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Workplace Violence Against Doctors and Nurses in Public Healthcare Services in AL- Majmaah City, Saudi Arabia

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Abstract

Workplace violence raises a significant concern in healthcare settings, with healthcare workers being at risk of physical and emotional harms. This phenomenon is, however, rarely investigated in Al-Majmaah city, Saudi Arabia. This study sought to estimate the prevalence of workplace violence against doctors and nurses working in public healthcare facilities in Al-Majmaah city. A cross-sectional study was conducted in public health facilities in Al-Majmaah city, Saudi Arabia, from June to August 2022. Healthcare workers were recruited to participate in a self-administered online questionnaire, which collected data on sociodemographic information, workplace violence exposure, and attitudes towards violence. Of the total participants, 41.9% reported experiencing workplace violence. The majority of incidents occurred in health institutions, with 92.3% involving verbal abuse, 2.6% physical violence, or both. Patients' families were responsible for 48.7% of the violence, followed by the patients themselves (43.6%). In response to violence, healthcare workers reported various coping mechanisms, including pretending the incident never happened (23.1%), attempting to stop the perpetrator (23.1%), and protecting themselves (18%). Regarding system satisfaction, 14% remained indifferent, 16% were dissatisfied, and 2% were satisfied. Furthermore, 15.1% of participants experienced disturbed thoughts or images of the attack, 14% avoided thinking or talking about incidents, and 11.8% were unaffected. Workplace violence is a significant problem affecting healthcare workers in public healthcare facilities in Al-Majmaah city, Saudi Arabia. The high prevalence of verbal abuse and physical violence highlights the need for effective prevention and intervention strategies to ensure a safe working environment for healthcare workers.

Keywords: Al-Majmaah city, healthcare workers, public healthcare facilities, Saudi Arabia, workplace violence

Introduction

Workplace violence has been an increasing threat in healthcare settings across the globe with serious psychological, physical, and social repercussions for both healthcare providers and the health system.[1–3] Most of the workplace violence (WPV), according to the Occupational Safety and Health Act (OSHA), occurs in environments connected to healthcare services.[4] World health organization (WHO) defines violence: "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation".[5] Moreover, it psychologically and physically impacts the health care providers. As a result, low self-esteem, increased absenteeism, low productivity, may result in medical errors and interfere with the quality of care. It may jeopardize the efficiency and enthusiasm of healthcare workers. Thus, it

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has the potential to decline healthcare quality and expose health care workers to vulnerability and, as a result, impact the health sector's financial status.[2] It financially affects the facility through worker compensation and managing staff shortages.

As stated by WHO, violence includes physical violence such as beating and psychological violence such as verbal abuse and bullying.[5] Workplace violence could be one of these four types: Type I incidents usually occur with a criminal motive, such as robbery, by the perpetrator who has no professional relationship with the healthcare providers or health care system which often can go to the extent of murder. Type II occurs when a patient or visitor poses as the attacker; this situation can occur in any department, more specifically in a mental health care facility.

Type III is related to interpersonal or work conflicts and involves a workfellow as a perpetrator. Type IV is a perpetrator who is not connected to the workplace professionally but has a personal relationship with the staff member outside of it.[1,4] The incidence of workplace violence varies depending on the department; emergency, geriatric, and mental health departments are susceptible to violence, according to OSHA.[4]

Factors that increase the probability of violence vary depending on the workplace, such as presence of individuals with a track record of aggression or drug abuse, working alone without others assistance, transferring patients, working in dimly lit corridors, improper communication, a lack of training programs and policies to deal with violence, a lack of security, or a long wait time in the workplace.[2,6] The highest incidence of workplace violence injuries occurs in the healthcare and social service domains, wherein employees are five times more likely to sustain an injury than other workers.[7] Furthermore, it is believed that workplace violence in the health sector accounts for about a quarter of all workplace violence.[8] The World Health Organization (WHO) states the figure is estimated to be between 8% and 38% of healthcare providers who suffer physical violence at some point in their professional lives. At the same time, many more suffer from or are threatened with verbal violence.[2,5]

Healthcare workers who are involved in patient care, in particular paramedics, emergency department staff, and nurses, are the most vulnerable.[2,5,9] According to ILO, ICN, WHO and PSI joint program, nurses are in jeopardy of workplace violence than other healthcare providers.[5,10] Doctors come as the second highest group facing workplace violence after nurses. Healthcare workers respond to violence at the workplace by remaining silent about the incident; that may lead to an underestimation of the magnitude of issue as some may believe it is a part of their job, they must embrace it and refrain from reporting any kind of violence they encounter.[6]

Most studies have shown that verbal violence is the most common form of workplace violence, followed by physical violence. A study conducted in China found that nurses working rotating shifts, in emergency departments, and in pediatric wards are at a significantly higher risk of experiencing workplace violence. Among these, emergency departments are particularly vulnerable. Much of the existing research has focused primarily on the prevalence of workplace violence among healthcare providers, often emphasizing a single profession—typically nurses. Despite the fact that workplace violence among healthcare workers in Saudi Arabia is not uncommon, there is a notable lack of comprehensive research in this area.[6]

Given this paucity of research, particularly in Al-Majmaah, Saudi Arabia, the present study aims to assess the level of awareness, preparedness, and responsiveness of doctors and nurses toward workplace violence. Specifically, it seeks to determine the prevalence and types of workplace violence encountered by these professionals in healthcare facilities in Al-Majmaah City, as well as to explore potential associations with sociodemographic factors..

Methods

A descriptive cross-sectional study was conducted between June and August 2022 at public healthcare facilities in Al-Majmaah City, Saudi Arabia. The study encompassed all public primary healthcare centers (PHCs) in the city that are affiliated with King Khaled Hospital (KKH), including Faisaliah PHC, Faiha'a PHC, Yarmouk PHC, Mata'ar PHC, and Majmaah PHC. Private healthcare facilities and public health centers not affiliated with King Khaled Hospital were excluded from the study.

The study included male and female doctors and nurses, both Saudi and non-Saudi, aged 24 years and above, who were employed at public healthcare facilities. Medical students, interns, and other categories of healthcare workers were

excluded from the study.

The sample size was calculated using the formula: $n = (z^2 \times p \times q)/d^2$, where n is the sample size, z is the Standard Error taken as 1.96, d is taken as 0.05, and p is the prevalence in this study considered according to a previous study conducted in Macau which reported 57.2% of doctors and nurses were victims of violence. Based on this formula, the calculated sample size was 93 participants.

Data were collected using a self-administered online questionnaire consisting of 18 items. The questionnaire included sections on sociodemographic characteristics, exposure to workplace violence (type and duration), factors influencing the reporting of violence, and awareness of institutional policies addressing workplace violence. Participants were provided with a brief explanation of the study's purpose, and written informed consent was obtained from all respondents. Confidentiality and anonymity were assured. Prior to data collection, a pilot study was conducted to assess the validity and reliability of the questionnaire, resulting in a Cronbach's alpha of 0.7, indicating acceptable internal consistency.

The questionnaire consisted of 18 questions that collected sociodemographic information, as well as data on workplace violence exposure, factors related to violence reporting, and policies against violence. These constructs were measured using a combination of question types, including categorical, ordinal, and nominal questions.

To ensure the reproducibility of the data analysis, the collected data underwent a rigorous transposition process. First, the data was cleaned to address any errors, inconsistencies, or missing values. Next, the questionnaire responses were coded into numerical or categorical variables to facilitate analysis. For instance, categorical variables such as gender were coded as 0 and 1, respectively. The data was then transformed into a suitable format for analysis, with ordinal variables such as the duration of exposure to workplace violence converted into numerical variables.

The present study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the Ministry of Health (IRB No: 21-IOE). Data were analyzed using IBM SPSS Statistics, version 25. Descriptive statistics, including frequencies and percentages, were used to summarize the data. The Pearson Chi-square test was applied to assess associations between categorical variables. A p-value of <0.05 was considered statistically significant.

Results

A total of 93 healthcare workers participated in the study. Of these, 54% were male and 46.2% were female. All participants were aged 24 years or older, with the majority (26.9%) falling within the 31–35 age group. Nearly half of the respondents were married (48.8%), while 15.1% were single, and 2.2% were divorced. he majority of participants (75.3%) were of Saudi

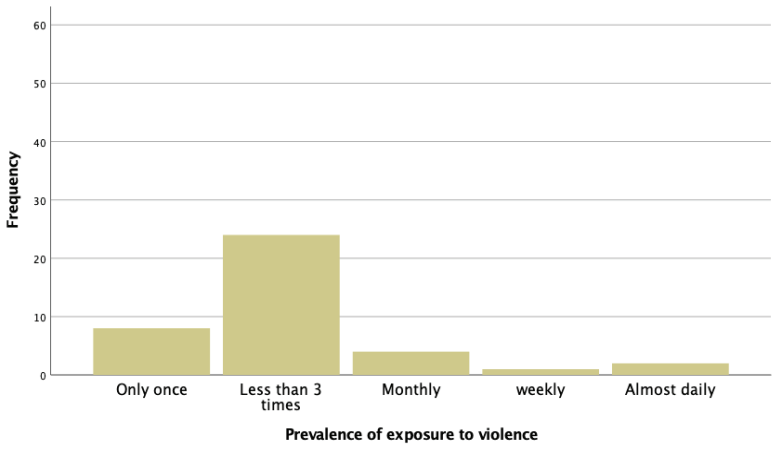

Figure 1 Prevalence of Exposure to Workplace Violence Among Healthcare Workers in Al-Majmaah, Saudi Arabia

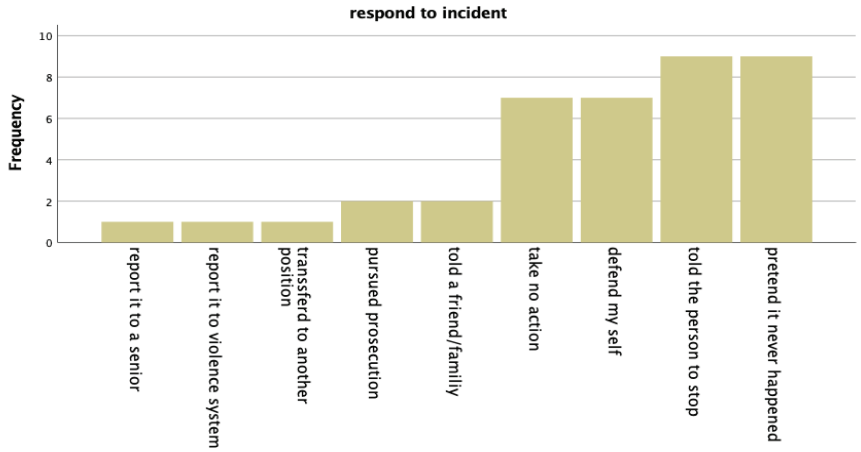

Figure 2 Summary of Participants' Responses to Incidents of Workplace Violence

nationality. Most were employed at primary healthcare centers (PHCs) (46.5%). Among those working at King Khaled Hospital, 11.8% were from the emergency department, followed by the operating room (10.8%) and specialized units (8.6%). From the King Khalid Hospital 11.8% were from Emergency department followed by staff from Operating Room (10.8%), then specialized unit (8.6%). In terms of work experience, 31.2% had 6 to 10 years of experience, and 23.7% had 11 to 15 years. More than half of the participants (51.6%) reported working in shift.

In this study, 41.9% of healthcare workers reported being exposed to workplace violence. Almost all incidents occurred within healthcare institutions, with only one respondent indicating that the violence took place at a patient's home. About 26% reported experiencing violence fewer than three times, while 8.6% had experienced it only once in their careers. Additionally, 4.3% reported monthly exposure to violence, and 2.2% indicated they faced violence almost daily (Figure 1).

Verbal abuse was the most common form of workplace violence, reported by 92.3% of affected participants. Physical assault alone was experienced by 2.6%, and 2.6% reported exposure to both physical and verbal violence. Another 2.6% reported other unspecified forms. Regarding the source of violence, 48.7% identified patients' relatives as the perpetrators, followed by the patients themselves (43.6%). A smaller proportion reported experiencing violence from staff members (2.2%) or supervisors (1.1%).

Reactions towards violence by the participants varied most of them tried to pretend it never happened (23.1%) while others stated they responded to the incidents by stopping the preparator from doing the violence (23.1%). While 18% stated they tried to defend themself in response to violence and 17.9% stated they ignored the incident and took no action. Few of them reported the incident to their seniors, pursued prosecution, reported to violence system and got transferred (Figure 2).

Those who did not respond to violence (37.6%) stated various reasons for not reacting against violence. Most of them stated that it was useless to report the violence (48.7%) followed by 25.6% who revealed it was not important to report and 7.7% of them did not know where to report the violent incidents least they were afraid of negative consequences (2.6%) (Table 1). Regarding the satisfaction of handling of the violent incidents ,14% of the participants remained neutral, while 16% were not satisfied

Table 1 Reasons for Not Reporting the Violence

Reasons for Not Reporting About the Violence	Frequency	Percentage
It was not important	10	25.6
Felt ashamed	2	5.1
Useless	19	48.7
Afraid of negative consequences	1	2.6
Did not know who to report	3	7.7

Table 2 Participants' attitudes Toward Violent incidents in the Workplace

Questions	Frequency (Percentage)				
	Not at all	A little bit	Moderately	Quite a bit	Extremely
Repeated, disturbing memories, thoughts, or images of the attack?	11 (11.8 %)	14 (15.1 %)	5(5.4%)	5 (5.4%)	5 (4.3 %)
Avoiding thinking about or talking about the attack or avoiding having feelings related to it?	4 (4.3 %)	11 (11.8 %)	6 (6.5%)	5 (6.5%)	13 (14%)
Being "super-alert" or watchful and on guard?	6 (6.5%)	8 (8.6 %)	5 (5.4%)	13 (14%)	7 (7.5 %)
Feeling like everything you did was an effort?	7(7.5 %)	4(4.3 %)	6 (6.5%)	15 (16.1%)	7 (7.5%)

and only 2% were satisfied.

As for their attitude towards violence, 15.1% had disturbing memories or images of the attack, while 11.8% were not affected followed by 14% of them avoiding thinking or talking about the incident, and 14% remained super alert or watchful against the violence. Regarding those who were exposed to violent behavior, only 6.5% of them took vacation after the violent incident. Duration of vacation varied between a few days to one year (Figure 2). Out of 6 participants, three healthcare workers took three days' vacation while the remaining three took one month, 6 months and one-year vacations respectively. Most of the participants were aware that there is a reporting system against workplace violence (37.6 %). About 23.7% of participants denied the existence of such a system while 37.6% did not know the answer (Table 2).

More than half of the participants (64.5%) reported that they did not know how to use the workplace violence reporting system, while 35.5% believed they knew how to use it. Most participants accepted workplace violence as part of their job and felt they had to adapt to it. Only 43% agreed that they had received training on how to deal with workplace violence, while nearly 86% stated they had not received any such training. Additionally, 11.8% of participants reported having received a training program on the issue, and only 2% mentioned that a training program was available at their workplace, though they were not interested in it. A statistically significant correlation was found between shift work and exposure to workplace violence, with 64.1% of shift workers reporting exposure to violent incidents. However, no significant correlation was found between exposure to workplace violence and sociodemographic factors such as age, gender, marital status, nationality, workplace, profession, division, or years of experience (Table 3).

Table 3 Inferential Analysis: Relationship Between Sociodemographic Factors and Prevalence of Workplace Violence

Demographic Data	p-value
Age	0.75
Gender	0.66
Nationality	0.10
Marital Status	0.24
Work	0.45
Profession	0.2
Division	0.17
Experience	0.23
Shifts	0.04*

*p<0.05 is significant

Discussion

Workplace violence is increasing in healthcare facilities against health care workers. Occupational Safety and Health Act (OSHA) reported that a high percentage of workplace violence occurs in healthcare work service settings.[4] Various factors contributed to

workplace violence in the health care institutions which can cause physical and mental trauma leading to absenteeism from work. Hence the present study investigated workplace among doctors and nurses at King Khalid Hospital and Primary health care centers at AL-Majmaah, Saudi Arabia.

The present study revealed that 41.9% had experienced workplace violence and the report was consistent with the findings of a study conducted by AL-Turki et al. in Riyadh (45.6%). While it was much lower in studies conducted by Alsmael et al in Al Khobar (30.7%) and Alsmael et al in Alhasa (28%).[6,11] In contrast to the present study the prevalence was much higher in studies conducted in Abha (57.5%), and in. Riyadh (67%).[2,12] The international studies reported violence ranging from 39% to 83% such as Karachi-44.9%; Macau -53.1%; Gondar, Ethiopia -58.2%; Palestine -80.4%; China -83%.[13–17]

A significant finding of this study was the lack of awareness and inadequate responsiveness to workplace violence among healthcare professionals. While 38.7% of participants were aware of the reporting system, a concerning 23.7% were unaware, and 37.6% responded with "I don't know." This lack of awareness reflects a critical gap in knowledge and highlights the need for improved communication and dissemination of information regarding reporting mechanisms. Furthermore, the study revealed that two-thirds of participants who experienced violence felt discouraged or unmotivated to utilize the reporting system. This finding underscores the need for healthcare institutions to foster a supportive and responsive environment that encourages reporting and addresses incidents of workplace violence effectively.

