant changes in sleep quality were observed in college students in the city of Seville. However, the study also reported a decrease in the amount of step/day by 68% during home confinement [2]. By contrast, Blanco found that during the COVID-19 lockdown, among Spanish health science students, there was a noticeable rise in their engagement with physical activity. [3] University students commonly reported that sleep is one of the initial health behaviors they neglect. Furthermore, in higher education, sleep deprivation is widely acknowledged and accepted as a feasible choice for students to effectively manage their academic responsibilities and social commitments. The consequence of this lack of sleep among most university students is a decline in their ability to learn and perform academically. Furthermore, insufficient sleep can have detrimental impacts on students' physical well-being, such as increased risk of obesity, hypertension, and diabetes [4].

High levels of daytime drowsiness and poor sleep quality were found to be strongly correlated with low academic performance, according to a recent meta-analysis of sleep disturbance and academic performance. A high number of medical students had excessive diurnal somnolence, inadequate sleep duration, and poor quality of sleep [5]. In addition to sleep quality, individuals with higher physical activity levels tend to have better executive function [6]. A study by Alhazmi et al. also confirmed that compared to physically active students, sedentary students have lower academic performance.[7] A study conducted in Indonesia revealed no correlation between sleep quality and academic performance in Medical Students. A high number of students (73.1%) were reported having poor sleep quality.[8] However another study conducted in first-year medical students showed that sleep quality was significantly correlated with academic performance.[9] Few studies have explored the relationship between physical activity and academic performance of University Students in Indonesia. One study showed no correlation between physical activity and academic performance in university students.[10]

Despite the critical role of sleep and its potential health consequences, physiotherapists are not typically educated about sleep or the health benefits of sleep as part of their entry-level education program. Thus, a physiotherapy education program needs to identify sleep deprivation and develop an early preventive plan to promote optimal health for future physiotherapists. A study conducted on Doctor of Physical Therapy (DPT) students has shown that poor sleep quality was experienced by almost half of DPT students.[11] Meanwhile, many studies have shown that healthcare professionals engage in the same

unhealthy habits as the broader public. It has been shown that health professionals with unhealthy behaviors may be less credible as health promoters [12]. Despite being knowledgeable regarding the benefits of physical activity, a high percentage of physiotherapy undergraduates were "inactive" [13].

To the best of our knowledge, no research has been conducted to examine the prevalence of physical activity level and sleep quality in undergraduate physiotherapy students in Indonesia. The relationship between physical activity, sleep quality, and academic performance in Indonesian undergraduate physiotherapy students has yet to be examined. Therefore, this study aimed to identify the prevalence of physical activity level and sleep quality, as well as to determine the association between physical activity, sleep quality, and academic performance in Indonesian undergraduate physiotherapy students.

Methods

This study was a cross-sectional design conducted from April to May 2021 among the students of Bachelor of Physiotherapy, Faculty of Nursing, at a university in South Sulawesi, Indonesia. A total of 134 physiotherapy students were enrolled. The following criteria were used for participant recruitment: registered female student of Bachelor of Physiotherapy by the time of recruitment, 17-25 years of age, willing to provide informed consent to participate in the study. Students with chronic diseases were excluded from the study.

Data collection was performed by a self-administered questionnaire posted through social media (WhatsApp Group). Demographic information such as age, academic year, and socioeconomic status were collected. Due to the assessment of physical activity level, the International Physical Activity Questionnaire-Short Form (IPAQ-SF) was administered [14]. IPAQ-SF has been recommended as a cost-effective method for assessing physical activity. The IPAQ-SF contains 7 items that assess the frequency and duration of vigorous-intensity activity, moderate-intensity activity, walking (classified as a moderate-intensity activity), and sitting behavior for the last 7 days.[15] The Pittsburgh Sleep Quality Index (PSQI) was selected to investigate sleep quality [16]. The PSQI had been studied in Indonesian. The Indonesian version of PSQI was validated with the reliability of $\alpha=0.79$, content validity of 0.89, and specificity of 81% [17]. The academic performance of the participant was evaluated based on the final grades of the selected course [18] due to being the course with the highest credit in each semester during the previous semester. The grades of the students were obtained from the course coordinators.

The statistical analysis in the study was conducted with SPSS 26. A descriptive analysis was performed to present the baseline characteristics of the participants. Mean and standard deviation (SD) were generated for continuous variables. The Kolmogorov-Smirnov test was carried out to assess the distribution of the data. Then, Spearman's correlation was calculated to determine the association between physical activities and sleep quality against academic performance. Significance was set at $p < 0.05$.