Regarding the type of violence, the present study reported verbal abuse was the most common violent behavior experienced by the participants (92.3%). Similar finding were reported by Alsaleem et al.[2] (90%), and Al-Turki et al.[18] (94%). El-Gilany et al.[11] (92.1%), Al Anazi et al.[19](83%). In contrast, Alsaleem reported 55.9%. Most of the international studies reported ranging from 32.2% to 72.5% [2,11,14,18,19]

The present study reported physical violence rate to be 2.6% which was comparatively lower than other studies ranging between 3 to 21 %.[2,17] Furthermore, both verbal and physical violence was 2.6%, and most of the participants/ healthcare providers who worked in shifts were exposed to violence (64.1%) as compared to those who worked normal working hours in the morning showed statistical significance between exposure to violence and working in shifts the results were in consistent with other studies,[11] while in contrast, it was much higher in a study conducted by Alsaleem et al (99%).[2]

In this study, 23.1% of participants responded to violent incidents by pretending as if nothing happened to them. A similar study reported 46% which is higher than the present study. Another 23% told the perpetrator to stop the violence, 5.1% disclosed it to their family or friends; 2.6% got transferred to other positions. 2.6% reported to the violence system and 2.6% reported to their seniors. While another 17.9% defended themselves and 17.9% did not take any action, as they believed that it was of no use to complain. Similarly, a study conducted by Sahar et al reported that most of the nurses calm down the offenders or talk to colleagues or their families.[10] In contrast Alsaleem's study it was reported that 39% of participants reported the incidents. [2,18,20]

A statistically significant association was found between exposure to violence and shift work. Healthcare providers working in shifts were more likely to experience violence compared to those working regular daytime hours. This finding is consistent with previous studies and suggests that shift work may be a risk factor for workplace violence.[18-22]

When asked about the reason behind ignorance of the violent incidents 87.7% responded with different reasons the results were consistent with obtained from one study conducted in Europe (71.7%).[21] The most common reason for the ignorance of violence was the participants felt it was not important to report (25.6%) in contrast to the study conducted by Al Saleem (58%) and the European study (69.9%).[2,21] Regarding the satisfaction of handling the handling violent situations, of 93 participants 16% expressed they were not satisfied while 14% remained neutral while 2% were satisfied with system, the result consistent with other studies.[2,18]

The psychological responses of participants exposed to workplace violence varied, ranging from no impact to being extremely affected, depending on the specific aspects assessed. A portion of participants (4.3% to 11.8%) reported experiencing repeated disturbing memories, thoughts, or images related to the violent incidents. Additionally, 4.3% to 14% avoided thoughts, feelings, or discussions about the events, even with relatives or friends. Hypervigilance was also noted, with 5.4% to 14% indicating they remained unusually alert or watchful in anticipation of future

incidents. Furthermore, 4.3% to 16% expressed feeling that even routine tasks required considerable effort, reflecting emotional strain. Similarly, a study conducted by Hogarth et al. found that many nurses accepted certain forms of violence as part of their job, particularly when the aggression originated from patients with medical or psychological conditions, and was therefore not perceived as intentional.[22]

Among those exposed to violence, 6 (15.4%) of them applied for vacation of which 3(2.6%) of them for 2–3 days, 1 (2.6%) each for one month, 2–6 months, and one year respectively. Lack of knowledge or absence of clear policies and training programs of identifying and managing hostile and violent behavior at the healthcare institution is thought to be cause of the workplace violence. Most of the participants in the present study were aware of the reporting system against violence (38.7%) while 23.7% were not aware for the remaining 37.6% of participants "I don't know was the answer". The results were similar to other studies.[2] Furthermore two third were not able to use the system. While the remaining one-third assumed they knew how to use the system. The results were consistent with studies conducted by Alsaleem et al and Al-Turki et al.[2,18] Similar study by K.M. Hogarth et al. showed the reason for not reporting Workplace violence was the system was complicated, there was no time to lodge a complaint, lack of clear policies and the institution did not encourage.[22]

NIOSM suggest that violence can be prevented by altering workers practice and training programs.[23] More than half of the participants who were exposed to violence revealed that they did not know how to use the system. Two thirds of the participants stated that they were not encouraged or motivated to use the system against violence. Similarly in a study conducted by Sahar et al., nurses neglected reporting violence due to lack of clear and explicit instruction on how to handle incidence. Among those who were exposed to violence most of them (37.6%) believed that it is a part of their job and they have to accept and adapt to the such an environment. This could be one of the important factors contributing to the underreporting and cause of workplace violence.[1,23] More than half of the total participants (57%) revealed that they did not receive any training program to deal with the workplace violence while 43% agreed that have received the same. And only 2 participants (2.2%) stated that they were aware of the training program, but they were not interested in the getting trained. In contrast a study conducted in Abha reported 60% of healthcare workers received the training. In another study in Oman conducted among the nurses reported 80.6% received the training.[2,24] NIOSH recommended that an atmosphere of open communication should be created in which health care workers are provided with written procedures about how to respond to and how report workplace violence.[23]

Concerningly, 23.1% of participants responded to workplace violence by pretending it had not occurred, highlighting a troubling trend of underreporting. Other common responses included confronting the perpetrator (23%), disclosing the incident to family or friends (5.1%), and self-defense (17.9%). Additionally, 17.9% of participants reported taking no action, believing that filing a complaint would be futile. These findings underscore the need for healthcare institutions to implement clear policies and procedures for reporting and addressing workplace violence, thereby ensuring that healthcare workers feel supported and empowered to report such incidents.

A significant gap in training and prevention programs related to workplace violence was also identified. More than half of the participants (57%) reported not having received any training on managing violent situations in the workplace. This highlights an immediate need for comprehensive, institution-wide training initiatives that equip healthcare professionals with the necessary knowledge and skills to recognize, prevent, and effectively respond to workplace violence.

In conclusion, this study reveals a high prevalence of workplace violence against doctors and nurses in public healthcare facilities in Al-Majmaah City, Saudi Arabia. Approximately 42% of participants reported experiencing violence, primarily in the form of verbal abuse. Despite the severity of these incidents, responses varied widely, with a considerable proportion of healthcare workers choosing to ignore or minimize them. These findings emphasize the critical need for targeted interventions, robust support mechanisms, and tailored training programs to mitigate workplace violence, protect healthcare professionals, and improve the overall quality of patient care.

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Characteristics of Patients with Anterior Cruciate Ligament Injury at Ulin Hospital Banjarmasin, Indonesia

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Abstract

Knee injuries are one of the common injuries, especially among athletes. Many studies have concluded that the main cause of these injuries were sudden movements while doing sports. The incidence of the knee joint injury in Indonesia was 38 to 78 per 100,000 patients with the prevalence of Anterior Cruciate Ligament (ACL) injuries of 16%.1 Recently, an increasing number of ACL injury patients was observed to be treated at the Ulin Hospital, Banjarmasin, Indonesia, when compared to the number of the previous years, making it important to understand the characteristics of patients experiencing these injuries. This study aimed to explore the characteristics of patients with ACL injuries in the hospital. Data for this retrospective descriptive study were collected from medical records during the period of March 2022 to June 2023 from Ulin Hospital, Banjarmasin. The inclusion criteria were patients diagnosed with an ACL injury with or without meniscus tear. From a total of 95 patients with ACL injuries, 30 (32%) were below 20 years old, 42 (44%) were 20–30 years old, 18 (19%) were 31–40 years old, 3 (3%) were 41–50 years old, and 2 (2%) were above 50 years old. The ratio between men and women was 11:1. There were 74 patients who had sports-related injuries while the remaining 21 patients experienced the injury due to other activities. Of the total 95 cases, 59 (62%) were treated nonoperatively and 36 (38%) received arthroscopy surgery. The arthroscopy was mostly performed to patients who also experienced a meniscus injury and in the chronic phase, with an average length of stay at the hospital of 2.6 days

Keywords: Anterior cruciate ligament, arthroscopy, knee injuries

Introduction

Knee injury is among the most common injuries experienced, especially by athletes. Four ligaments in the knee stabilize knee movement; they are *anterior cruciate ligament* (ACL), *posterior cruciate ligament* (PCL), *medial collateral ligament* (MCL), and *lateral collateral ligament* (LCL).[1] ACL is the ligament that holds a crucial role in knee joint stability. In normal conditions, ACL limits the neutral-anterior movement, and functions as a major secondary restraint to internal rotation, particularly when the join is nearly fully extended.[2]

ACL injury often occurs in athletes, especially rupture of the ACL, which is sometimes accompanied by a tear in the meniscus. ACL ruptures due to noncontact mechanisms happen mostly during pivoting and jumping when the knee is slightly flexed and in valgus position, which can make anterior and rotatory instability, limiting anterior tibial translation and internal rotation thus resulting in instability of the knee joint.[3] ACL injuries are influenced by various factors that can or cannot be changed, including environmental factors, equipment used, surrounding environment, anatomy, neuromuscular, and hormonal.[4]

The incidence of knee joint injury in Indonesia was 38–78 per 100,000 patients with the prevalence of ACL injury being 16% of total patients, which is mostly caused by trauma while doing sports that include sudden stop of movements, pivoting, and jumping.[1] ACL injury commonly occurs between the ages of 16–39 years.[3] ACL injury can be treated with nonoperative treatment or operative treatment.

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ACL reconstruction is a procedure that attempts to restore normal joint arthrokinematics, improve the patient's potential to return to sports and decrease the likelihood of post-traumatic osteoarthritis.[5]

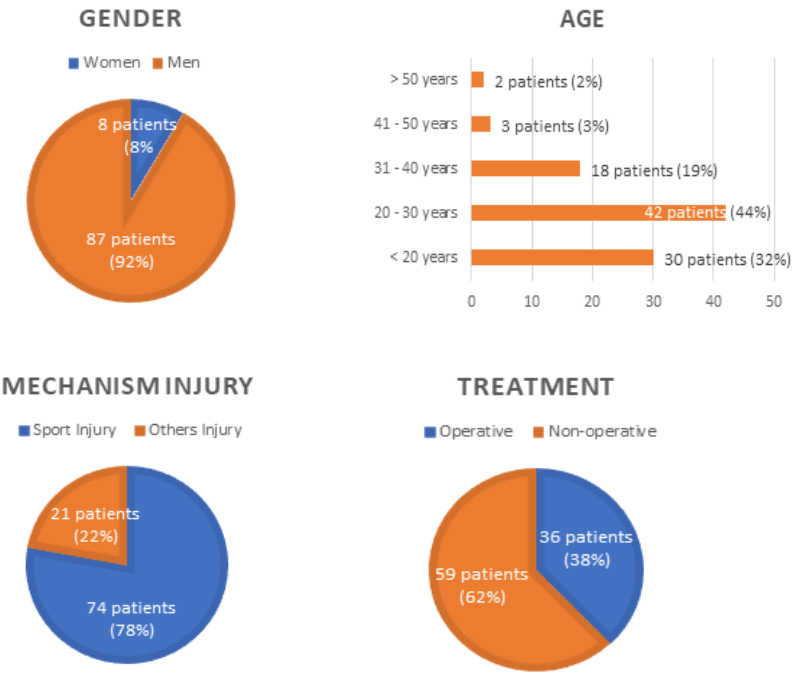
Studies on ACL injuries in Indonesia remain limited, despite the relatively high incidence of such cases across the country, including in Banjarmasin, South Borneo. Notably, there has been an increase in the number of ACL injury cases treated at Ulin General Hospital, Banjarmasin, compared to the previous year. This study aims to provide healthcare providers with a more comprehensive understanding of the characteristics of patients admitted with ACL injuries at Ulin General Hospital, in order to enhance the quality of care and improve health services through a better understanding of patient demographics and clinical profiles.

Methods

This retrospective descriptive study was conducted at Ulin General Hospital, Banjarmasin, with data collected from March 2022 to June 2023 through patient medical records. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Lambung Mangkurat University (Approval No. 021/KEPK-FKIK ULM/EC/II/2024), and permission from hospital management was also secured prior to data collection.

The study included all patients diagnosed with anterior cruciate ligament (ACL) injury under ICD-10 code S83.53 (sprain and strain of knee: tear of the anterior cruciate ligament) during the study period. Following identification, patients were contacted to obtain informed consent for the use of their data in this research. Inclusion criteria comprised patients diagnosed with ACL injury—with or without a meniscal tear—based on a clinical history, a positive anterior drawer test, and Magnetic Resonance Imaging (MRI) of the knee confirming an ACL tear. Exclusion criteria included patients diagnosed with additional ligament injuries such as posterior cruciate ligament (PCL), medial collateral ligament (MCL), or lateral collateral ligament (LCL) tears.

Collected data were categorized and analyzed using IBM SPSS Statistics version 25. Variables analyzed included gender, age, mechanism of injury, treatment approach (operative or non-operative), presence of meniscal injury based on arthroscopic findings, and the time interval between the injury and surgical intervention.



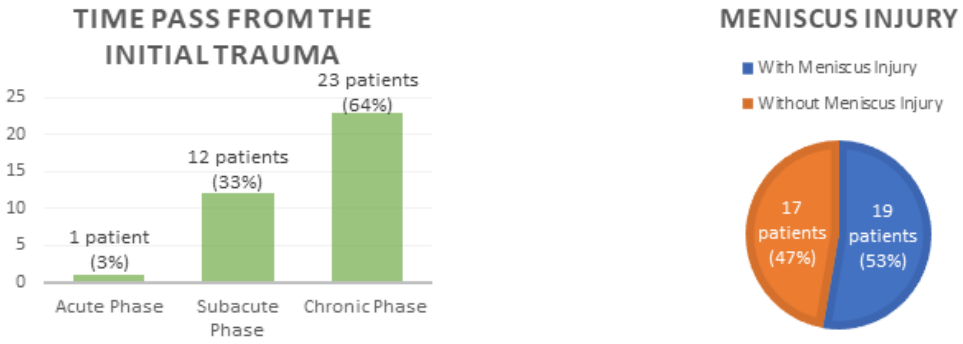


Figure 1 Prevalence of anterior cruciate ligament (ACL) injury categorized by: (a) Gender, (b) Age group, (c) Mechanism of injury, (d) Type of treatment (operative vs. non-operative), (e) Time interval between injury and surgery, (f) Presence of associated meniscal injury

Table 1 Modifiable and Non-Modifiable Risk Factors for ACL Injury[4]

Modifiable Risk Factors	Non-modifiable Risk Factors
Environmental	Environmental
Meteorological conditions (E)	Playing situation (E)
Playing surface (E)	Opponent behavior (E)
Rules (E)	Unanticipated events during play
Referees (E)	(E)
Coaching (E)	Anatomical
Equipment	Q angle (I)
Footwear (E)	Navicular drop (I)
Knee braces (E)	Structural knee valgus (I)
Anatomical	Postural alignment (I)
Foot pronation (I)	Notch size, ACL geometry and properties (I)
Body composition and body mass index (I)	Tibial slope angle (I)
Neuromuscular	Generalized joint hypermobility or laxity (I)
Dynamic knee valgus (I)	Hormonal
Muscle strength (I)	Menstrual phase (I)
Muscle strength ratios (I)	Hormone concentrations (I)
Muscle activation patterns (I)	Demographic
Muscle stiffness (I)	Age (I)
Physical fitness and muscle fatigue (I)	Maturation (I)
Skill level (I)	Previous contralateral knee ACL
Neuromuscular control (O)	injury (I)
Proprioception (I)	Familial history and genetics (I)
Psychological (I)	Sex (I)
Personality (I)	Height (I)
Stress response (I)	Race (I)
	Sports played (I)

Results

A total of 95 patients were diagnosed with anterior cruciate ligament (ACL) injury at Ulin General Hospital between March 2022 and June 2023. The majority of the patients were male, with a male-to-female ratio of 11:1, comprising 87 men (92%) and 8 women (8%).

The age of patients ranged from 15 to 66 years, with a mean age of 25.9 years. Thirty patients (32%) were under the age of 20, 42 patients (44%) were between 20 and 30 years old, 18 patients (19%) were aged 31 to 40 years, 3 patients (3%) were aged 41 to 50 years, and only 2 patients (2%) were over 50 years old. The highest incidence was observed in the 20–30 years age group.

Regarding the mechanism of injury, 74 patients (78%) sustained ACL injuries due to sports activities, while 21 patients (22%) experienced injuries from non-sport-related causes. In terms of treatment, 59 patients (62%) received non-operative management, and 36 patients (38%) underwent arthroscopic surgery. The average length of hospital stay for surgical cases was 2.6 days. Among those who underwent surgery, 1 patient (3%) was operated on during the acute phase (less than two weeks post-injury), 12 patients (33%) during the subacute phase (two weeks to three months), and 23 patients (64%) during the chronic phase (more than three months post-injury). Furthermore, of the 36 patients who underwent surgery, 19 (53%) had associated meniscal injuries, while 17 (47%) did not.

Discussion

The ligament in the knee maintains the stability of the knee joint. The most common injuries that affect knee ligaments are ACL, PCL, MCL, and LCL. Partial rupture of ACL is very rare since almost all ACL ruptures are complete or near complete tears.[1] The grade of ACL injury was based on the tears that occur. ACL injury grade 1 is when the microtears occur in the ligament, and the ligament is slightly stretched but can still help to maintain the stability of the knee joint. ACL injury grade 2 is diagnosed when the ligament is stretched to the point where it becomes loose, which can be diagnosed with partial ligament rupture. Grade 3 injuries represent a complete rupture of the ligament, which may include a full tear or an avulsion (where the ligament pulls away from the bone), resulting in significant knee joint instability.[1]

ACL injury occurs due to numerous factors, which can be categorized into modifiable and nonmodifiable risk factors and also extrinsic (E) and intrinsic (I) risk factors (Table 1).[4] In this study it was found that patients with ACL injury in Ulin Hospital were mostly men (92%) compared to women (8%). In contrast to a study by Devana et al.,[6] who reported that compared to male athletes in the same sport, female athletes are two to eight times more likely to sustain an ACL injury.[6] This is because women have a smaller *notch width index* (NWI) when compared to men. NWI is a measuring method that attempts to standardize notch width relative to the overall distal femoral and is commonly employed to define the size of the *femoral intercondylar notch*.[6] Hormonal factors also influence the incidence of ACL injury because hormones including estrogen, progesterone, and androgen receptors were found in the fibroblast and endothelial cells in the ACL.[6] However, this study was not able to describe the cause of the injury due to a lack of information in the medical record.

In this study, the majority of subjects were within the 20–30 year age range (44%), followed by those under 20 years (32%), 31–40 years (19%), 41–50 years (3%), and over 50 years (2%). These findings align with a study by Diermeier et al. (2020), which concluded that ACL injuries most commonly occur between the ages of 16 and 39.[3] Similarly, this study observed ACL injuries in patients aged 15 to 66 years, with a mean age of 25.9 years. The highest incidence was found among individuals aged 20–30 years (44%). This pattern may be attributed to the higher levels of physical activity and sports participation typically seen in this age group.

Parsons, et al.[4] in their study in 2021 stated that movements such as pivoting, decelerating, or landing for a jump often manifest as abnormal posture and alignment during the movement that can lead to ACL rupture.[4] Examples of sports that often cause an ACL injury are football and basketball. ACL injury can also be caused by other injuries but only in a small percentage. Biomechanical abnormalities that may cause ACL rupture are due to increased ACL strain. This is in line with the result of this study, which shows that ACL rupture happened mostly to sports-related injuries (78%), in comparison to injuries due to other causes (22%).

It was found that the number of patients treated with operative method is 36 patients (38%) while non-operative 59 patients (62%).

This result in line with a study conducted by Paterno[5] in 2017 which stated that ACL injury can be treated using nonoperative or operative methods.[5] ACL reconstruction was performed in an attempt to restore normal joint arthrokinematics, improve the patient's potential to return to sports, and decrease the likelihood of post-traumatic osteoarthritis.[5] However recent evidence suggests that operative methods has higher secondary ACL injury rates, lower return to sport rates, and higher incidence of osteoarthritis than previously reported, despite ACL reconstruction.[5] Nevertheless the study by Paterno also stated that systematic review also indicates weak evidence to support the superiority of ACL reconstruction over conservative management.[5]

In this study, it was found that 3% of the total sample had undergone surgery in the acute phase, 33% in the subacute phase, and 64% in the chronic phase. According to Batista et al.,[7], to ensure the result of a good quality, the ACL repair should be performed in the acute or subacute phase, between 1 week and 3 months after the injury has occurred.[7] Good quality is defined as a consistent ACL that can be grasped and simplified (can reach the footprint); by contrast, poor-quality ACL tissue is when the ligament is hypoplastic with poorly defined margins and friability, which is difficult to grasp.[7]

Of a total of 36 patients who underwent surgery, 53% (19 patients) were accompanied by meniscus injury. Meanwhile, the incidence of meniscus injury associated with ACL rupture is as high as 55–80%, with approximately 25–35% experiencing a medial meniscus injury and 31–65% experiencing a lateral meniscus injury.[8] The result of this study is in line with a study by Venkataraman et al.[9] which stated that 77% of meniscus injuries are related to ACL injury.[9] Patients with chronic ACL rupture who do not undergo repair may experience secondary meniscus injury, due to functional instability. The incidence increases as more time passes from the initial trauma (approximately 40% after 1 year, over 60% after 5 years, and over 80% after 10 years).[8] Meniscus injuries must be repaired; otherwise, the tear will become more complex and irreparable over time, especially on the lateral side.[8]

The average length of stay for patients with ACL injury in Ulin Hospital was 2.6 days. Several studies on post-operative arthroscopy patients stated that post-operative nausea and vomiting can last for up to 72 hours and they must also undergo physiotherapy, which resulted in the length of hospital stay of 3 days after surgery.[10] This result supports the result of this study which shows that good procedure and treatment during hospitalization will have a good impact on the length of hospitalization.

This study has several limitations, primarily due to the lack of detailed information in medical records, such as the type and intensity of the physical activity at the time of the injury. These factors are crucial for understanding the cause of ACL injuries. Future research could further investigate the intensity of physical activity when the injury occurred, as the longer the time elapsed from the incident, the more likely recall bias may affect the patient's memory of the event.

In conclusion, the study found that ACL injuries at Ulin Hospital in Banjarmasin were predominantly observed in men aged 20–30 years, with sports activities being the primary cause. The injuries were managed through both operative and non-operative methods, resulting in an average hospital stay of 2.6 days. These findings suggest that effective treatment protocols during hospitalization contribute to shorter hospital stays and potentially quicker recoveries.

In this study, the incidence of ACL injury at Ulin Hospital from March 2022 to June 2023 was observed in 95 patients, with a higher frequency in men (91.6%) and sports-related injuries being the leading cause (78%). However, the exact cause of the injuries could not be determined due to insufficient details in the medical records. More than 50% of patients underwent surgery, predominantly in the chronic phase, and meniscus injuries were frequently found during surgery. All patients had a hospital stay of less than 5 days, with an average hospitalization duration of 2.6 days.

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Effect of Isocenter Placement at Nasion and Symphysis Menti on the Quality of MRI Images in Cases of Nasopharyngeal Cancer

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Abstract

Magnetic Resonance Imaging (MRI) examinations require precise placement of the isocenter as it directly influences the quality of MRI images. In the context of nasopharyngeal MRI examinations, different opinions regarding the optimal placement of the isocenter exist. Currently, two methods of isocenter placement are commonly applied, i.e., nasion and symphysis menti isocenter placement. This study aimed to analyze how these different isocenter placements affect the quality of MRI images in T2 Turbo Spin Echo sequences of the nasopharynx in the coronal plane. This study was conducted in June 2023 at the Radiology Installation of Dharmais Cancer Hospital, Jakarta, Indonesia. This study used the quantitative experimental approach. Six samples were purposively selected from nasopharyngeal cancer patients, and two treatments were conducted: isocenter placement at the nasion and isocenter placement at the symphysis menti. Data processing was performed using a statistical software. The results of the Wilcoxon test for image quality from the perspective of the signal-to-noise ratio (SNR) yielded a p-value of 0.173, which was greater than 0.05, indicating that there was no significant difference in image quality as measured by the SNR between the two isocenter placements. Similarly, the paired sample t-test for image quality in terms of the contrast-to-noise ratio (CNR) resulted in a p-value of 0.610, which was also greater than 0.05. This demonstrated no significant difference in the image quality between the two isocenter placements from the perspective of the CNR measures. Thus, both isocenter placements resulted in comparable image quality.

Keywords: Image quality, isocenter, nasopharyngeal MRI

Introduction

Many cases of nasopharyngeal cancer are found in more advanced stages. The diagnosis of this cancer needs to be established early to determine the therapy and prognosis of the disease. The type of cancer most commonly observed in Indonesia, ranking fourth after cervical, breast, and skin cancer, is nasopharyngeal cancer.[1] There were 348,809 new cases and 207,210 deaths caused by nasopharyngeal cancer in Indonesia[2]. Quality of life assessed in cancer patients is often used as a reference for the success of therapy.[3] The therapy given to patients with nasopharyngeal cancer is radiotherapy and followed by chemotherapy.[4]

Consideration of the impact of cancer treatment on the patient's psychosocial and functional health is obtained from assessing the patient's quality of life.[5] MRI (Magnetic Resonance Imaging) is a body imaging technique based on the principle of magnetic resonance of the atomic nucleus and produces coronal, transverse, and axial cuts.[6] MRI imaging has become the primary method for examining patients with suspected pathology in the nasopharynx because it can provide contrast resolution for soft tissue. Another advantage of MRI is that it can detect tumor grade, perineural spread, and intracranial tumor extension.[7] MRI imaging can also show a better image of the tumor than examining nasopharyngeal cancer using endoscopy and endoscopic biopsy.

Optimal MRI image results need to be achieved for maximum diagnosis, so a suitable examination protocol is also needed. IMR image results have four characteristics: high signal-to-noise ratio (SNR), good contrast-to-noise ratio (CNR), high spatial resolution, and short imaging time.[8–10]SNR is the ratio between the amount of noise produced by the MR system and the amount of signal received from the tissue being imaged.

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The difference in SNR between the two relevant types of networks is called CNR, a relationship between contrast and noise.[11] The meaning of the signal is the voltage induced in the receiver coil by precise coherent magnetization in the transverse plane at, or around, the time of Time Echo (TE), and noise represents frequencies that exist randomly in space and time.[8]

The MRI examination procedure starts with positioning the patient or object correctly. The object's center in an MRI examination is placed at the isocenter (B0) or the center point of the magnet. Each gradient in MRI will be centered at the midpoint of the isocenter.[6] Inappropriate object placement will reduce the accuracy and precision of image measurements, and good placement will increase statistical power in research to understand a particular clinical issue.[6] Also, incorrect isocenter placement will affect the quality of the resulting image, namely SNR and CNR.[8]

There are differences in isocenter placement during nasopharyngeal MRI examinations for nasopharyngeal cancer patients in several major hospitals, particularly regarding the positioning of the isocenter at the nasion or symphysis menti. This research is important due to the lack of consensus on this issue, with no robust studies supporting either method. To date, no previous research has examined the impact of different isocenter placements on image quality in these two areas. Therefore, this study aims to statistically assess the differences in isocenter placement at the nasion and symphysis menti during nasopharyngeal MRI examinations in nasopharyngeal cancer patients, specifically in relation to image quality metrics such as the Signal-to-Noise Ratio (SNR) and Contrast-to-Noise Ratio (CNR). The ultimate goal is to clarify the discrepancies in isocenter placement practices observed across different hospitals.

Methods

This study employed an experimental design with purposive sampling and a quantitative approach. Data collection was conducted in June 2023 at the Radiology Department of Dharmais Cancer Hospital. Practical considerations such as available resources, time constraints, and data accessibility resulted in a total sample size of six participants. Ethical approval for this research was granted by the Medical Research Ethics Committee of Dharmais Cancer Hospital under clearance number 124/KEPK/IV/2023.

The inclusion criteria are patients diagnosed with nasopharyngeal cancer, who are willing to participate in the study, and who do not have a pacemaker. To maintain the integrity of the research results and ensure the safety of participants during the study, individuals who experience claustrophobia or have conditions that could cause discomfort or complications during the procedure are excluded from participation. Each sample underwent two treatments: placing the isocenter at nasion and at symphysis menti. The parameters used are Time Repetition (TR) 5200 ms, Time Echo (TE) 110 ms, concatenations, and averages each with a value of 1. The only difference between the two procedures is the placement of the isocenter so that the results can be controlled. This research was conducted only on the T2 Turbo Spin Echo Fat Saturation coronal cut sequence. The samples chosen were patients with clinical nasopharyngeal cancer post-radiotherapy and post-chemotherapy at the request of the sending doctor for post-therapy evaluation images.

The data obtained was processed using the ImageJ application, which is an application that can provide information in the form of numbers for the blackness value of an image in the form of mean to standard deviation.[12]Measurements were taken from ten distinct Regions of Interest (ROIs) as illustrated in Figure 1. ROIs 1–4 were located in the nasopharyngeal area, ROI 5 represented the brightest point in the image, ROIs 6–8 were selected from other anatomical areas including residual tumor regions (taken consistently across all samples), and ROIs 9–10 were selected from the background or darkest areas of the image. The mean values obtained were then used to calculate Signal-to-Noise Ratio (SNR) and Contrast-to-Noise Ratio (CNR) using standard formulas.

The resulting data—including mean intensity, standard deviation, SNR, and CNR—were statistically analyzed using SPSS software. These analyses were conducted for both isocenter placement conditions to determine whether placement at the nasion or symphysis menti influenced image quality. A sample of data processed using ImageJ is shown in Figure 1.

Results

Data processing using the ImageJ application produces two data variations and is continued using statistical applications. The first test is the data normality test to determine the type of

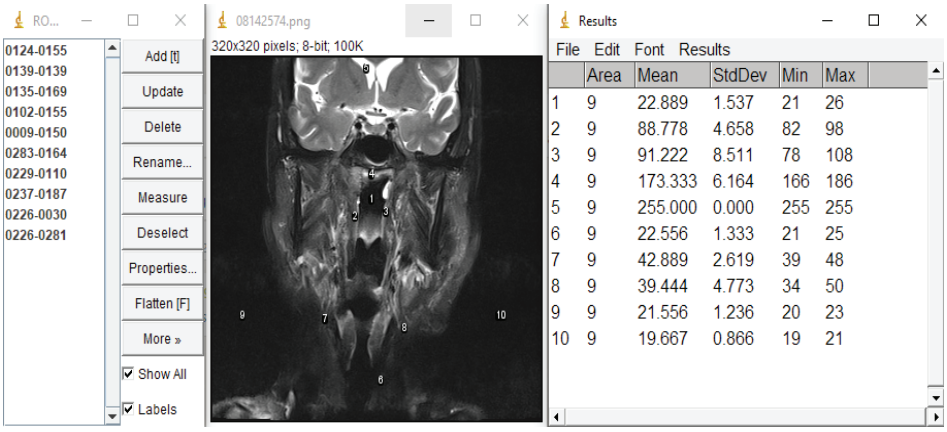

Figure 1 Example of Data Processing using ImageJ Application

statistical analysis that will be used in the next.[13] The first data processing is for image quality in the form of SNR and, after that, CNR. Table 1 shows the result.

Based on Table 1, the Shapiro-Wilk normality test showed that the SNR values from images with isocenter placement at the nasion had a p-value of 0.001 (≤0.05), indicating that the data were not normally distributed. In contrast, the SNR values for images with isocenter placement at the symphysis menti yielded a p-value of 0.387 (≥0.05), indicating normal distribution. Since one of the datasets did not meet the assumption of normality, a non-parametric statistical test was used. To determine whether there was a significant difference between the two isocenter placements, a Wilcoxon signed-rank test was conducted.

Table 2 presents the results of the Wilcoxon two-sample test, non-parametric test in assessing image quality in the form of SNR at the isocenter placement in nasion, obtaining a mean value of 22.471, a minimum value of 9.082, a maximum value of 69.990, and standard deviation is 23.614. In contrast, the isocenter placement at symphysis menti has a mean value of 11.228, a minimum value is 5.637, a maximum value is 14.703, and a standard deviation is 3.516, and a p-value is (0.173) ≥0.05. Therefore, no significant difference exists between the image quality

Tabel 1 Normality Test Results for Image Quality Based on SNR

Image Quality (SNR)	Normality Test *Shapiro-wilk*		
	Statistic	df	Sig. (p-value)
SNR isocenter at Nasion	0.636	6	0.001
SNR isocenter at Symphysis Menti	0.902	6	0.387

df=degree of freedom; Sig.=significance value

Tabel 2 Non-parametric Wilcoxon Test for Image Quality in SNR

Image Quality (SNR)	Non-Parametric Wilcoxon Two-Sample Test					
	N	Mean	SD	Min.	Max.	Asymp. Sig
SNR isocenter at Nasion	6	22.471	23.614	9.082	69.990	0.173
SNR isocenter at Symphysis Menti	6	11.228	3.561	5.637	14.703	

N=number; SD=standard deviation; Min=minimum; Max=maximum; Asyimp. Sig=asymtotic significance

Tabel 3 Normality Test for Image Quality in CNR

Image Quality (SNR)	Normality Test *Shapiro-wilk*		
	Statistic	df	Sig. (p-value)
SNR isocenter at Nasion	0.953	6	0.766
SNR isocenter at Symphysis Menti	0.868	6	0.220

df=degree of freedom; Sig.=significance value

Tabel 4 Parametric Paired Sample T-Test for Image Quality in CNR

Image Quality (CNR)	Parametric paired sample T-Test			
	Mean	Std. Deviation	Asymp. Sig	
CNR isocenter at Nasion	6	89.357	41.003	0.610
CNR isocenter at Symphysis Menti	6	100.657	75.588	

N=number; SD=standard deviation; Min=minimum; Max=maximum; Asyimp. Sig=asymptotic significance

(SNR) at the isocenter placement in nasion and symphysis menti on the coronal section T2 TSE nasopharyngeal sequence MRI examination.

Table 3 present the result of the normality test that was conducted on the isocenter positioning data at nasion and symphysis menti for assessing image quality in terms of CNR.

Based on Table 3, information is obtained that image quality in the form of CNR at isocenter placement in nasion using the Shapiro Wilk method produces p-value (0.766) ≥0.05 and at isocenter placement at symphysis menti produces a p-value (0.220) ≥0.05, so both data declared to be normally distributed. Therefore, the image quality assessment (CNR) data for the two isocenter locations at nasion and symphisis menti will be tested using parametric statistics to conduct statistical inference.[14] The Parametric paired sample T-test is used for two groups of samples that differ in certain variables.

Table 4 presents the results of assessing image quality in CNR with different isocenter placements. For the isocenter placement at the nasion, the mean value is 89.357, with a standard deviation of 41.003. In contrast, for the isocenter placement at the symphysis menti, the mean value is 100.657, with a standard deviation of 75.588. The p-value obtained is 0.610, which is greater than 0.05. Based on this, we conclude that there is no significant difference in image quality between the isocenter placements at the nasion and symphysis menti in the coronal section MRI nasopharyngeal sequence T2 TSE examination.

Discussion

Radiotherapy and chemotherapy are two modalities that are generally used to treat nasopharyngeal cancer.[4] Radiotherapy for nasopharyngeal cancer causes many changes in the patient. Changes that may occur are damage to brain tissue, necrosis of the nasopharynx exposed to radiation and the surrounding area, changes in the skull base, or the appearance of trismus symptoms in patients due to abnormal masticator muscles.[15,16] An imaging examination with MRI is needed to evaluate the patient's condition after therapy or to continue the patient's treatment to the next stage.[17]

Post-radiotherapy MRI imaging examination is needed to assess the anatomical structure in the area of nasopharyngeal cancer being treated and the surrounding area. Placement of the isocenter is important so that the resulting MRI imaging is optimal and helps radiologists or oncologists evaluate the patient's condition correctly to adjust the dose for subsequent radiotherapy.[17]

Isocenter placement in the nasopharyngeal MRI examination with clinical nasopharyngeal cancer in nasion and symphysis menti shows no difference in the respective image quality in SNR

and CNR. According to statistical analysis using various test calculations, both the SNR and CNR display values of 0.173 and 0.610, respectively. Both values surpass the threshold of 0.05, indicating no noteworthy distinction between two isocenter positions at nasion and symphysis menti concerning image quality in both SNR and CNR.

This study presents the average for each experiment with isocenter placement, specifically at nasion and symphysis menti. The statistical findings indicate a greater SNR value for isocenter placement at nasion and a higher CNR value for isocenter placement at symphysis menti. Yet these variations lack significance, aligning with the outcomes of other statistical assessments conducted.

Hence, MRI scans for nasopharyngeal cancer patients can employ two isocenter placement techniques at nasion and symphysis menti-since there's no discernible distinction in the resulting image quality between the two methods.

Further research can be carried out to assess isocenter placement with a higher level of validity through radiometric and dosimetric simulations using the model.[18] Research into the influence of other factors that can improve the quality of MRI imaging is needed to assess minor brain damage through MRI imaging. In this way, it is hoped that damage to the anatomical structure of the brain due to the nasopharyngeal cancer therapy process can be assessed early and can improve therapy management in the future.[17]

Although this study only utilized two isocenter placement variations and had a limited sample size, the findings from this research can be used as a reference. Based on the results of this study, the placement of the isocenter in two different places, the nasion or symphysis menti, on the nasopharyngeal MRI imaging sequence T2 turbo spin echo fat saturation coronal section provides no different imaging picture. Both can be used as isocenter options in nasopharyngeal MRI imaging procedures.

In conclusions, isocenter placement for nasopharyngeal MRI examinations for nasopharyngeal cancer patients can be carried out at Nasion and Symphysis. The results showed no significant difference in image quality between the two isocenter placements. It is hoped that these results can provide options for those responsible for implementing and overseeing the MRI examinations, and enable the selection of isocenter placement appropriate to each inspection location's environmental conditions.