This study was approved by The Health Research Ethics Committee, Faculty of Public Health, at a large University in South Sulawesi, Indonesia (3004/UN4/14.1/TP.02.02/2021). The participant were informed about the objective of the study, and they could withdraw at any time.

Result

A total of 134 participants were enrolled in this study. The characteristics of the participants are shown in Table 1. Overall, the mean age of participants was 19.78 years. All participants in this study were in their first, second, third and fourth years at university. Most participants (85.6%) had medium socioeconomic status in this study. We also observed a high prevalence of low physical activity (63%). 67.9% of participants reported insufficient sleep (less than 6 hours). This study also found that 95.5% of participants were classified as poor sleepers (PSQI score > 5). The majority of participants reported having B grades in academic performance.

Table 1. Characteristics of study participants

Characteristics	Total (N=134)
Age, years	19.78 ± 1.31
Year of study, n (%)	
1st year	46 (34.3)
2nd year	34 (25.4)
3rd year	20 (14.9)
4th year	34 (25.4)
Socioeconomic status, n (%)	
Medium	115 (85.8)
High	19 (14.2)
Physical Activity	
Low	84 (63)
Moderate	40 (30)
High	10 (7)
Sleep Duration	
≥6 hours	43 (32.1)
<6 hours	91 (67.9)
Sleep Quality	
Poor	128 (95.5)
Good	6 (4.5)
Academic Performance	
A Grade	14 (10.4)
B Grade	76 (56.7)
C Grade	31 (23.1)
Failing Grade	13 (9.7)

Source: Primary Data, 2021

There is no significant relationship was found between physical activity levels and academic performance. However, sleep quality had a significant correlation with academic performance. Among

PSQI domains, our study also demonstrated that only sleep disturbance was significantly correlated with academic performance (Table 2).

Table. 2 Correlation between Physical Activity, Sleep Quality, and Academic Performance

Variables	Academic performance level	
	r_s	p
Physical activity	0.108	0.214
Global sleep quality	0.281**	0.001
Subjective sleep quality	0.124	0.154
Sleep duration	0.152	0.080
Sleep latency	0.053	0.544
Sleep efficiency	0.064	0.465
Sleep disturbance	0.0276**	0.001
The use of sleeping meditation	-0.011	0.902
Daytime dysfunction	0.121	0.162

**: $p < 0.01$

Source: Primary Data, 2021

Discussion

This study revealed that most physiotherapy students (63%) had low physical activity levels. Also, almost all physiotherapy students (studied participants) reported poor sleep quality. Furthermore, our findings revealed no significant correlation was found between physical activity and academic performance in undergraduate physiotherapy students. However, we found that sleep quality was significantly correlated with academic performance.

To be a credible future health promoter in the community, undergraduate physiotherapy students should demonstrate high physical activity. Furthermore, physiotherapy students are expected to know about recommended physical activity and its benefits. However, our study revealed that most physiotherapy students (63%) had low physical activity levels. Only 7.5% of students participated in high physical activity. Our findings agree with another study conducted in Poland which reported that most Polish Physiotherapy students (40.4%) had low physical activity levels [19]. We assumed that the COVID-19 pandemic also reduced physical activity levels in physiotherapy students. However, in 2013, a study conducted in Sri Lanka found that a larger percentage of undergraduate physiotherapy students were classified as inactive (48.7%), while only 15.9% were falling into the highly active group [13]. We can conclude from the previous studies that even before the COVID-19 pandemic, the proportion of physiotherapy students with low physical activity levels was very high. However, our results contrast to those of previous researchers who reported that physical therapist students in Poland demonstrated the highest level of physical activity, 54% had moderate physical activity level, and none had low physical

activity level [20]. To the authors' knowledge, our study reported the highest percentage of physical therapy students with low physical activity levels compared to those in other countries. Many factors contribute to physical inactivity in physical therapy students. One study indicated that the primary contributing factors include insufficient time, lack of motivation and support, inadequate facilities, and other personal reasons[13]. Because physical therapy students are the future physical therapists who play a role in promoting physical activity in the community, this study encourages the urgent need to diminish the knowledge-practice gap about physical activity in studied participants. In this study, we also observed no significant correlation between physical activity level and participants' academic performance. However, it is noted that 64% of students with A and B grades had low physical activity levels. It indicates that students with better grades tend to have low physical activity levels. However, future research is warranted to investigate the causal relationship between physical activity and academic performance.