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Effect of Nigella Sativa on Growth and IGF-1 Levels in Rats Prenatally Exposed to Pesticides

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Abstract

Nigella sativa contains antioxidants and can potentially improve growth disorders due to prenatal pesticide exposure. Pesticides affect the work of thyroid hormone, insulin, and Insulin-like Growth Factor that play essential roles in the growth and development processes. This study aimed to determine the effect of Nigella sativa supplementation on body weight and IGF-1 levels in mice, with a history of pesticide exposure in the womb. This study was conducted from October 14, 2023 to December 1, 2023 at the laboratory of the Center for Food and Nutrition Studies, Inter-University Center, Gajah Mada University, Indonesia. This experimental study used a cohort design and involved 20 pregnant female rats as the experimental animals. These rats were divided into several groups: K0 (control group with standard feed), K1 (group exposed to pesticides during pregnancy), and P1 and P2 (group exposed to pesticides. Followed by 10.8 mg/200gBW/day and 21.6 mg/200 gBW/day of Nigella sativa after birth, respectively). The pesticide dose used was 10 mg/200gBW/day orally. Anthropometric examinations was conducted at birth, and on day 7, day 14, day 21, and day 28. The examination of IGF-1 levels was performed on day 28 using the ELISA method. Results showed that the mean birth weights (g) of the rats by group were as follows: K0:6.09±0.12; K1:4.03±0.03, P1:4.03±0.02 P2:4.05±0.03. On day 28, the mean body weights (g) were as follows: K0:104.0±1.79; K1:65.17±1.47; P1:92.17 ± 3.19; and P2:102.00±1.41. The mean IGF-1 level (pg/mL) were as follows: K0:23.76±0.68; K1:9.03±0.24, P1:14.94±0.37; and P2:19.51±0.56. The ANOVA test presented a p-value of <0.001. Hence, Nigella sativa supplementation after birth significantly affects body weight and IGF-1 levels in rat model of prenatally exposed to pesticides.

Keywords: Body weight, IGF-1, nigella sativa, pesticide, womb

Introduction

Stunting is a chronic condition of stunted growth determined by calculating the Z score of the Height for an Age index of less than -2 Standard Deviation World Health Organization Child Growth Standards median.[1] Stunting increases the risk of various other health problems, delays in motor development, neurodevelopmental disorders, and cognitive function.[1] Stunting begins in the first thousand days of life, from the womb until 2 years post-natal life.[2] Stunting prevalence based on the results of the 2017 Nutritional Status Monitoring, in Indonesia reached 29.6 percent (aged 0-59 months), which potentially causes maternal nutritional status and sanitation.[3] Stunting is a health problem in Indonesia, with a prevalence of more than 20%, especially in 14 provinces, which exceeds the national figure.[3] Research by Aryastami et al.[4] found that low birth weight increases the risk of stunting by 1.74 times compared to normal birth weight. Prenatal exposure to pesticides also increases the risk of low birth weight. In a study conducted in Brebes, Central Java, Widyawati et al.[5] reported an odds ratio of 6.8 (95% CI: 2.0–22.9) for low birth weight in pesticide-exposed pregnancies. They also observed significantly lower IGF-1 levels among exposed subjects (OR 3.6; 95% CI: 1.2–11.1).

Organophosphate and carbamate class pesticides, which farmers in Indonesia widely use, are classified as endocrine-disrupting chemicals (EDCs), which can affect the work of hormones that play an essential role in the growth and development process, such as thyroid hormone, insulin, and Insulin-Like Growth Factor-1 (IGF-1).[5,6] IGF-1 affects placental trophoblast cells' metabolism, mitogenesis, and differentiation,

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affecting the fetus in pregnancy.[5]

Nigella sativa is an herbal ingredient known for a long time because it is useful as an antioxidant, anti-inflammatory, and immunomodulator, and it improves metabolism to prevent low birth weight and stunting.[7] Nigella sativa, known as black cumin, has been used as an adjuvant therapy since the time of the Prophet Muhammad, SAW, as stated in the hadith: "In black cumin, there is a cure for every disease except death." Black cumin is also mentioned in the Holy Bible as a "Curative black seed" and is described as *'Melanthion by Hippocrates and Dioscorides'* and as *'Gitch of Pliny.*[7] The content of active substances in black cumin such as thymoquinone (TQ), dithymoquinone (DTQ), carvone, limonene, transanethol , p-cymene, indazole alkaloids such as nigellidine and nigellicine , and isoquinoline alkaloids including nigellicimine, nigellicimine-N-oxide and α-Hederin has various benefits such as antioxidant, anti-inflammatory, immunomodulatory, antitussive, antihypertensive and balancing blood sugar levels.[7] Pesticides induce ROS and pro-inflammatory responses.[8] High oxidative stress in endothelial cells of placentae impairs cell function and angiogenesis, reducing fetal growth by poor placental blood vessel development and weakening the blood flow and exchange of nutrition or oxygen.[9] The antioxidants in Nigella sativa are expected to be able to prevent this.

Growth is a dynamic process involving nutritional, hormonal and nervous system factors. Linear growth in the first year of life is mainly influenced by nutrition, although hormonal factors such as IGF-1 and leptin also play a role. Research in Bangladesh compared the control group of stunted children and found significant differences in leptin levels, leptin: adiponectin ratio, and IGF-1 levels.[10]

Thymoquinone, the active compound in *Nigella sativa,* is believed to help repair cell, tissue, and organ damage that occurs during pregnancy. It acts through the production of thymohydroquinone via a two-step one-electron reduction or a one-step two-electron reduction process. These mechanisms enable it to scavenge free radicals and prevent oxidative damage.[11] As a result, *Nigella sativa* supplementation is thought to increase body weight and IGF-1 expression in offspring that were exposed to pesticides in utero. This study aims to investigate the effect of *Nigella sativa* supplementation on body weight and IGF-1 expression in rats prenatally exposed to pesticides.

Methods

This research has received approval from the Bioethics Commission for Medical/Health Research, Faculty of Medical, Sultan Agung Islamic University, Semarang, with number. 467/XI/2023/Bioethics Commission. This research is an experimental study on experimental animals, pregnant white Wistar rats, using a cohort design. Animal models are used to evaluate the efficacy, safety, and potential side effects of drugs or chemicals, including teratogenicity, toxicity, and carcinogenicity, before advancing to human trials.[12]

The study was carried out at the Laboratory of the Center for Food and Nutrition Studies, Inter-University Center (PAU), Gadjah Mada University, Yogyakarta, from October 14, 2023 to December 1, 2023. The rats underwent a one-week acclimatization period starting on October 7, 2023. Mating and confirmed pregnancy began on October 14, 2023. The pregnant rats were exposed to pesticides from October 14 to November 3, 2023 (21 days), followed by Nigella sativa supplementation from November 4 to December 1, 2023 (28 days).

The study involved 24 pregnant Wistar white rats, randomly divided into four groups, with each group consisting of six rats.

The K0 group (negative control) received only standard feed and water *ad libitum*. The K1 group (positive control) received standard feed and water *ad libitum* along with pesticide exposure at a dose of 10 mg/200 g body weight (BW) per day during pregnancy. The P1 group (treatment group 1) received standard feed and water ad libitum, pesticide exposure at 10 mg/200 g BW per day during pregnancy, followed by *Nigella sativa* supplementation at a dose of 10.8 mg/200 g BW per day for 28 days. The P2 group (treatment group 2) received standard feed and water *ad libitum*, pesticide exposure at 10 mg/200 g BW per day during pregnancy, followed by *Nigella sativa* supplementation at a dose of 21.6 mg/200 g BW per day for 28 days.

Gramoxone, a herbicide liquid (LD50 1,098 mg/gBW) was used in this research, administrated orally by sonde from fertilization (day 1 of pregnancy marked by a vaginal plug after mating) until day 20. Herbicides are well absorbed from the Gastrointestinal tract but are not well absorbed after inhalation or dermal exposure.[13]

After giving birth (21st day), the average number of children born and the average body weight were calculated. Observations were

Table 1 Mean Body Weight of Rats (Grams) According to Age and Treatment Group

Group	Day 1	Day 7	Day 14	Day 21	Day 28
K0	6.09±0.12	21.33±0.82	48.83 ± 1.69	76.67±1.63	104.0±1.79
K1	4.03±0.03	14.50±0.55	30.67±4.18	46.00±0.89	65.17±1.47
P1	4.03±0.02	16.67±0.52	39.17±0.98	63.17±0.75	92.17±3.19
P2	4.05±0.03	20.33±0.82	45.67±0.82	73.33±0.82	102.00±1.41

Noted: K0: Control group which only received standard feed and drink ad libitum; K1: Positive control group that received standard feed + drinking ad libitum and exposure to pesticides at a dose of 10 mg/200gBW/day during pregnancy; P1: Treatment Group 1: received standard feed + drinking ad libitum + exposure to pesticides 10 mg/200g BW/day in the womb followed by Nigella sativa 10.8 mg/200g BW/day for 28 days; P2: Treatment Group 2: received standard feed + drinking ad libitum + exposure to pesticides 10 mg/200gBW/day in the womb followed by Nigella sativa 21.6 mg/200gBW/day for 28 days

continued to determine the growth of the rat pups by providing standard feed and drinking ad libitum and Nigella sativa for 28 days. IGF-1 levels were measured with blood samples taken from the orbital vein. Measuring body weight using electronic scales brand: Mettler Toledo, checking levels IGF-1 using the spectrophotometric method (ELISA). The data obtained were tested for normality and homogeneity; the data were normal and homogeneous using the Kolmogorov Smirnov test and the Levene test. The data were normally distributed and homogeneous, so a statistical test was carried out using one-way ANOVA followed by LSD post hoc test to determine the differences between groups, which were considered statistically significant if $p<0.05$.

Results

On the 21st day of pregnancy, all pups gave birth safely, and no pregnant rats died during the study. The average number of pups in the K0 group=9.67; K1=8.7; P1=8.8, and P2=8.7. To reduce bias in the number of pups, six individuals were taken to equalize the number of samples for each group, as samples for further treatment in the form of Nigella sativa at a dose of 10.8 mg/200 gBW/day (P1 group) and Nigella sativa at a dose of 21.6 mg/200 gBW/day ((P2 group) given for 28 days. Nigella sativa oil is administrated orally by sonde. Body weight of rats' children monitoring was carried out on days 1, 7, 14, 21, and 28.

The increase in body weight in the group that received *Nigella sativa* supplementation was superior when compared with the group that

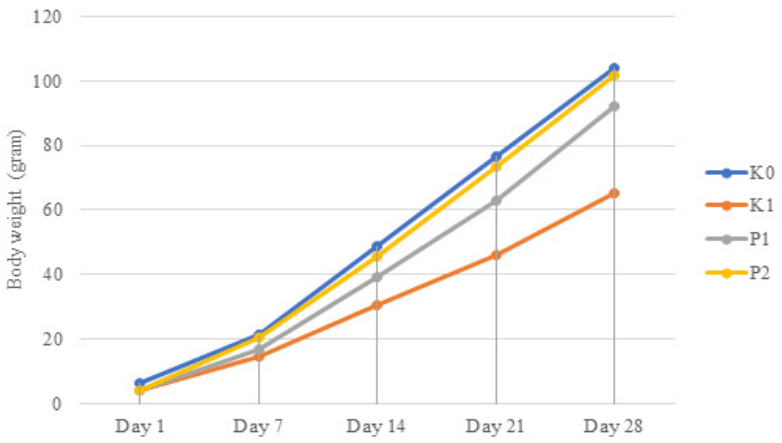

Figure 1 Rat Body Weight Growth (Grams) On Days 1, 7, 14, 21, and 28 According to Treatment Groups

Table 2 Mean IGF-1 levels (pg/mL) on day 28 based on treatment group

Group	n	IGF-1 Levels (pg/mL)
K0	6	23.76±0.68*
K1	6	9.03±0.24*
P1	6	14.94±0.37*
P2	6	19.51±0.56*

Noted: K0: Control group which only received standard feed and drink ad libitum; K1: Positive control group that received standard feed + drinking ad libitum and exposure to pesticides at a dose of 10 mg/200gBWday during pregnancy; P1: Treatment Group 1: received standard feed + drinking ad libitum + exposure to pesticides 10 mg/200g BW/day in the womb followed by Nigella sativa 10.8 mg/200g BW/day for 28 days; P2 : Treatment Group 2: received standard feed + drinking ad libitum + exposure to pesticides 10 mg/200gBW/day in the womb followed by Nigella sativa 21.6 mg/200gBW/day for 28 days

received exposure to pesticides without *Nigella sativa* supplementation, but lower than a control group that had no pesticides exposures. Post hoc test found significant differences in all groups (p<0.001), except for body weight between the control group and the group that received Nigella sativa supplementation at a dose of 21.6 mg/ 200gBW/day (p=0.114)

IGF-1 levels in the group that received the exposure to pesticides were significantly lower when compared with other groups (p<0.001), while the levels in the control group that only received standard feed had the highest levels. In the ANOVA test, the p-value was obtained < 0.05, followed by the LSD post hoc test, the p-value was obtained <0.05 in all groups (p<0.001) including between P1 and P2 groups.

Discussion

Research in the agricultural area of Magelang Regency show a significant relationship between children's habits of playing in agricultural areas (p=0.011), storing pesticides in the house (p=0.036), mother's involvement in spraying (p=0.040), washing spray tools (p=0.040), mixing pesticides (p=0.040) with the incidence of *stunting*. There was no significant relationship between the incidence of stunting and the use of insecticides in the house (p=0.304).[1]

Pesticide-induced oxidative stress is caused by Reactive oxygen species (ROS) and Reactive Nitrogen Species (RNS) which activate signaling pathways in mitochondria and induce apoptosis.[14] Epidemiological studies on workers exposed to pesticides found increased oxidative stress and damage at the gene level caused by free radical reactions, characterized by a positive relationship between levels of Thiobarbituric Acid Reactive Substances (TBARS), Total Glutathione (TG), oxidized glutathione (GSSG) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), this situation explains that exposure

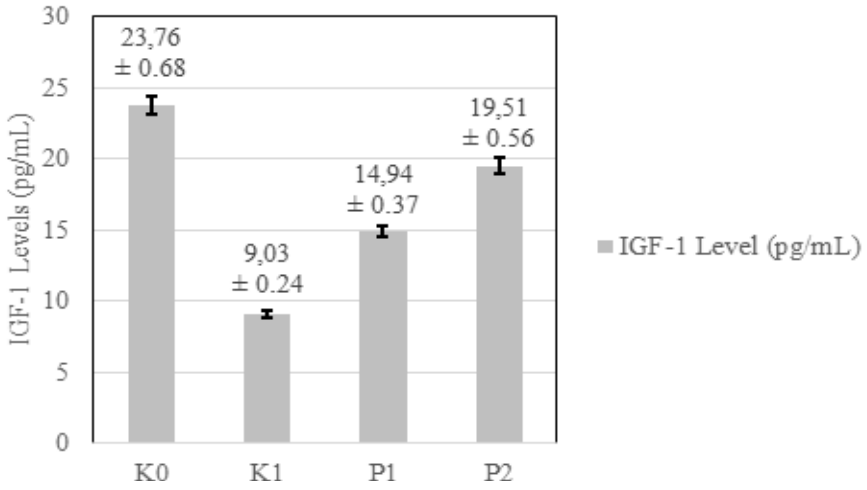

Figure 2 IGF-1 Levels on Day 28, According to the Treatment Group

to pesticides can induce oxidative stress by increasing the production of free radicals which can accumulate in cells and damage biological systems including macromolecules, RNA, DNA, DNA repair systems and modifying detoxification systems and antioxidant defense systems.[15]

Some pesticides such as Organophosphate and carbamate identified as Endocrine Disrupting Chemicals (EDCs) can bind to steroid hormone receptors such as the glucocorticoid receptor (GR) which play an essential role in metabolic processes, hormonal function, the immune system, and the central nervous system. Research on 34 types of pesticides in their role in the effects of glucocorticoids and antiglucocorticoids on the glucocorticoid receptor found 12 chemicals that showed real antagonistic effects.[16]

Endocrine Disrupting Chemicals has an indirect influence on the fetus through the placenta, it can interfere with the synthesis and metabolism of steroid hormones and disrupt the hypothalamic-pituitary-adrenal axis during the fetal growth process, resulting in delayed fetal growth.[17,18] EDC is lipophilic so that it can accumulate longer in adipose tissue.[18] Exposure to pesticides increases oxidative stress, damaging cell biological systems such as macromolecules, proteins, DNA, RNA, and other proteins in the detoxification and antioxidant systems.[15]

Epidemiological studies show that there is a relationship between pesticide exposure and impaired intrauterine growth, fetal death, premature birth, and congenital abnormalities.[19] In this study, all pups were born safely and had no birth defects.

This research shows that growth disorders during pregnancy can still be corrected with supplementation after birth, and Nigella sativa is a natural ingredient that has the potential to improve stunting and the consequences it causes in later life, such as cognitive disorders and degenerative diseases. Nigella sativa contains important minerals such as potassium, phosphorus, calcium, Mg, Na, Fe, Zn, Mn, and Cu. Nigella sativa is also a source of fatty acid esters such as arachidonic acid, myristic acid, stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid, DHA, EPA, Thymoquinone (TQ) which has broad pharmacological effects as an antioxidant: reducing lipid peroxidation and levels of oxidative stress in body tissues, anti-inflammatory, anti-diabetic, anti-cancer, antimicrobial, hepatoprotective and has a kidney protective effect.[7,20,21]

Exposure to pesticides is also a risk factor for stunting in children in rural areas. Research conducted by Kartini found a significant relationship between exposure to pesticides and stunting and low levels of insulin-like growth factor-1 (IGF-1) in children exposed to it. Pesticide.[6] Children with low IGF-1 levels have a risk of stunting 8.35 times higher than the group with normal IGF-1 levels.[6] Insulin-like growth factor-1 (IGF-I) is a polypeptide hormone produced mainly by the liver but also secreted by other tissues as autocrine/paracrine. IGF-1 plays an active role in intrauterine fetal growth, proliferation and differentiation, until after birth. IGF-I, in response to growth hormone stimulation, is partly responsible for systemic GH activity, although it has several other cellular activities (anabolic, antioxidant, anti-inflammatory, and cytoprotective).[22]

Previous research shows that IGF-1 influences intrauterine linear growth. This hormone deficiency has an effect from the beginning of birth until childhood, causing skeletal maturation and stunted organ growth. This growth abnormality causes small brain volume (visible from head circumference), small heart size, and acromicria (small chin, undeveloped facial bones, small hands, and feet). IGF-1 deficiency also causes developmental delays and weakness of the muscular system.[22]

The results of this research give rise to a new optimism in treating stunting in the future by utilizing the potential of herbs such as Nigella sativa because supplementation with Nigella sativa in mice with a history of pesticide exposure succeeded in increasing body weight by catch-up growth as evidenced by the average body weight on day 28. However, the average was slightly lower than the control group which only received standard feed there was no significant difference ($p=0.114$). Nigella sativa supplementation was able to increase IGF-1 levels, although not as high as the control group. The increase in body weight and IGF-1 levels in the group that received Nigella sativa supplementation was not able to improve growth disorders caused by exposure to pesticides during pregnancy. Genetic factors also play a role in the pathophysiology of stunting, this situation is to the findings of research conducted by Mweetwa et al which states that genetic variations are associated with stunting and the state of enteropathy that precedes it and various part ways related to gene expression, glycosylation, nerve signaling, sensitivity to nutrients and changes in the microbiota.[23]

Higher IGF-1 levels in the group that received Nigella sativa supplementation when compared

to the control group that received pesticide exposure prove that the active substance content in Nigella sativa can repair cellular level damage that occurs due to pesticide exposure. Mitochondria are one of the cell organelles that can be damaged due to pesticide exposure, characterized by low IGF-1 levels. Previous research has shown that IGF-1 is protective of mitochondria. Treatment with low doses of IGF-1 shows several beneficial effects, including restoring physiological levels of IGF-1, improving insulin resistance and lipid metabolism, providing mitochondrial protection, and having hepatoprotective, neuroprotective, antioxidant, and antifibrogenic effects.[24]

In this study, it was found that low birth weight and the lowest post-natal weight gain (day 28) in the (K+) group who only received exposure to pesticides, this situation is possible due to the effect of free radicals exposure in the womb, decrease in hemoglobin and total protein levels, such as research conducted by Masuda Sultana in 2020, which proved that total protein and hemoglobin levels are related to low birth weight and poor nutrition in the fetus.[25]

This research has various limitations that may affect the research results. It is hoped that future research will measure hemoglobin levels and other blood profiles, observing part ways that may occur, for example, epigenetic modifications that affect gene expression, especially genes responsible for growth, intestinal microbiota profiles that occur due to nigella sativa supplementation, which can affect the immune system and gene expression, the repair mechanism that occurs due to Nigella sativa supplementation.