One published article has shown that as healthcare professionals, physiotherapists should integrate sleep into health prevention, promotion, and wellness. In addition, physiotherapy education programs should include sleep health in their curriculum [21]. Thus, physiotherapy students are expected to have knowledge and awareness of the importance of sleep health. In fact, our study indicated that almost all physiotherapy students (studied participants) reported poor sleep quality. Only one-third of the participants had adequate sleep ($\geq$6 hours). Both inadequate sleep and poor sleep quality are health problems among university students. Despite the importance of sleep duration, sleep quality appeared to be a main concern in this population. A study observed that nearly 45% of students reported sleeping more during COVID-19 [22]. Several factors might contribute to poor sleep quality. A study conducted on university students indicated that being female, having less sleep a night, and spending more than an hour using social media before sleep were significant predictor for poor sleep quality [23]. Another study reported that body mass index and lack of sleep hygiene practice were associated with poor sleep quality [24].

Research revealed a correlation between sleep issues and lower declarative and procedural learning, neurocognitive function, and academic success.[25] The results of our study indicated a significant correlation between academic achievement and sleep quality. Students who slept poorly performed worse academically. It is well recognized that getting enough sleep is crucial for memory consolidation, which in turn helps students succeed academically. Insufficient sleep has been connected to issues with focus and working memory. [26] In general, long-term sleep deprivation has an impact on quality of life and an increase in risk of health issues including obesity, diabetes, and cardiovascular disease.[27] At the same time, low physical activity levels or physical inactivity can increase the risk of a range of diseases.[28]

Several limitations are worth noting in this study. The cross-sectional design of the study could not confirm the causality between sleep quality and academic performance. Also, objective measurement of

physical activity was not used in this study, therefore it could not reflect the objective physical activity level of participants. Using self-administered questionnaires may have the potential for over or underreporting.

Conclusion

This study showed a significant association between sleep quality and academic performance. Students with poor sleep quality had lower academic performance. Although no significant correlation was found between physical activity level and participants' academic performance, it is noted that 64% of students with A and B grades had low physical activity levels. This shows that students with better grades tend to be less physically active. Future studies should evaluate what factors may impact physiotherapy students' sleep duration and quality. In addition, physiotherapy education programs should provide promotion on sleep hygiene practices to improve sleep quality in their students. By doing so, we can expect better academic performance in physiotherapy students.

Conflicts of Interest

There is no conflict of interest.

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Literature Review   **Open Access**

The Relationship of Aggressiveness and Depression during the COVID-19 Pandemic: A Literature Review

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ABSTRACT

Introduction: The COVID-19 pandemic has a significant impact on the mental health of people around the world, including increased levels of aggressiveness and depression. This study aims to identify the relationship between aggressiveness and depression during the COVID-19 pandemic.

Methods: This research uses the literature review with the PICO method which selects relevant sources based on patient, population or problem, intervention, comparison, and outcome. Articles were collected using search engines such as EBSCO, Pubmed, ScienceDirect, and Proquest. The criteria for articles used were those published in 2019-2024.

Results: The literature review conducted in this study identified 22 relevant articles addressing the issue of aggressiveness and depression during the COVID-19 pandemic. These articles provide critical insights into the complex relationship between these two mental health challenges, particularly in the context of the unique stressors introduced by the pandemic. The analysis of these sources highlights the significant increase in both depression and aggressive behaviors, emphasizing the need for comprehensive mental health interventions to address the dual impact of these conditions during global health crises.

Conclusion: The pandemic has exacerbated mental health conditions, with depression becoming more prevalent and often leading to aggressive behavior due to impaired emotion regulation. Contributing factors include psychological distress, social isolation, economic uncertainty, and disrupted routines. The findings highlight the need for holistic mental health interventions and adequate social support to mitigate these effects.

Keywords: Aggressiveness; depression; COVID-19 pandemic; mental health

Introduction

The COVID-19 pandemic has significantly impacted global mental health, leading to a rise in various psychological disorders, particularly depression. Previous studies have consistently shown that individuals suffering from depression often exhibit aggressive behaviors, primarily due to challenges in emotion regulation. Research during the pandemic has highlighted key contributing factors such as psychological distress, social isolation, economic instability, and disruptions to daily life, all of which have exacerbated these mental health issue.[1]

Based on data on the incidence of violence in the United States released by the Federal Bureau of Investigation in 2013, there were an estimated 1,163,146 violent crimes that occurred nationwide where firearms were used in 69% of homicides, 40% of robberies, and 21.6% of aggravated assaults. It was also reported that a woman is beaten every 9 seconds and almost 20 people per minute are physically abused by their partners. During one year, one in five women and one in seventy-one men in the United States are raped.[1]

During the pandemic, there has been an increase in cases of aggressiveness, this can be seen, among others, from the rampant news about the high incidence of domestic violence, both violence against children and women. Research in Egypt stated that violence in the form of discipline occurred in child respondents by 90.5%, aggressiveness in the form of psychic by 88.7%, and severe physical punishment by 43.2%.[2]

In Indonesia, the Ministry of Women's Empowerment and Child Protection (PPPA) stated that there were 1,913 cases of violence against women before the pandemic. Then during the pandemic, there was an increase in cases by five times to more than 5,500 cases. Meanwhile, cases of violence against children have experienced a significant increase. Before the pandemic, there were 2,851 cases of child abuse, which were later reported to have increased to more than 7,190 cases during the pandemic.[3]

This study aims to build upon existing literature by exploring the intricate relationship between depression and aggressiveness during the pandemic, underscoring the urgent need for comprehensive mental health interventions and support systems to mitigate the pandemic's adverse effects on mental well-being. This study is expected to provide knowledge to health workers, especially to psychiatrists about the relationship between aggressiveness and depression during the COVID-19 pandemic. It canenrich the repertoire of science in the field of psychiatry in terms of the relationship between aggressiveness and depression during the COVID-19 pandemic.

Methods

This study uses the literature review method to identify and analyze the relationship between

aggressiveness and depression during the COVID-19 pandemic. The data sources were from the various relevant scientific journals, articles, and research reports published in the last 5 years. The search process was conducted using specific keywords such as "aggressiveness," "depression," "COVID-19 pandemic," "mental health," and "social isolation" in scientific databases such as PubMed, Google Scholar, and ScienceDirect. These databases were chosen for their extensive coverage of peer-reviewed medical and psychological literature, ensuring the inclusion of high-quality and relevant studies. Additionally, their advanced search algorithms and filtering options allow for the precise identification of studies that focused on the impact of the pandemic on mental health, with particular attention to aspects of aggressiveness and depression.

Inclusion criteria in this study included articles written in Indonesian and English, articles that had empirical data on aggressiveness and depression during the pandemic, and articles that had been peer-reviewed. The exclusion criteria for this study include articles not written in Indonesian or English, articles that do not provide empirical data on aggressiveness and depression during the pandemic, articles that have not undergone peer review, and articles that do not explicitly test the relationship between aggressiveness and depression. Once relevant articles were identified, a study quality assessment was conducted using quality assessment tools such as the Critical Appraisal Skills Program (CASP) to ensure the validity and reliability of the findings presented.

Data analysis was conducted by categorizing key findings from the selected studies. Furthermore, the data collected was analyzed by identify the patterns, trends, and relationships between aggressiveness and depression during the pandemic. Emphasis was placed on the causal factors underlying the increase in aggressiveness and depression and how these two conditions interact with each other. The results of this review were used to develop recommendations for more effective mental health interventions and adequate social support for vulnerable individuals.

Result

This study identified 22 relevant articles addressing the issue of aggressiveness and depression during the COVID-19 pandemic. The research studies cited provide a comprehensive exploration of the relationship between stress, aggression, and depression, particularly in the context of social isolation and the COVID-19 pandemic. Chang and Gean (2019) and Chang et al. (2020) examined how stress-induced aggression in mice is controlled by neural mechanisms and regulated by microRNAs, providing insights into the biological underpinnings of aggressive behavior. De Bles et al. (2019) and Deng and Feng (2022) further explored the psychological factors that contribute to aggressive tendencies, highlighting the role of perceived threats and emotional distress during the pandemic. Drndarević et al. (2021) and Girasek et al. (2022) investigated how sensory processing sensitivity and trait emotional intelligence mediate the

relationship between depression and aggression. Collectively, these studies underscore the complex interplay between psychological stressors, biological mechanisms, and behavioral outcomes in the context of aggression and depression during times of crisis.[4–9]