In conclusion, Nigella sativa supplementation can improve growth that is disrupted due to exposure to pesticides during pregnancy, characterized by an increase in body weight approaching normal growth (catch-up growth). The mean body weight of the group that received Nigella sativa supplementation of 21.6 mg/200gBW/day was not significantly different compared to the control group that received standard feed ($p=0.114$). The mean body weight of the group exposed to pesticides during pregnancy was the lowest compared to other groups in the ANOVA test, with a value of $p<0.001$. Increased IGF-1 levels prove that there is an improvement in cellular levels. Hormonal dysfunction that occurs due to exposure to pesticides is still reversible, so with Nigella sativa supplementation, which contains bioactive compounds as antioxidants, anti-inflammatory, anti-diabetic, immunomodulatory, and other mineral content in critical periods in the first 1000 days of life, the damage that occurs can still be repaired.

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Evaluation of Kidney Proximal Tubule Following Immunization with Plasmodium falciparum CIDR1α-PfEMP1 Recombinant Protein in Rats

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Abstract

Malaria vaccines are continuously explored as an approach to eradicate malaria. The cysteine-rich interdomain region 1α-Plasmodium falciparum erythrocyte membrane protein 1 (CIDR1α-PfEMP1) is an antigenic protein that can bind to the endothelial protein C receptor (EPCR) and CD36, resulting in microvascular obstruction. The PfEMP1-induced antibody can induce antibodies, reducing the severity of malaria risk by impeding cytoadherence and destructing rosette formation. Preclinical safety testing is an important step of vaccine development,including safety testing of the kidney as the main excretory organ. The proximal tubule has the most mitochondria to support its main role in reabsorption and excretion, making it prone to oxidative stress caused by foreign substances. This study aimed to evaluate kidney proximal tubule cells after CIDR1α-PfEMP1 immunization in rats. This study was conducted at the Laboratory of Biology Molecular and Biotechnology, Faculty of Medicine, University of Jember. Eight rats were injected subcutaneously with 150 µg of the protein and four rats were injected with 0.9% NaCl on days 0, 21, and 42. The rats were euthanized on day 56. The kidney histopathological slides were stained using Hematoxylin-Eosin (HE) and the necrotic proximal tubule cells were counted at five (5) visual fields (100 cells/visual fields). The average number of necrotic cells of the control and the treatment groups were 0.125±0.25 and 2.438±2.5972 while the Mann-Whitney test showed a significance value of p=0.12, indicating no significant difference between the control and treatment groups. In conclusion, there is no change in the kidney histopathology based on the proximal tubule necrotic cell count after CIDR1α-PfEMP1 immunization in rats.

Keywords: CIDR1α, histopathology, kidney, malaria, PfEMP1

Introduction

Malaria remains a significant health concern with high mortality rates, particularly in tropical and subtropical regions such as Africa, Asia, and South America. Based on data from the 2022 World Malaria Report, there were approximately 241 million cases of malaria worldwide, resulting in 619,000 deaths globally.[1] The majority of malaria-related deaths are caused by severe malaria complications stemming from *Plasmodium falciparum* infections.[2] The pathogenesis of severe malaria involves cytoadherence and rosetting processes mediated by *Plasmodium falciparum Erythrocyte Membrane Protein-1* (PfEMP1), an adhesion molecule encoded by the *var* gene, which consists of 2 exons, i.e., exon 1 and exon 2, and separated by an intron. The molecule is encoded mostly by exon 1, which is polymorphic, 3.5–9 kb in size, and is expressed on the surface of *P. falciparum*-infected erythrocytes in the knob protrusion region. Exon 1 encodes an extracellular domain consisting of an N-terminal segment (NTS), several Duffy-binding-like (DBL) domains, several cysteine-rich interdomain region (CIDR) domains, and a transmembrane segment (TMS). The CIDR domain flanked by two DBL domains is consistently found in the head structure of the *var* gene as a conserved head structure. Exon 2 is relatively short at 1–1.3 kb and encodes the intracellular acidic terminal segment (ATS) domain.[3]

The CIDR1α-PfEMP1 specifically binds

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to *endothelial protein C receptor* (EPCR) and CD36 receptors, playing key roles in severe malaria pathogenesis. Infected erythrocytes can adhere to endothelium, platelets, or uninfected erythrocytes resulting in microvascular obstruction in vital organs, ultimately leading to organ failure.[4] Protein C activation will regulate coagulation, blood vessel inflammation, and increase blood vessel permeability so that PfEMP1 binding to EPCR triggers inflammation and coagulation of cerebral blood vessels. Pathological processes in the brain will result in brain edema which then causes clinical manifestations of cerebral malaria. A previous study showed that the proportion of the *var* gene encoding the CIDR1α bound to EPCR was higher in severe malaria patients than in uncomplicated malaria patients, with a median percentage of 54.1% vs. 7.4%.[5]

One potential strategy in malaria control is the malaria vaccine. In 2015, the Malaria Vaccine Initiative (MVI) launched the first-generation malaria vaccine based on the *Circumsporozoite Protein* (CSP), named RTS,S/AS01, with a vaccine efficacy of 34.8% against severe malaria.[6] However, due to the complexity of *P. falciparum* antigen proteins throughout its life cycle, malaria vaccine development encounters significant challenges. Further research utilizing other *P. falciparum* antigen proteins is necessary. We have selected CIDR1α-PfEMP1 as a protein target for peptide-based malaria vaccine development. The previous study demonstrated that injection of 150 µg CIDR1a-PfEMP1 in rats increased the IgM level after primary injection ($p<0.05$), IgG level after primary and secondary 1 and 2 injections ($p<0.05$), and CD4+ level after secondary 2 injections.[7] The production of these antibodies is expected to prevent the binding of CIDR1α domain to EPCR and CD36 receptors. Another previous study revealed that antibodies induced by DBL2β-PfEMP1 reduced the risk of severe malaria by 37% through blockade of cytoadherence and disruption of rosette formation.[8]

Vaccine development is a long way process, from laboratory, preclinical and further clinical steps. After choosing the immunogenic candidate, the next step is the safety assessment. Safety assessments of vaccine candidates are necessary to ensure that immune responses and pharmacodynamic effects post-vaccination do not endanger vital organs, such as the kidneys. The kidney is an essential organ responsible for blood filtration and the excretion of toxins and metabolic waste, making it vulnerable to exposure to foreign substances and the risk of pathological changes. The renal proximal tubules are particularly susceptible to free radicals resulting from toxic substances, as they have a high level of cytochrome P450.[9]

Histopathology is recognized as the single most appropriate screen for evidence of drug-induced kidney injury. Three of the most common renal tubular changes associated with drug-induced kidney injury are vacuolation, degeneration, and necrosis.[10] Previous studies have reported cellular damage and narrowing of the proximal tubules following herbal compound administration, as well as proximal tubule cell necrosis after oral administration of *Archidendron pauciflorum*.[11] To date, no safety evaluations have been conducted on the kidneys in relation to the CIDR domain of PfEMP1, a potential malaria vaccine candidate. Accordingly, this study was designed to evaluate histopathological changes in renal proximal tubule cells following immunization with CIDR1α-PfEMP1 in rats.

Methods

This study was conducted at the Laboratory of Molecular Biology and Biotechnology, Faculty of Medicine, University of Jember, from June to November 2023. Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine, University of Jember (Ref. No. 1826/H25.1.11/KE/2023). The recombinant CIDR1α-PfEMP1 protein was produced and purified prior to administration. The protein was injected into experimental animals, and histopathological assessment of proximal tubule kidney cell nucleus necrosis was performed following animal termination.

The CIDR1α-PfEMP1 domain amplification was conducted before the ligation of the target gene into the pET-30a (EMD Biosciences, catalog number 69909-3) plasmid and subsequently transformed into *Escherichia coli* BL21 (DE3) cells (Thermo Fisher Scientific Inc, catalog number C600003). All steps were conducted based on the previous studies.[12] *Escherichia coli* BL21 (DE3) cells were cultured in Luria–Bertani (LiofilchemS.r.l., Teramo, Italy, cat. number 610245) containing 50 µg/mL kanamycin (Thermo Fisher Scientific Inc., Waltham, MA, USA, cat. number 11815024) at 37°C by shaking at 190 rpm until reaching OD_{600} 0.6-0.8. Induction of recombinant protein production was done using 0.3 M isopropyl-D-1-thiogalactopyranoside (IPTG) (Promega

Co., Madison, WI, USA, cat. number V3955) by shaking at 190 rpm at room temperature (RT) for eight hours and was harvested through centrifugation afterward. The harvested pellet was solubilized using an extraction buffer (300 mM NaCl, 50 mM NaH_2PO_4, and 5 mM imidazole in a pH of 8.0). The lysate was incubated using 1 mg/mL lysozyme (VWR International LLC, Radnor, PA, USA, cat. number 470301-618) for 30 min at 4°C prior to sonication.[7]

The crude protein was purified by Ni-NTA resin (Qiagen, Hilden, Germany, cat. number 30210) based on the affinity chromatography method, washed with 1 mL of wash buffer I (300 mM NaCl, 50 mM NaH_2PO_4 and 20 mM imidazole; pH 8.0) and wash buffer II (300 mM NaCl, 50 mM NaH_2PO_4, and 50 mM imidazole; pH 8.0). A stepwise manner was used to elute the protein with elution buffer (300 mM NaCl, 50 mM NaH_2PO_4; pH 8.0) containing 80 mM, 100 mM, or 120 mM imidazole (Sigma-Aldrich Co., St.Louis, MO, USA, cat. number I5513-5G). To determine the purified protein, the elution was visualized using SDS-PAGE (Bio-Rad Laboratories Inc., Hercules, CA, USA), and the concentration was measured using the Bradford protein assay (HiMedia Laboratories, Maharashtra, India, cat. number ML106-500 ML) at 595 nm.[7]

Wistar rats (Rattus norvegicus) were used in this study. Sample size determination was carried out using the resource equation method.[13] This method calculates the value "E," representing the degrees of freedom for the analysis of variance (ANOVA). An E-value between 10 and 20 is generally considered adequate. An E-value below 10 suggests the need for more animals to increase the likelihood of obtaining statistically significant results, whereas an E-value above 20 indicates that additional animals are unlikely to enhance statistical power. In the present study, two experimental groups were used, with eight rats per group. The E-value was calculated using the following formula:

E=(number of groups x number of experimental animals)-number of groups

E=(2x8)-2

E=16-2

E=14

An E-value of 14 was obtained, which falls within the acceptable range for adequate sample size. However, in alignment with the 3Rs principle—particularly the reduction principle—the number of animals in the control group was limited to four, representing half the number used in the treatment group. This adjustment was made to minimize animal use while still maintaining sufficient statistical power. Reducing the number of animals in the control group is supported by ethical, practical, and research efficiency considerations.[13]

Twelve rats were divided into two groups, i.e. a treatment group consisting of 8 rats injected with recombinant CIDR1α-PfEMP1 protein at a dose of 150 µg and a control group consisting of 4 rats injected with 0.9% NaCl solution subcutaneously on days 0, 21, and 42.[14] Subcutaneous administration was chosen to increase the possibility of encountering Langerhans cells whose role as an antigen-presenting cell thus increases the generated immune response. In addition, the recombinant protein has a molecular weight >20 kDa, causing limited transport into the capillaries and predominantly crossing into the circulation system via the lymphatic system accessed through subcutaneous injection.[15]

Recombinant CIDR1α-PfEMP1 protein was mixed with Complete Freund's Adjuvant (Santa Cruz, sc-3727) for the primary injection and Incomplete Freund's Adjuvant (Santa Cruz, sc-24019) for the secondary injection at a 1:1 ratio, respectively. The Freund's Adjuvant was employed to ensure a continuous release of antigens, essential for inducing a robust and enduring immune response. The Complete Freund's Adjuvant (CFA) was administered on the initial injection due to its heat-killed *Mycobacterium tuberculosis* to attract macrophages and other immune cells to the injection site. It will maximize the exposure of the recombinant protein to the antigen-presenting cell to enhance the immune response. The Incomplete Freund's Adjuvant (IFA) has the same compound as CFA without the mycobacteria, and was used for booster immunization without the side effects of CFA.[16]

Rats were euthanized on day 56, and kidney slides were prepared and stained using Hematoxylin-Eosin (HE) for histopathology examination. Kidney slides were observed using an Olympus CX23LED light microscope at a magnification of 400X connected to an Optilab 3.0 camera. Two observers examined by counting 100 proximal tubule cells in the kidney cortex from 5 visual fields using the Fiji ImageJ application with a double-blind technique. The observers have the same interpretation of the characteristics of necrotic proximal tubule cells used as the parameters to count, i.e. pyknosis (shrunken/condensed cell nucleus, denser and darker, loss of chromatin), karyorrhexis (cell nucleus divides into several fragments),

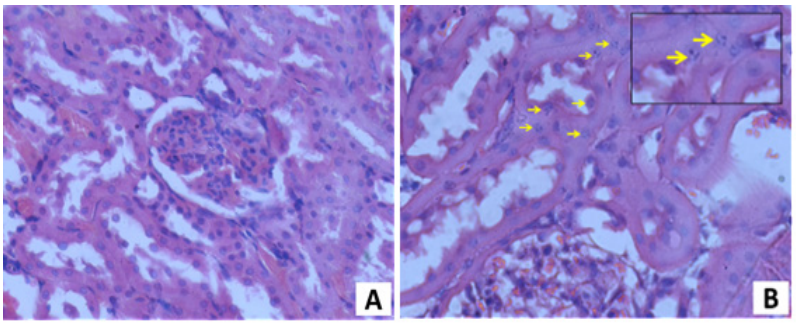

Figure 1 Kidney Histopathological Damage with H.E. Staining (400X). A: control group, B: treatment group with 150 µg CIDR1α-PfEMP1 recombinant protein. Yellow arrow: necrosis of renal proximal tubule cell nuclei, stage of karyorrhexis

and karyolysis (cell nucleus disappears).[11] To measure the consistency among the observers, the Cronbach alpha reliability test was applied. It is a test developed to measure whether the same interpretation and concept were used toward the item within a research test or questions, estimating the reliability to ensure the test validity. This statistical test has been used to assess the reliability and consistency among histopathology observers.[17] The Cronbach alpha is expressed as a number between 0 and 1, and α>0.7 is considered acceptable in most research.

Data analysis was performed using SPSS software. The Shapiro–Wilk test and Levene's test were employed to assess the normality and homogeneity of the data, respectively. As the data on proximal tubule cell nucleus necrosis did not meet parametric assumptions, the non-parametric Mann–Whitney U test was applied for statistical comparison between groups.

Results

Qualitative observations of kidney histopathology showed normal features which was simple cuboidal epithelial with intact nucleus, without any vacuolization or granules in the cytoplasm, and no cell enlargement. In addition, some karyorrhexis cells were also observed with the characteristics of fragmented cell nuclei (Figure 1). Those two histopathological characteristics

Table 1 Mean Number of Proximal Tubule Kidney Cells Undergoing Necrosis

Groups	Rats	Necrosis Cells Count		Mean/rat	Mean/group ± SD
		1st Observer	2nd Observer		
Control	1	0	0	0	0.125±0.25
	2	0	0	0	
	3	0	0	0	
	4	1	0	0.5	
Treatment	1	4	3	3.5	2.438±2.5972
(150 µg)	2	8	7	7.5	
	3	4	4	4	
	4	2	2	2	
	5	3	2	2.5	
	6	0	0	0	
	7	0	0	0	
	8	0	0	0	

were observed in both, the normal group and the treatment group, but the karyorrhexis cells were observed more in the treatment group.

The Cronbach alpha test showed a value of α=0.991, indicating that the result of proximal tubule necrotic cell counting was consistent between two observers and that the data obtained were reliable. The average number of proximal tubule kidney cells undergoing necrosis in both groups can be seen in Table 1.

Shapiro-Wilk test results indicated abnormally distributed data ($p<0.05$) and the Levene test showed data inhomogeneity ($p<0.05$). Subsequently, a non-parametric Mann-Whitney test was conducted with a significance level of 0.12 ($p>0.05$). This indicates that there is no significant difference between the control group and the treatment group.

Discussion

This study selected the kidney as the organ to be assessed following immunization with recombinant CIDR1α-PfEMP1 protein. The kidney plays a crucial role in the filtration and elimination of foreign compounds entering the body through urine. Each kidney comprises approximately 1 million nephrons located in the renal cortex. Kidney damage can be caused by toxic compounds, which can be identified through histological structure observations, including tubular cell nucleus necrosis.[10,18]

The renal proximal tubule functions to reabsorb substances still needed by the body, such as glucose, amino acids, and electrolytes. The proximal tubule is the first segment of the nephron which eliminates protein-bound molecules including substances from the glomerulus and systemic circulation and makes up for more than 70% of all absorption and secretion activities.[19] This role requires a high rate of oxidative metabolism, hence making the proximal tubule prone to the toxic effect of foreign substances. Furthermore, the tubular cells have relatively high cytochrome P450 level, which can result in the formation of reactive metabolites.[10] It causes tubular toxicity, prohibiting tubular transport processes, reducing mitochondrial function, and diminishing ATP production – which in turn will increase free radicals, apoptosis, and cell necrosis on the proximal tubule epithelial.[20,21]

Changes in kidney histological structure can be influenced by the type and amount of compounds entering the body and their concentration within tubular cells. Foreign substances initially accumulate in the proximal tubule, and if reabsorbed, these substances pass through tubular epithelial cells at high concentrations, potentially causing structural and functional changes in the kidney.[20]

Qualitative observations of kidney histological preparations in all samples showed normal proximal tubule cells and karyorrhexis characteristics. Microscopic features of cell necrosis include shrunken or wrinkled nuclei, denser and darker appearance, and loss of chromatin known as pyknosis; nuclei divided into several fragments known as karyorrhexis; and disappearing nuclei known as karyolysis. Based on the sequence of damage stages, necrosis begins with pyknosis, followed by karyorrhexis, and finally, karyolysis. Cell death can be caused by various factors that induce abnormal stress, including exposure to necrosis-causing agents such as chemicals, biological agents like viruses, and metabolic disorders.[22] Necrosis is also associated with ATP depletion due to exposure to foreign substances, which subsequently triggers compensatory mechanisms by increasing anaerobic glycolysis. This process leads to decreased glycogen levels and increased lactic acid, resulting in pH changes that further cause chromatin condensation, nuclear fragmentation, and nuclear loss.[23] A previous study showed that proximal tubular cells necrosis indicated a kidney injury that is extensive enough to disrupt the normal function of the kidney and usually accompanied by changes in kidney BUN and creatinine levels.