The results showed that there was a significant increase in the prevalence of depression and aggressive behavior during the COVID-19 pandemic. From the analysis of various studies, it was found that depression rates increased dramatically during the pandemic, with some studies reporting an increase of up to two times compared to the pre-pandemic period. Aggressive behavior, both verbal and physical, has also increased, especially in individuals experiencing social isolation and high psychological distress. Data shows that depressed individuals tend to exhibit aggressive behavior more often as a response to the inability to regulate emotions and stress caused by the pandemic situation. [4,5,6,7,10]

In addition, factors such as economic uncertainty, changes in daily routines, and lack of social support contribute to increased aggressiveness and depression. The studies analyzed show that economic stress, such as job loss or reduced income, is a significant factor affecting individuals' mental health. Social isolation resulting from physical and social restrictions also exacerbated mental conditions, with many individuals reporting feelings of loneliness and helplessness. Research has also found that individuals with low social support are more prone to depression and aggressive behavior than those with strong social support networks. [8,9,11,12,13,14,15]

In children and adolescents, several studies have shown that high levels of depression are associated with increased aggressive behavior. These studies found that depression, which is exacerbated by social isolation, uncertainty and academic pressure, often leads to irritability and frustration that manifests as aggression. Research also shows that peer victimization can increase depressive symptoms, which in turn triggers aggressive behavior. Therefore, interventions targeting depression reduction and adequate social support are critical to reducing aggressiveness in adolescents.[16–25]

These studies suggest a complex relationship between depression and aggressiveness, with factors such as gender, social conditions, and environmental support playing important roles in the development and manifestation of both conditions.

Discussion

A pandemic situation that causes stress in various aspects of life is a negative event that certainly risks increasing the occurrence of mental disorders. Aggressiveness and depression are two of the mental disorders that have increased the most among other mental disorders. Apart from physical and economic conditions, isolation or quarantine also plays a role in increasing stress. Isolation or quarantine, which is essentially intended to maintain physical health, actually causes psychological problems, due to the lack

of mental and physical interaction with people around them. This risks the development of psychopathology, such as depression, anxiety, and aggressiveness. Shimizu et al.examined aggressive behavior and depressive symptoms in chronically isolated rats. The study suggested that chronic isolation not only causes aggressive behavior but also depression-like behavior.[26]

Depression which is synonymous with sadness, weakness, lethargy looks very different from aggressive behavior. Individuals with depression tend to attribute negative events to internal causes (self-blame), causes that cannot be changed and are chronic. According to Burns and Seligman, these internal causes are referred to as "explanatory styles" that occur throughout the lifespan and thus are a "perpetual risk for depression". Aggressive individuals, on the other hand, externalize blame, ascribe negative events to the behavior of others, and view others as having hostile attitudes or intentions. Despite these seemingly contradictory attributions, depression often co-occurs with aggressive behavior. [4,10,27]

Depressive sequelae such as self-isolation, loss of social support, increased alcohol use, angry rumination, and impulsivity may contribute to increased risk of aggression. Affective displacement related to negative feelings from internalizing and externalizing attributions becomes fused and indistinguishable. Therefore, the affective impact of negative events can lead to depression and anger. One result of this affective displacement is the emergence of "scapegoating", where depressed individuals find externalized individuals to blame for "causing" hostility. For this reason, depression is both a routine indicator of mental health assessment and seen as a risk factor for aggression. [4–7]

Aggressive behavior can result in rejection and lack of support by important others (e.g., parents), ultimately leading to widespread experiences of failure in social interactions with others. Experiences of failure, lack of support, and rejection from others may ultimately lead to an increased risk of depressive moods.

Longitudinal research has mixed results, possibly due to differences in the age of respondents, research methods that use self-report data, data obtained from only one source, using different measures or instruments, and no research has specifically examined the bidirectional relationship between aggressive behavior and depression. The first multi-informant study on the longitudinal relationship between aggressive behavior and depressive symptoms. The results suggest that aggressive behavior in early adolescence predicts the occurrence of depressive symptoms later in life. Although this study used multi-informants, the small number of informants for each depression or aggressive domain assessment still allows for bias. The results of this study are limited to early adolescence, so they cannot be generalized to other age limits.[11–14]

Liu & Cole's research (2021) is the first study in a large population, namely a survey conducted on 5692 respondents in the United States. The results stated that aggressiveness is related to the occurrence of Major Depressive Disorder (MDD). Research in the same year on 2539 respondents with unipolar