The results of proximal tubule cell necrosis counting in the control group were 0.125±0.25, and in the treatment group were 2.438±2.5972. Statistical analysis using the Mann-Whitney test showed no significant difference in the number of necrotic cells between the control and treatment groups ($p>0.05$), likely due to the high standard deviation in the treatment group. The high standard deviation in the data results can be attributed to several factors. Firstly, inter-individual variations in immune response among rats contribute significantly to the variability.[24] Secondly, technical differences in determining the visual field chosen and the counted cells for calculations introduce additional inconsistencies. These factors collectively contribute to the observed variability in the data. The insignificant difference between the control and treatment groups indicates that immunization with recombinant CIDR1α-PfEMP1 protein did not result in histopathological changes, specifically

necrosis, in renal proximal tubules. A similar finding of a previous study on *Circum-sporozoite Protein* (FMP013) for malaria vaccine candidates suggested that the compound was safe in animals.[25]

In conclusion, this study found no change in the kidney histopathology based on the counting of proximal tubule necrotic cells after CIDR1α-PfEMP1 immunization in rats *(Rattus norvegicus)*. However, histopathology evaluation cannot be used as a screening method as the diminished kidney function happens before any histopathological alteration. Hence, it is necessary to measure kidney function through serum creatinine examination, identify necrotic renal tubule cells using immunohistochemistry methods, and observe other microscopic kidney structures, such as glomeruli, considering the limitations of this study. To address more specific proximal tubule function, biomarkers such as Kim-1, CysC, β2M levels, α-glutathione S-transferase (α-GST), γ-glutamyl transferase (GGT), and alkaline phosphatase (ALP) are important to measure.

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Sexual Violence among University Medical Students in Sumatera, Indonesia

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Abstract

Sexual violence is a pervasive issue affecting both adults and children globally, resulting in severe trauma for victims. Due to the power dynamics, this problem also extends to educational institutions, including universities. Therefore, this study aimed to investigate incidents of sexual violence among medical students at a state university in West Sumatra, Indonesia in 2023. A descriptive cross-sectional survey was conducted using a questionnaire distributed to pre-clinical and clinical medical students. A total of 1,170 students were included as respondents, of which 9.7% of them reported experiencing sexual violence. Specifically, 46.0% of respondents had previous experience of sexual violence, and 42.5% of these occurred during their time as university students. The most common forms were non-physical sexual violence, accounting for 35% of reported cases, with 30.3% of the perpetrators being strangers. Over half of the victims experienced sexual violence more than once, and only 46.2% of victims reported their experience. This study showed that sexual violence affected medical students, mainly in non-physical forms, with a low reporting rate. Consequently, collaboration between campus leaders and the academic community is crucial to empower victims in participating and creating an environment that is free from sexual violence. Preventive efforts must also be comprehensive, engaging multiple sectors and community, to effectively combat sexual violence in universities.

Keywords: Medical student, sexual violence, Universities

Introduction

Sexual violence is a pervasive issue affecting individuals across all age groups and social environments, including private settings, families, workplaces, and educational institutions.[1] In Indonesia, sexual violence is defined as any act that degrades, harasses, insults, or assaults an individual's body and/or reproductive function. These acts are often rooted in gender inequality and power imbalances, potentially resulting in physical and psychological harm, disruption of reproductive health, and the loss of opportunities to pursue higher education safely and effectively.[2]

According to the World Health Organization (WHO), approximately 120 million women under the age of 20 have experienced some form of sexual violence.[3] However, the actual prevalence remains uncertain, as nearly 50% of cases are never reported.[4] In Indonesia, data from the Ministry of Women's Empowerment and Child Protection (2021) identified the education sector—particularly universities—as a significant setting for sexual violence.[5] Most incidents occurring in these supposedly "safe" environments, such as schools and campuses, are perpetrated by individuals known to the victims, including peers, teachers, lecturers, or institutional leaders. These perpetrators exploit their power dynamics to indoctrinate victims into complying with their desires.[5,6] Moreover, victims of sexual violence are often discovered late due to the absence of witnesses, lack of evidence, feelings of shame, the existence of power relations, or threats from the perpetrator.[7] This phenomenon can disrupt the entire education process of students on campus and their quality of life.[8,9]

In Indonesia, especially Sumatra, the medical education program consists of 2 stages. Pre-clinic stage and clinical stage. These two stages allow medical students to meet many strangers in short interactions, such as patients and patient families. Educational conditions, which sometimes require students to remain active at

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night in hospitals, provide more opportunities for them to receive sexual violence from various people.[10] Traumatic experiences of victims can potentially cause acute or long-term emotional, physical, social, and economic disorders.[7] Studies have shown that victims usually develop anxiety disorders (smoking, consumption of alcohol and drugs, and unsafe sexual relations), suffer from chronic diseases (cancer, diabetes, and heart problems), infectious diseases (HIV), and social issues (breakup education, become perpetrators of violence and crime) in the future.[3] Therefore, to build a campus environment free from sexual violence, there is a need to implement preventive measures and management for handling sexual violence cases. These efforts must focus on addressing factors that contribute to the occurrence of sexual violence in the university environment. Currently, there are still many cases that have not been disclosed, which might be kept by higher education leaders to reduce the number of reported cases in their institutions. Due to the demanding academic activities of medical students, it is essential to consider their well-being. Therefore, this study aimed to analyze the incidence of sexual violence among pre-clinic and clinical medical students.

Methods

This descriptive cross-sectional study was conducted in 2023 among pre-clinical and clinical medical students at a state university in West Sumatra, Indonesia. Data were collected using a structured questionnaire designed to capture students' experiences related to sexual violence. The development of the questionnaire was guided by the Indonesian Minister of Education and Culture Regulation No. 30 of 2021. Participants were asked about the characteristics of the respondents (gender, age, year of program, type of student, and sexual orientation), then about sexual violence history (frequency, age of first experiencing sexual violence, type of sexual violence, perpetrated history of sexual violence, and report status), and sexual violence experience behavior consisting of 27 questions with the responses consisted of three choices (1= yes, 2=uncertain, 3=no). This survey consisted of a maximum of 52 questions, depending on the respondents' answers, and took 5–7 minutes to complete. Before sending out the survey, a pilot test was run with 30 participants with different profiles to screen the study for possible bias and confusion.

A content validity test was conducted on the questionnaire through expert judgment. We asked a forensic doctor and a psychologist to evaluate the items already created based on quantitative and qualitative criteria (giving scores) and suggest or add any wording changes. Then to evaluate the reliability, we assessed internal consistency by evaluating Cronbach's alpha, which is 0.914.

The inclusion criteria encompassed all active medical students, with a total sampling population of 1,181 individuals. Of these, 1,170 students consented to participate and completed the questionnaire. Data collection was facilitated by contacting class leaders via telephone and individually reaching out to students through WhatsApp messages to request their voluntary participation. The exclusion criteria included medical students who declined to participate or those who did not respond after being contacted directly at least twice.

Due to the sensitive nature of the questions, participants were not required to disclose their real names, allowing them to respond honestly and comfortably. The researchers ensured the confidentiality of all respondents' personal

Table 1 Characteristics of Medical Student Respondents

Respondents Characteristics	(n=1170) (%)
Gender	
Male	389 (33.2)
Female	781 (66.8)
Age (year)	21 (1.9)
Year in Program	
Second	230 (19.7)
Third	227 (19.4)
Fourth or more	713 (60.9)
Type of Student	
Pre-clinical	668 (57.1)
Clinical	502 (42.9)
Sexual Orientation (by self-report)	
Heterosexual	1134 (96.9)
Lesbian/Gay	2 (0.17)
Bisexual	2 (0.17)
Unsure	32 (2.7)
Sexual Violence Experience	
Never	937 (80)
Ever	113 (9.7)
Do not know	120 (10.3)

Table 2 Characteristics of Medical Students Who Have Experienced Sexual Violence

Respondents Characteristics	n (%)
Ever experienced sexual violence	113 (9.7)
Age (year)	
5–10	26 (23.0)
11-15	40 (35.4)
16–20	31 (27.4)
21–25	10 (8.9)
>25	1 (0.9)
Not sure	5 (4.4)
Gender	
Male	11 (9.7)
Female	102 (90.3)
Sexual Orientation	
Heterosexual	108 (95.6)
Lesbian/Gay	0
Bisexual	1 (0.9)
Unsure	4 (3.5)
Time of occurrence of sexual violence in medical faculty	
Pre-clinical period	32 (28.3)
Clinical period	16 (14.2)
Both	13 (11.5)
Before becoming a medical student	52 (46.0)
How many times have you experienced sexual violence?	
1	27 (23.9)
2	14 (12.4)
>2	72 (63.7)
When did you experience sexual violence?	
06.00–17.59	69 (61.1)
18.00–23.59	44 (38.9)
When you experienced sexual violence, did you report it?	
No	56 (49.6)
Yes	52 (46.1)
Do not remember	5 (4.4)

information. Data were analyzed using SPSS software. Ethical approval for this study was obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas (Approval No. 349/UN.16.2/KEP-FK/2023).

Results

This study included 1,170 respondents, consisting of 668 (57.1%) pre-clinical and 502 (42.9%) clinical students. The sample was further divided by gender, with 389 (33.2%) male and 781 (66.8%) female participants. Among the respondents, 113 (9.7%) reported having experienced sexual violence. Of these, 52 (46.0%) reported experiencing sexual violence prior to becoming medical students, while 61 students (54.0%) experienced it during their university studies. Additionally, 24 respondents (21.2%) reported experiencing sexual violence only while attending university, and 42 (37.2%) experienced sexual violence in both pre-university and university settings. The majority of respondents indicated that their first experience of sexual violence occurred between the ages of 11 and 15 years (35.4%).

The analysis based on the occurrence during medical studies showed that sexual violence mainly occurred in the pre-clinical period

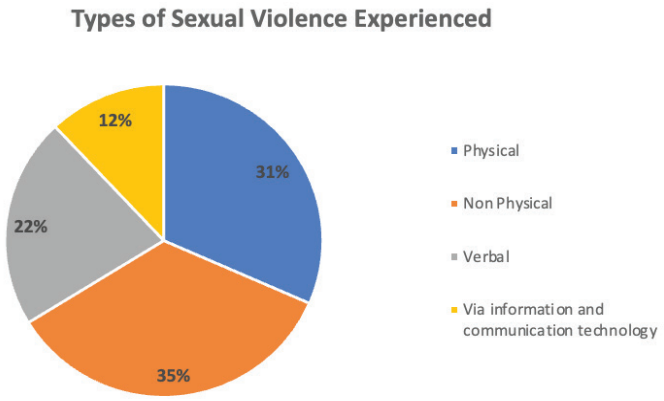

Figure 1 Types of Sexual Violence Experienced

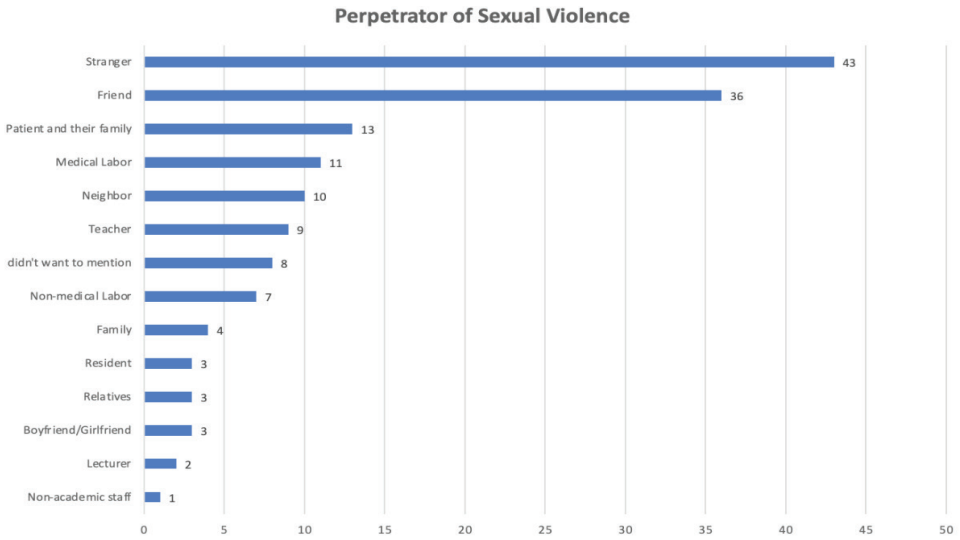

Figure 2 Perpetrator of Sexual Violence in Medical Students

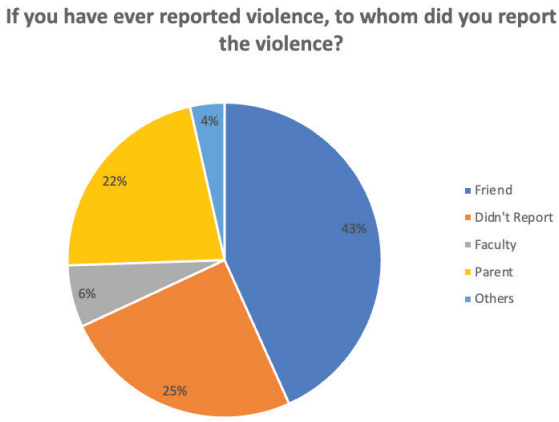

Figure 3 Reporting by Victims of Sexual Violence

(28.3%), compared to in the clinic (14.1%). A total of 72 respondents (63.7%) admitted experiencing sexual violence more than twice, occurring mainly between 06.00 am to 06.00 pm (61.1%).

The predominant type reported was through information and communication technology (for example, receiving inappropriate photos and videos), accounting for 35%, followed by physical contact (31%), as shown in Figure 1. Furthermore, Figure 2 showed that perpetrators were dominated by individual's unknown to the victim (43 events), followed by friends (36 events).

Approximately 46.0% of respondents had the courage to report their experience, while others remained silent regarding the incident. Among those who reported, the majority (43%) only told their friends, and 6% reported to lecturers or authorized university leaders (Figure 3).

Discussion

This study focused on medical students, showing that the risk of becoming victims of sexual violence is significantly high among children (<18 years old). Based on the results of the study, among students who were victims of sexual violence, 41.59% of respondents admitted to experiencing sexual violence before entering college, while others were sexually assaulted at 11 years old. However, a previous study by Zilkens et al. in Australia showed a more mature age, ranging from 20–29 years old.[11,12]

In this study, 9.7% of medical students had experienced sexual violence, with victims being dominated by women. Similar studies at universities in Australia stated that 30.6% of students were victims of sexual violence, predominantly women, respectively.[13] The prevalence of sexual violence against women is related to several factors, including a robust patriarchal culture, the presence of gender inequality, power dynamics, a lack of education on sexual violence, and underreporting of sexual harassment on campus.[14,15] Moreover, the close hierarchical structure in medical education between senior and junior has the potential to cause abuse of authority, including acts of sexual violence in lower hierarchical groups.[5,16] However, this study showed that only 3% of victims experienced sexual violence related to power relations in the educational environment (lecturers and residents).

Recently, the scope of sexual violence is no longer limited to touch or physical contact. This study showed that the use of information and communication technology (for example, receiving inappropriate photos or videos) facilities was the main form of sexual violence occurring among medical students. In contrast, the results obtained from Norway showed that verbal violence sexual expressions and suggestions, comments about the body, appearance, or private life, including physical violence (unwanted touching, hugging, or kissing) were the most common forms.[17] Although limited numbers were recorded from institutions, most of the perpetrators of sexual violence in this study were unknown to the victims, such as public transportation drivers and people who met accidentally in public areas.

Compared to the study by Zilkens et al.,[12] the majority of perpetrators of sexual violence were friends of victims. This shows the negative impact of the rapid development of information and communication technology facilities, with the increase in cybercrime, particularly among students.[18] Through easy access to the internet, pornography, and various social media that support online grooming, predators can easily access the child, initiate the abuse, and conceal the process.[19,20]

Significant information was obtained in this study, where 61.06% of victims experienced sexual violence not at night but during routine activity times (06.00 am to 06.00 pm). Despite the high prevalence rates, the majority of victims in this study preferred not to report their experiences. Although most respondents admitted being victims of sexual violence more than twice, the desire to report is still challenging. When victims attempt to speak up, most report the incident to their friends and not institutional leaders or authorities capable of following the reported cases. These delays in reporting have an impact on the slow handling of victims, which indirectly provides opportunities for perpetrators. According to Nikmatullah[21], victims of sexual violence in college often feel embarrassed, unsure of where to complain, and worried that reporting incidents could affect academic activities, leading to dropping out of college.

Fitri et al.[22] stated that several factors contributed to the vulnerability of students to becoming victims of sexual violence, including insufficient understanding and the tendency of universities to prioritize their reputation. This often leads to mediation between victims and perpetrators to reconcile without formal

reporting. Therefore, the concern of university structures in preventing and handling sexual violence on campus is very crucial, considering the large impact on students who become victims in the future. Currently, there is a regulatory policy of the Indonesian Minister of Education and Culture regarding handling sexual violence in higher education environments, including establishing a Task Force for preventing and controlling sexual violence at the university level.[2]

The limitation of this study is that the sample is only one university in Sumatra and the lack of analysis regarding factors contributing to the vulnerability of students to becoming victims of sexual violence. In addition, the questions in this study are in the form of answer choices. Further research using open questions (essays) certainly provides wider opportunities for analyzing findings. Therefore, future study is recommended to explore these factors to explain the results obtained in this study in some universities.

In conclusion, medical students are not significant as a vulnerable group to experience sexual violence. All students can experience sexual violence anytime and anywhere, especially the number of students who experience sexual violence is higher at the pre-clinical stage (meaning almost the same as the situation of students from other faculties). The results of this study indicate the great potential to become victims of violence at the age of children (school age). Efforts to eradicate sexual violence must not only address known cases but also require preventive measures. Creating an environment free from sexual violence requires the role of university structures and student bodies with a high awareness of gender equality perspectives and the issue of sexual violence. Coordination efforts should also be comprehensive and integrated across the entire university community. Furthermore, the establishment of Task Force for preventing and handling sexual violence ("*Satuan Tugas Pencegahan dan Penanganan Kekerasan Seksual-Satgas/PPKS*") is expected to help eradicate sexual violence by increasing awareness of times and potential risk areas. However, the major challenge is developing effective screening methods to identify people at high risk or victims of sexual violence that have not been reported. Thus, it is necessary to carry out further research regarding the considerations of victims in choosing whether to report the sexual violence they have experienced or not.

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Acid-Base and Electrolytes Profile in Critically Ill Pediatric Patients Admitted to Pediatric Intensive Care Unit (PICU)

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Abstract

Critically ill pediatric patients are known to experience more frequent episodes of acid-base and electrolyte imbalances when compared to adults, which can significantly impact morbidity and mortality with higher mortality rates and longer hospital stays. Data on the profile of acid-base and electrolyte imbalances in critically ill pediatric patients is very limited in Indonesia. This study was conducted to describe the electrolytes and acid-base profile of critically ill pediatric patients admitted to the Pediatric Intensive Care Unit (PICU). This was a cross-sectional study using secondary data from medical records of critically ill pediatric patients aged 1 month to 18 years admitted to the PICU of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, from January 1 to December 31, 2021. Results indicated that 131 (50.8%) of 258 patients experienced electrolytes and acid-base imbalances. The majority of patients were boys (53.0%) and infants (32.8%). The most common primary diagnosis was respiratory (28.2%), central nervous system (19.8%), and gastrointestinal disorders (15.3%). A total of 366 electrolyte imbalance events and 111 acid-base imbalance events were recorded. The most common electrolyte imbalance events were hyponatremia (75.6%), hypocalcemia (48.9%), and hypokalemia (42.7%), respectively, while the most frequent acid-base imbalance events were respiratory alkalosis (33.6%) and metabolic acidosis (21.4%). Electrolyte and acid-base imbalances are common among critically ill pediatric patients in PICU. Thus, early evaluation and recognition of acid-base and electrolyte imbalances are crucial in order to prevent poor outcomes in these patients.

Keywords: Acid-base, critically ill, electrolyte, pediatric intensive care units

Introduction

Electrolytes play a critical role in maintaining physiological processes and fluid balance within the body. The five major electrolytes routinely measured include sodium, potassium, calcium, chloride, and magnesium. Infants and children are more prone to experiencing episodes of acid-base and electrolyte imbalances compared to adults.[1] Each year, approximately 200 critically ill children are admitted to the Pediatric Intensive Care Unit (PICU) of Dr. Hasan Sadikin General Hospital in Bandung. Acid-base and electrolyte abnormalities are common among children requiring intensive care.[2] Acid-base and electrolyte abnormalities are common in children who need intensive care.[3] A study by Naseem et al. found that 84.15% of children admitted to the PICU experienced electrolyte imbalances.[4] Meanwhile a study at the PICU of dr. Soetomo National Hospital in Surabaya noted that 61.7% of pediatric patients who had just entered the PICU experienced electrolyte imbalances.[5] Furthermore, during follow-up, an estimated 61% of children with Chronic Kidney Disease (CKD) stage four exhibited metabolic acidosis (with levels <22 mmol/L).[6]

Acid-base and electrolyte imbalances can have an impact on morbidity and mortality, both in terms of the level of care needed and the emergence of complications in PICU patients. For example, children with hypernatremia have an 8.9 times higher risk of death than children with normal sodium levels.[1] Children with hyperkalemia were found to have an eight times higher risk of death.[7] In addition, children with hypomagnesemia have a longer mean duration of stay in the PICU and higher mortality.[8] Metabolic acidosis is one of the most common acid-base

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imbalances, and it is associated with increased length of stay and higher mortality rates.[9] Various critical conditions are often related to conditions that will impact various vital organs. In conditions of lack of oxygen (hypoxemia) or malnutrition due to prolonged or severe circulatory failure (hyperfusion), acute kidney failure often occurs, which can often present initially with electrolyte imbalances. Early detection through screening of serum electrolytes may help identify kidney dysfunction in critical patients. While serum electrolyte levels alone may not be definitive in diagnosing AKI, monitoring them in critical conditions, especially for developing countries with limited facilities, such as Indonesia, can aid in the timely recognition of potential kidney failure.

Given the various causes of acid-base and electrolyte imbalances, early recognition and prompt treatment are crucial to restoring balance and preventing poor outcomes in PICU patients. However, data on the profile of acid-base and electrolyte imbalances in critically ill pediatric patients remains limited in Indonesia, particularly in West Java. This study aims to identify the profile of these imbalances in critically ill pediatric patients treated at the PICU of Dr. Hasan Sadikin General Hospital in Bandung, the main referral hospital in West Java, during the year 2021.

Methods

This cross-sectional study was conducted from January to December 2021 in the Pediatric Intensive Care Unit (PICU) of Dr. Hasan Sadikin General Hospital, Bandung. The study utilized secondary data, specifically patients' medical records, as the primary instrument. The subjects included critically ill pediatric patients who experienced acid-base and electrolyte imbalances and received treatment at the PICU during the study period. The inclusion criteria were pediatric patients aged one month to 18 years. Exclusion criteria consisted of incomplete patient information in medical records (e.g., age, sex, type of acid-base and electrolyte imbalance, main diagnosis, length of stay, and mortality).

This study referred to the normal reference values that were used at the PICU Dr. Hasan Sadikin General Hospital, Bandung. Blood samples were drawn on patients' admission and repeated several times during their stay in PICU, and any acid-base and electrolyte imbalances were noted. The initial diagnosis of acid-base and electrolyte imbalance was made if any value was below or above the normal values. If a patient has more than one acid-base and electrolyte imbalance in the results, the highest and lowest values (most severe) were used to determine the diagnosis. Below are the cut-off values:

The sampling method used in this study was consecutive sampling, and the sample size was determined using a sample calculation formula for categorical descriptive data. A total of 147 cases of acid-base and electrolyte imbalances were identified; however, only 131 cases were evaluable from 258 pediatric patients admitted to the PICU between January and December 2021. This study was approved by the Health Research Ethics Committee of Universitas Padjadjaran (931/UN6.KEP/EC/2022). Data analysis was conducted using Microsoft® Excel® 2019, and descriptive statistics were employed to present the results in terms of percentages and frequencies.

Results

During the study period, a total of 147 cases of electrolytes and acid-base imbalance were found among 258 patients admitted to the PICU of Dr. Hasan Sadikin General Hospital Bandung. Therefore, the frequency of critically ill children presenting with electrolytes and acid-base imbalance in the PICU was 57%. From this, 16 patients were excluded because the data in medical records were incomplete; due to incomplete value results, lack of main diagnosis, length of stay, or mortality.

A total of 131 patients (50.8%) with electrolytes and acid-base imbalances were analyzed in this study, with the ages ranging

Table 1 Normal Reference Values in the PICU of Dr. Hasan Sadikin General Hospital

Variable	Normal Values
Na^+ (Sodium)	135–145 mEq/L
K+ (Potassium)	3.5–5.1 mEq/L
Ca^{2+} (Ionized Calcium)	4.5–5.6 mg/dL
Cl^- (Chloride)	98–109 mEq/L
Mg^{2+} (Magnesium)	1.8–2.4 mg/dL
pH	7.35–7.45
PCO_2	35–45 mmHg
HCO_{3-}	22–26 mEq/L
Standardized base excess	(-2)–(+2) mmol/L

Table 2 Characteristics of Study Population (n=131)

Characteristics	n	%
Age groups		
Infants (1–11 months)	43	32.8
Toddler (12–59 months)	29	22.14
Children (6–12 years)	38	29.0
Adolescent (13–18 years)	21	16.0
Gender		
Males	70	53.0
Females	61	47.0
Main diagnosis		
Respiratory disorders	37	28.2
Cardiovascular system disorders	17	13.0
Kidney disorders	2	1.5
Endocrine and metabolism disorders	1	0.8
CNS disorders	26	19.8
Gastrointestinal disorders	20	15.3
Trauma	8	6.1
Malignancy	12	9.2
Others	8	6.1
Length of stay		
≤7 days	83	63.4
>7 days	48	36.6
Mortality		
Died	40	30.5
Survived	91	69.5

Table 3 Incidence of Electrolyte Imbalances (n=131)

Variable	n	%
Electrolyte imbalances*		
Hypernatremia	20	15.3
Hyponatremia	99	75.6
Hyperkalemia	19	14.5
Hypokalemia	56	42.7
Hyperchloremia	42	32.1
Hypochloremia	28	21.4
Hypercalcemia	24	18.3
Hypocalcemia	64	48.9
Hypermagnesemia	4	3.1
Hypomagnesemia	10	7.6
Acid-base imbalances**		
Metabolic acidosis	28	21.4
Respiratory acidosis	23	17.6
Metabolic alkalosis	16	12.2
Respiratory alkalosis	44	33.6

* **Each patient(s) could experience more than one acid-base and electrolyte imbalance

from one month to 17 years old (Table 1). Among those, 70 (53%) patients were males and 61 (47%) were females. The majority of the patients were infants in the age group 1 to 11 months with a total number of 43 (32.8%), followed by children (6–12 years old) in 38 (29%), toddlers (1–5 years old) for 29 (22.1%), and adolescents (12–18 years old) for 21 (16%).

For the admitting diagnosis, the majority i.e 37 (28.2%) patients have respiratory disorders, followed by central nervous system disorders in 26 (15.3%), followed by gastrointestinal disorders (20 (15.3%)), and 8 (6.1%) were categorized in other disorders including congenital and musculoskeletal disorders. Out of these 131 patients, as many as 83 (63.4%) stayed in the PICU for less and equal to 7 days. For the outcomes, it was found that 91 (69.5%) patients survived (transferred to another unit or discharged) and 40 (30.5%) died during hospitalization.

Out of 131 patients, a total of 366 events of electrolyte imbalance and 111 events of simple acid-base imbalance were reported. The most frequently noted acid-base and electrolyte imbalances abnormality was hyponatremia seen in 99 (75.6%) patients and respiratory alkalosis seen in 44 (33.6%) patients (Table 2). The incidence was followed by hypocalcemia in 64 (48.9%) and metabolic acidosis in 28 (21.4%) patients, followed by hypokalemia in 56 (42.7%) and respiratory acidosis in 23 (17.6%), followed by hyperchloremia seen in 42 (32.1%) and metabolic alkalosis in 16 (12.2%) patients. The less common electrolyte imbalances were hypomagnesemia in 10 (7.6%), and hypermagnesemia in 4 (3.1%) patients.

Regarding gender, it was found that electrolyte imbalances were more frequently

Table 4 Distribution of Electrolytes and Acid-Base Imbalances by Gender (n=131)

Types of Imbalances	Gender (n(%))		Total
	Males (n=70)	Females (n=61)	
Electrolyte imbalances*			
Hypernatremia	11 (15.7)	9 (14.8)	20
Hyponatremia	52 (74.3)	47 (77.0)	99
Hyperkalemia	10 (14.3)	9 (14.8)	19
Hypokalemia	24 (34.3)	32 (52.5)	56
Hyperchloremia	23 (32.9)	19 (31.1)	42
Hypochloremia	15 (21.4)	13 (21.3)	28
Hypercalcemia	14 (20.0)	10 (16.4)	24
Hypocalcemia	33 (47.1)	31 (50.8)	64
Hypermagnesemia	2 (2.9)	2 (3.3)	4
Hypomagnesemia	3 (4.3)	7 (11.5)	10
Acid-base imbalances**			
Metabolic acidosis	16 (22.9)	12 (19.7)	28
Respiratory acidosis	10 (14.3)	13 (21.3)	23
Metabolic alkalosis	9 (12.9)	7 (11.5)	16
Respiratory alkalosis	21 (30.0)	23 (37.7)	44

*,**Each patient(s) could experience more than one acid-base and electrolyte imbalance

seen in males (187 (51.1%)) than females (179 (48.9%)) (Table 3). Hyponatremia is the most common electrolyte imbalance seen in males and females, as seen in 52 (74.3%) and 47 (77%) patients, respectively. However, the incidence of hypokalemia was higher in females (32 (52.5%)) than in males (24 (34.3%)). As many as 56 (50.5%) out of 111 cases of acid-base imbalances were found in males with the most common disturbance being respiratory alkalosis (21 (30.0%)). The remaining cases of acid-base imbalances (55 (49.5%)) were found in females, with respiratory alkalosis (23 (37.7%)) presenting as the most common acid-base imbalance seen in females.

Based on the age group, the percentage of electrolyte imbalances was highest in children aged 6 to 12 years (120 (32.8%)). Hyponatremia was the most prevalent electrolyte imbalance in all groups, i.e infants (31 (72.1%)), toddlers (21 (72.4%)), children (32 (84.2%)), and adolescents (15 (71.4%)) (Table 4). In toddlers and children, hypocalcemia was more common (16 (55.2%) and 23 (60.5%), respectively) compared to the incidence in other age groups. Hypermagnesemia was rare, presenting only in infants (1 (2.3%)), children (1 (2.6%)), and adolescents (2(9.5%)). The most common acid-base imbalance found in infants was respiratory acidosis (14 (32.6%)), meanwhile, in toddlers, respiratory alkalosis is the most frequently noted (12 (41.4%)).

As shown in Table 5, in sodium, the prevalence of hypernatremia in deceased patients was higher than in alive children, with a mean of 161.00 ± 14.38 mEq/L. The same was found with potassium, where the prevalence of hyperkalemia in patients who were deceased (11 (27.5%)) was higher than in alive children (9 (9.9%)). However, hyponatremia was the leading electrolyte imbalance among the deceased patients, accounting for 75% of the deceased patients. The remaining mortality profiles of the patients with electrolyte imbalances are presented in Table 5.

A normal acid-base level was found in only 4 (10%) patients among the deceased patients (Table 6). Acid-base imbalance among the deceased patients was almost evenly distributed, as seen with metabolic acidosis, respiratory acidosis, and respiratory alkalosis that were found in 14 (35%) of the deceased patients.

Discussion

This study identified 147 cases (57.0%) of

Table 5 Distribution of Electrolytes and Acid-Base Imbalances by Age Groups (N=131)

Imbalances	Age groups (n(%))				Total
	Infants	Toddler	Children	Adolescent	
Electrolyte imbalances*					
Hypernatremia	3 (7.0)	9 (31.0)	5 (13.2)	3 (14.3)	20
Hyponatremia	31 (72.1)	21 (72.4)	32 (84.2)	15 (71.4)	99
Hyperkalemia	8 (18.6)	3 (10.3)	5 (13.2)	3 (14.3)	19
Hypokalemia	13 (30.2)	14 (48.3)	20 (52.6)	9 (42.9)	56
Hyperchloremia	13 (30.2)	9 (31)	12 (31.6)	8 (38.1)	42
Hypochloremia	9 (20.9)	8 (27.6)	9 (23.7)	2 (9.5)	28
Hypercalcemia	10 (23.3)	4 (13.8)	7 (18.4)	3 (14.3)	24
Hypocalcemia	14 (32.6)	16 (55.2)	23 (60.5)	11 (52.4)	64
Hypermagnesemia	1 (2.3)	0 (0.0)	1 (2.6)	2 (9.5)	4
Hypomagnesemia	1 (2.3)	2 (6.9)	6 (15.8)	1 (4.8)	10
Acid-base imbalances**					
Metabolic acidosis	6 (14.0)	4 (13.8)	11 (28.9)	7 (33.3)	28
Respiratory acidosis	14 (32.6)	5 (17.2)	3 (7.9)	1 (4.8)	23
Metabolic alkalosis	6 (14.0)	4 (13.8)	4 (10.5)	2 (9.5)	16
Respiratory alkalosis	6 (14.0)	12 (41.4)	17 (44.7)	9 (42.9)	44

*, **Each patient(s) could experience more than one acid-base and electrolyte imbalance

acid-base and electrolyte imbalances among 258 critically ill pediatric patients admitted to the PICU of Dr. Hasan Sadikin General Hospital Bandung from January to December 2021. After excluding 16 patients due to incomplete medical records, 131 cases (50.8%) were included in the final analysis. The exclusion of these cases did not significantly impact the overall incidence percentages, which remained relatively stable. Nevertheless, this exclusion may slightly limit the generalizability of the findings, particularly in representing patients with incomplete documentation or shorter durations of hospitalization.