MDD stated that 58.7% of respondents behaved aggressively. Despite the large number of respondents, unfortunately this study still does not answer the causal relationship between aggression and depression. However, this study found that all types of aggressive behavior were independently associated with increased odds of MDD diagnosis. Conversely, MDD characteristics were also associated with the presence and frequency of aggressive behaviors. Property destruction and physical assault were associated with severity and early onset of depression. In addition, early onset of depression was associated with frequency of aggressive behavior.[14,16]

Psychic aggressiveness, which is considered less aggressive and therefore more acceptable than physical aggressiveness, is actually a risk for negative mental development, such as depression, anxiety, and bullying. Parents often commit psychological aggressiveness to their children without realizing it. Research by Wang et al. (2021) in China examined psychological aggressiveness from parents to children. The results of this study are interesting because it turns out that psychological aggressiveness is transmitted from generation to generation and this transmission is moderated by anxiety and depression from the mother, not the father. This may be related to the Chinese culture of: "nan zhu wai, nv zhu nei" which means men take care of things outside the home and women take care of things inside the family. A longitudinal study by Hasegawa et al. (2022) on university students in Japan stated that aggressive behavior was a factor leading to interpersonal stress generation and all negative event experiences predicted an increase in future depressive symptoms.[11,18]

Child and adolescent studies show that the COVID-19 pandemic has had a significant impact on adolescent mental health, especially in terms of depression and aggressiveness. Social isolation, economic uncertainty and activity restrictions are the main factors that exacerbate these conditions. Social isolation triggers hormonal reactions and brain circuits that lead to aggressive behavior, especially in individuals prone to anxiety and depression. Gender differences were also found, with men more prone to increased aggressiveness in difficult financial situations or family loss, while women were more prone to increased depressive symptoms. These findings emphasize the importance of early intervention and appropriate social support to prevent the escalation of mental health problems among adolescents during the pandemic.[23–25]

Several factors such as gender and family conditions, some studies have found that individuals living with children experience higher levels of depression and anxiety. In addition, women tend to experience higher levels of depression than men, especially during times of crisis such as the pandemic. It has also been found that aggressiveness levels increase in men as lockdown tightness increases, especially when there is a decrease in income or loss of loved ones due to the pandemic.

Depression is generally considered the opposite of aggression due to the apparent contradiction in

energy levels or blaming behaviour. However, there is ample evidence of a significant relationship between depression and aggression. Most studies are cross-sectional and retrospective, so there is little empirical evidence to suggest that depression causes aggression or aggression causes depression.

Psychic and physical aggressiveness are both intolerable because they have a negative impact on oneself and others. Psychic aggressiveness can be transmitted from generation to generation and this transmission is moderated by the anxiety and depression of the mother or people who frequently interact with the child. Culture has a strong influence on aggressiveness and depressive behaviours. Aggressive behaviour may be more damaging to interpersonal relationships in Japan (Asia) than in the West because Japanese people tend to emphasize harmonious interpersonal relationships. Isolation or quarantine during the pandemic increased the risk of aggressive behaviour and depressive symptoms. Further research is needed that analyses the correlates of different types and levels of aggression and moderators of the relationship between aggressiveness and depression.

The COVID-19 pandemic has had a significant impact on mental health, exacerbating disorders such as depression and aggressiveness. Social isolation and quarantine, while aimed at maintaining physical health, add psychological stress that risks triggering mental disorders. Research shows that isolation can increase aggressive behaviour and depressive symptoms, with individuals experiencing affective displacement of negative feelings that coalesce, resulting in concurrent aggression and depression. Factors such as gender, family conditions, and the strictness of lockdown affect the level of depression and aggressiveness, with women being more prone to depression and men to aggressiveness. Therefore, it is important to intervene early and provide adequate social support to prevent and address mental health issues during times of crisis.

Conclusion

The COVID-19 pandemic has significantly impacted mental health, particularly by increasing the prevalence of depression and aggressive behavior. The enforced social isolation and quarantine measures, although necessary for physical health, have exacerbated psychological stress, leading to a higher risk of mental disorders. Research indicates that isolation not only heightens aggressive tendencies but also intensifies depressive symptoms, with individuals often experiencing a fusion of these affective states. Factors such as gender, family dynamics, and the severity of lockdown measures further influence the degree of depression and aggressiveness, with women being more susceptible to depression and men to aggression. These findings underscore the urgent need for early intervention and comprehensive social support to mitigate the adverse mental health effects during crises like the pandemic.

Conflicts of Interest

Funding sources

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