The findings of this study are consistent with those reported by Agarwal and Octavia et al., which identified electrolyte imbalances in 60% and 61.7% of PICU patients, respectively.[3,5] In this study, a total of 366 electrolyte imbalance events were recorded. This relatively high number may be attributed to the inclusion of five electrolytes—sodium, potassium, calcium, chloride, and magnesium—where an imbalance in any of them was counted. In contrast, many previous studies examined fewer electrolytes. For instance, Octavia et al. reported 97 cases of electrolyte disturbances, focusing only on four electrolytes, and their study period was limited to four months, which was significantly shorter than the duration of this study.[5]

The total cases of acid-base imbalances in this study were 111 events. This study focused only on four major simple acid-base disturbances, namely metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. Currently, there are no available recent data regarding the incidence of acid-base imbalance in critically ill pediatric patients. This might be due to the complexity of the interpretation of complex acid-base status, and a large number of calculations cannot be carried out manually.[10]

This study found that infants aged 1 to 11 months were the majority of the patients, accounting for 43 (32.8%) patients. This was

Table 6 Mortality Profile in Patients with Electrolyte Imbalances (n = 131)

Type of Imbalances	Mean ± SD*	Mortality (n (%))	
		Survived (n=91)	Died (n=40)
Sodium			
Normal	137.94 ± 2.95	11 (12.1)	6 (15.0)
Hyponatremia	5.92 ± 5.27	69 (75.8)	30 (75.0)
Hypernatremia	161.00 ± 14.38	9 (9.9)	11 (27.5)
Potassium			
Normal	4.26 ± 0.49	44 (48.4)	10 (25.0)
Hypokalemia	2.79 ± 0.53	35 (38.5)	23 (57.5)
Hyperkalemia	6.41 ± 0.87	9 (9.9)	11 (27.5)
Chloride			
Normal	103.10 ± 3.20	19 (20.9)	12 (30.0)
Hypochloremia	91.33 ± 5.78	16 (17.6)	12 (30.0)
Hyperchloremia	119.62 ± 12.39	25 (27.5)	17 (42.5)
Magnesium			
Normal	2.80 ± 0.35	4 (4.4)	2 (5.0)
Hypomagnesemia	1.60 ± 0.09	8 (8.8)	1 (2.5)
Hypermagnesemia	2.12 ± 0.18	4 (4.4)	1 (2.5)
Calcium			
Normal	4.85 ± 0.26	34 (37.4)	9 (22.5)
Hypocalcemia	3.94 ± 0.62	39 (42.9)	25 (62.5)
Hypercalcemia	6.26 ± 0.72	15 (16.5)	9 (22.5)

*Values are presented in the following units; sodium = mEq/L; potassium = mEq/L; chloride = mEq/L; magnesium = mg/dL; and calcium = mg/dL

similar to the previous studies that noted the majority of the patients experiencing electrolyte imbalance were in the age group of less than 5 years old, including children of less than one year of age. [1,3–5] The reason for this is that physiologically, infants are more susceptible to fluid and electrolyte imbalances. Significant changes occur in TBW during the first year of life, from 75% of body weight at birth to 60% at 1 year.[11] Also, in the first year of life, there is immaturity of the kidney which causes disruption of sodium and water resorption.[12]

Table 7 Mortality Profile in Patients with Acid-Base Imbalances (n=131)

Type of Imbalances	Mortality (n(%))	
	Survived (n=91)	Died (n=40)
Normal	41 (45.1)	4 (10)
Metabolic acidosis	14 (15.4)	14 (35)
Respiratory acidosis	9 (9.9)	14 (35)
Metabolic alkalosis	9 (9.9)	7 (17.5)
Respiratory alkalosis	30 (33)	14 (35)

In the present study, the patients with electrolytes and acid-base imbalances were dominated by males in 70 (53%) compared to females in 61 (47%). Other studies conducted by Naseem et al., Agarwal, and Ali also found that males experienced more frequent episodes of electrolyte imbalances than females.[1,3,4] Ishaque, et al. also found that the incidence of metabolic acidosis was higher in males.[9] However, there is only limited explanation about the reasons for higher incidence among the males that were reported in the literature. One study found that males had a higher risk of developing hyperkalemia than females.[1]

The majority of the patients had respiratory (37 (28.2%)) and neurological (26 (19.8%)) disorders, as noted in previous studies.[3,4] However, this was different from the study conducted in Dr. Soetomo General Hospital Surabaya, in which digestive system disorder is the most common diagnosis.[5] In this study, the gastrointestinal disorder was the third most common (20 (15.3%)) diagnosis, but since the electrolyte abnormalities are well known, some of them might have received treatments or correction in the preceding unit and later shifted towards improvement, thus bypassing the PICU stay.

As many as 40 (30.5%) of patients with acid-base and electrolyte imbalances died during their course of hospitalization in PICU. This is comparable to the study of Agarwal N which states the mortality rate was 30.5%.[3] Compared to the patients with normal electrolyte levels, mortality rates in children having electrolyte imbalances are higher. The majority of the patients having acid-base and electrolyte imbalances stayed for less than 7 days (83 (63.4%)), as noted in other studies.[3,4] The remaining 48 (36.6%) stayed for more than 7 days. The previous studies mentioned that acid-base and electrolyte imbalances increase the length of stay as compared to patients with normal electrolyte levels.[4,7] However, this was not observed in this study.

Among sodium imbalances, hyponatremia was the most widespread, presenting in 99 (75.6%) of the patients. This is higher than earlier reports where it was 67.2% in a Saudi tertiary hospital[13], 36% in an emergency unit of an Egypt hospital[1], and much higher than a study done in Pakistani children which showed hyponatremia presented in 23.52% cases[4]. This may be attributable to the prevalence of underlying etiologies among the studied children. As mentioned before, the most common main diagnosis of these patients is respiratory and CNS disorders, in which both have been known to present with a high incidence of hyponatremia.

In potassium electrolytes, it was found that the results were dominated by hypokalemia in 56 (42.7%) patients, meanwhile, hyperkalemia was present in only 19 (14.5%) patients. Hypokalemia is the third most common electrolyte imbalance in this study and this was comparable to the study done by Naseem et al.[4] which found that hypokalemia was observed in 30.58%, also as the third most common imbalance in that study. A study in Dr. Soetomo General Hospital Surabaya[5] reported that hypokalemia is the second most common electrolyte disorder found in 54.1% of the patients. Other studies found the incidence of hypokalemia at 34.4%[3] and 64%[1] of the patients. Hyperkalemia in other studies has been reported as 18.82%[4] and 16.1%[3], which is in proximity to our observations.

Regarding chloride imbalance, hyperchloremia was more common than hypochloremia, found in 42 patients (32.1%) and 28 patients (21.4%), respectively. This contrasts with the findings of Octavia et al.,[5] who reported hypochloremia as the dominant disorder, occurring in 35.1% of patients. The higher prevalence of hyperchloremia in our study may be associated with the high incidence of metabolic acidosis, a known contributor to elevated chloride levels.

In cases of calcium disturbances, hypocalcemia was the most frequent imbalance found, accounting for 64 (48.9%) of the patients. Many studies found that hypocalcemia was the most common electrolyte imbalance as noted in 57.4%[4], 59.5%[5], and 56.6%[7] of the patients. Hypercalcemia was less common, found in 24 (18.3%) of the patients. However, this was higher than previous studies that mentioned hypercalcemia was only found in 0-8.1% of patients[4,5]. This might be related to the underlying disease e.g. malignancy that is found in 12 (9.2%) patients in this study, which is not observed in the other studies. Malignancies are known to produce hypercalcemia.

In our study, the incidence of magnesium disorders was the least common among the other electrolytes. Imbalance most frequently noted was hypomagnesemia, presenting in 10 (7.6%) of cases. Hypermagnesemia was rare, as observed in only 4 (3.1%) of the patients. This was similar to the study done by Sadeghi-Bojd et al. that found 13.8% of patients had hypomagnesemia compared to 2.3% who had hypermagnesemia.[7] Magnesium imbalances

were mostly asymptomatic and a strong clinical suspicion to check for the insoluble level is needed. Also, they are not routinely measured compared to other electrolytes in the PICU of Dr. Hasan Sadikin General Hospital, thus this might be the reason for the low incidence of magnesium imbalances.

The interpretation of complex acid-base disturbances was cumbersome and an understanding of dynamic processes is needed to accurately interpret the blood gas analysis. Until now, a convenient method with an understandable, clinically instant result is still lacking, especially in our hospital. Therefore, this study focused only on the simple (primary) acid-base disturbances. In this study, respiratory alkalosis was the most common acid-base disturbance found (44 (33.6%)). This was appropriate with the fact that respiratory alkalosis is the most common acid-base abnormality observed in critically ill patients. However, Forsal et al. found that respiratory acidosis was the primary disturbance in 31% of the cohort.[10] The reason for this is probably because respiratory acidosis was more commonly found as a mixed disorder[14,15], and the incidence of it in this study was masked with the primary disturbance.

Based on gender, the frequency of hyponatremia is more common in males (52 (74.3%)). These findings were similar to the previous studies by Prabaharan K and Al-Sofyani K, which found hyponatremia in 66.7% and 61.1% of male patients, respectively[13,16]. The third most common electrolyte imbalance in males was hypokalemia 24 (34.3%). Although, the frequency was higher in females (32 (52.5%)). This was dissimilar with Cummings[17] who found hypokalemia was less likely in females. Hormonal differences in developing females and males regarding to their potassium homeostasis and total body stores may be one of the explanations for this difference. Hyperkalemia observed in the present study was more common in males (10 (14.3%)). This is similar to and also supported the findings of Ali et al. that males had a higher risk of developing hyperkalemia than females. Regarding magnesium, there is no difference in the frequency of hypermagnesemia in males (2 (2.9%)) and females (2 (3.3%)). However, the frequency of hypomagnesemia is higher in females (7 (11.5%)) than in males (3 (4.3%)). This was different with Dandinavar who reported hypomagnesemia in 57.3% of males, but current data shows there was no significant association between hypomagnesemia and gender.[8]

The most common acid-base imbalance seen in both genders was respiratory alkalosis, accounting for 21 (30%) in males and 23 (37.7%) in females. This supports the current knowledge that there has not appeared to be a significant gender distribution to alkalosis. Meanwhile, for respiratory acidosis, the incidence was higher in females (12 (21.3%)). This might be related to the underlying diseases, where severe lung disease will reduce the effectiveness of the lungs in removing CO2, and diseases of chest nerves will impair the ventilation of the lungs. In this study, the majority of the respiratory and CNS disorders were experienced by females.

As stated before, based on age groups, the most common electrolyte imbalance in all ages was hyponatremia, with the highest in infants 31 (72.1%). This finding aligns with previous reports, which also indicated that hyponatremia is predominant in children aged 0–12 months.[13,16] However, current data shows no statistically significant association found between hyponatremia and gender and age.[13] The frequency of hypokalemia was highest in children aged 6–12 years (20 (52.6%)). This was different from the study by Gauns A which reported that hypokalemia was higher in children aged 1 to 5 years old.[18] This might be caused by the different age ranges used in the studies. In the case of acid-base imbalance, respiratory alkalosis was the most commonly noted acid-base disorder in almost all of the age groups. However, in infants, the most commonly noted imbalance was respiratory acidosis. This finding was important. Acidosis in neonates and infants is supposedly less frequent since they have a relatively greater increase in plasma HCO_3^- concentrations and decrease in plasma hydrogen ion concentrations, due to a large amount of hemoglobin and interstitial fluid for their body weight than those of older children.[20] However, there is very limited literature discussing respiratory acidosis in infants or its correlation with age. Further study is needed to investigate the relationship.

Hyponatremia was the most frequently occurring electrolyte imbalance found in 30 (75%) of the deceased patients, similar with previous study that found hyponatremia in deceased children was significantly higher.[7] Out of 40 deceased patients, only 4 (10%) of them had normal acid-base levels. However, a previous study found that currently there is no association between acid-base disorders and in-hospital death.[14]

This study has several limitations. First,

this was a descriptive study that did not help determine the association between the acid-base and electrolyte imbalances with the factors mentioned in this study e.g. age, gender, mortality, or length of stay in PICU. Also, many acid-base and electrolyte imbalances were not included as a diagnosis in the patient's medical records, thus the author needed to interpret the results manually. This process did not escape the risk of human-based errors. However, behind the imperfection previously mentioned, in conclusion, the present study found that electrolyte (n=366) and acid-base imbalances (n=111) are common in critically ill children admitted to the PICU of Dr. Hasan Sadikin General Hospital Bandung from January to December 2021. The most frequent electrolyte imbalance was hyponatremia (75.6%), while respiratory alkalosis (33.6%) was the most common acid-base disturbance. The majority of patients are infants and males, with respiratory disorders as the most frequent primary diagnosis. These factors should be warning signs of acid-base and electrolyte imbalances. It is important to note that several findings differ from the previous studies. The reason is probably related to the differences in socio-demographic and clinical factors between Indonesia and other countries, as well as differences in the period of the study.

It is recommended that acid-base and electrolyte imbalances be consistently recorded as part of the diagnostic information in patient medical records. This study may serve as a valuable reference to support further evaluation and management strategies aimed at preventing adverse outcomes in critically ill pediatric patients with such imbalances. Future research should include statistical analyses to explore the correlation between acid-base and electrolyte disturbances and clinical outcomes in this population.

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Clinical Features of Drug Eruption in An Indonesian Tertiary Hospital

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Abstract

Drug eruption is a response to drugs undergoing sensitization, which is mediated by the immune system. Clinical features of drug eruptions, such as maculopapular drug eruption, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), are known as common drug reactions. This study aimed to explore the characteristics and clinical features of patients with drug eruptions at the Department of Dermatology and Venereology of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. This retrospective descriptive study used data from the department from patients treated between January 1, 2014 and December 31, 2018. Data were analyzed using Excel and SPSS software. In this study, 200 subjects were included, mainly consisting of female subjects (50.5%) and aged between 19 and 65 (89%). Maculopapular drug eruption (45%) was the most typical clinical presentation, followed by SJS/TEN (37.5%), and DRESS (3%). The analgesics and non-steroidal anti-inflammatory drugs (NSAID) group was the most commonly suspected causative drug (36.91%), with paracetamol (29.18% of total drugs consumed) as the most frequent NSAID causing the eruption. This was followed by the antibiotic-type drugs group (36.48%), with cotrimoxazole (9.87% of total drugs consumed) as the most common one. So, maculopapular drug eruption is the most common clinical presentation of drug eruption, with analgesics and non-steroidal anti-inflammatory drugs (NSAID) class as the most suspected causative drug. Further investigations are needed to get the accurate result.

Keywords: Clinical features, drug eruption, maculopapular drug eruption, non-steroidal anti-inflammatory drugs (NSAID)

Introduction

Adverse drug reaction (ADR) is a dangerous, undesirable, and unpredictable effect caused by using a drug that is intended for prevention, diagnosis, or treatment. Adverse Drug Reactions are divided into two categories, namely type A and type B. Drug eruption is one of the B-type reactions from ADR.[1] Drug eruption is a response mediated by the immune system to drugs undergoing a sensitization process.[2] Incidence of drug eruption in hospitals is 0.1% to 2% of hospitalized patients.[3] Clinical features arising from drug eruptions include urticaria, maculopapular, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS).[4]

Clinical features can be used as a diagnostic approach in patients with drug eruptions if there are hypersensitivity reactions, signs and symptoms, skin morphology, and clear laboratory tests. Not infrequently, the clinical picture sometimes produces negative results because many types of drugs are consumed simultaneously, and each type of drug produces different reactions, so it can only occasionally be relied upon. Additional investigations, such as skin prick and provocation tests, are needed.[5]

The most recent research and literature studies on the clinical features of drug eruption at Dr. Hasan Sadikin General Hospital, Bandung, have yet to be found. Proper identification and anamnesis of the cause of drug reactions is one important thing to provide fast and appropriate management for patients, with the aim of

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improving prognosis and reducing morbidity rates. Thus, this condition encourages the authors to research the clinical picture of drug eruption at Dr. Hasan Sadikin General Hospital, Bandung, from 2014 to 2018.

Methods

This research was conducted using a retrospective descriptive method using data from the Department of Dermatology and Venereology at Dr. Hasan Sadikin General Hospital, Bandung, on January 1st, 2014, and December 31st, 2018. The number of subjects was determined by the total sampling method. The inclusion criteria were complete data on drug eruption patients (age, gender, number of drugs consumed, clinical features, and drug type). Exclusion criteria were drug eruption patients' data that were incomplete, inaccessible, and duplicate data. The Ethics Committee of Universitas Padjadjaran Bandung approved this study with the number 679/UN6.KEP/EC/2019.

The data was collected using Microsoft® Excel 2021 and processed in table form, with percentages determined and unique codes created for statistical analysis. The statistical analysis was performed by IBM® SPSS® 26th version using the Spearman rho test to determine the correlation and strength of correlation between two variables.[6,7]

Results

During the study, a total of 200 subjects met the inclusion criteria. Table 1 shows the characteristics of drug eruption patients. Based on gender, most research subjects were female, and there were as many as 101 patients (50.5%). On the other hand, drug eruptions are most affected at ages 19-65 years (adults) (178 patients, 89%) and taking only one drug (107 patients; 53.5%). Statistical analysis shows that age, gender, and number of drugs have weak and no significant correlation with drug eruption.

Table 2 shows the clinical features of drug eruption from data obtained from the Department of Dermatology and Venereology at Dr. Hasan Sadikin General Hospital, Bandung. The most common clinical feature was maculopapular in 90 patients (45%). Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) was the second most common clinical feature in 75 patients (37.5%), followed by Drug reaction with eosinophilia and systemic symptoms (DRESS) in 6 patients (3%).

Table 3 shows a cross-tabulation of clinical features with causative drug classes. There are four classes of drugs, namely antibiotics, NSAIDs and analgesics, antiretrovirals and anticonvulsants and several other drugs

Table 1 Drug Eruption Patient Characteristics

Characteristics	Subject (n=200)		Spearman Rho Test	
	n	%	Correlation Coefficient	Significant
Age			-0.123	0.084
Baby (0-2 years)	-	-		
Kids (2-18 years)	12	6		
Adults (19-65 years)	178	89		
Old Adults (>65 years)	10	5		
Gender			-0.012	0.871
Female	101	50.5		
Male	99	49.5		
Number of Drugs Consumed			0.003	0.962
One Drug	107	53.5		
Two Drugs	60	30		
Three Drugs	16	8		
>Three Drugs		17	8.5	

Table 2 Clinical Features of Drug Eruption

Clinical Features	Subject (n=200)	
	n	%
Maculopapular	90	45
Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)	75	37.5
Drug reaction with eosinophilia and systemic symptoms (DRESS)	6	3
Fixed Drug Eruption	11	5.5
Erythroderma	8	4
Acute generalized exanthematous pustulosis (AGEP)	7	3.5
Angioedema	2	1
Urticaria	1	0.5

such as antiuricemia (allopurinol), antifungal (fluconazole), antidyslipidemia (simvastatin), cardiovascular drugs (amlodipine, amiodarone, captopril, procardio), antianxiety (alprazolam), gastrointestinal disturbances (metoclopramide, ranitidine, lanzoprazole), antithyroid medications (propylthiouracil /PTU and NPTU), chemotherapy (hydrea, methotrexate), common-cold remedies (pseudoephedrine, guaifenesin), antimalarial (chloroquine) and antivertigo medications (betahistine mesylate). The most suspected drug group that caused drug eruptions were analgesics and non-steroidal anti-inflammatory drugs (NSAID) group used alone or with other drugs in 86 patients (36.91%), followed by antibiotic-type drugs used alone or with other drugs in 85 patients (36.48%). Based on the type of drug consumed, the drug most suspected of drug eruptions was paracetamol taken alone or together with other drugs in 68 patients (29.18%), followed by co-trimoxazole taken alone or together with other drugs in 23 patients (9.87%), and antituberculosis drugs (ATD) which were consumed alone or together with other drugs in 19 patients (8.15%).

Discussion

Drug eruption hypersensitivity reactions are divided into immediate reactions (acute) and non-immediate reactions (delayed).[2] Immediate reactions are mediated by IgE antibody or non-specific histamine release.[8] IgE antibodies will bind with FcRI on mast cells and basophil surfaces and form a binding place multivalent to drug antigens. Then hapten-protein complex antigens will cross-link with IgE and stimulate the release of mediators such as histamine, tryptase, and TNF-α and produce new mediators such as leukotrienes, prostaglandins, kinins, and other cytokines. Clinical features caused by this reaction are urticaria, angioedema, and anaphylactic shock.[4]

Non-immediate reactions are reactions mediated by T lymphocytes.[4] These reactions are divided based on the type of cytokines produced by T lymphocytes and immune cells stimulated by these cytokines, such as eosinophils and neutrophils.[9] In normal circumstances, antigens will be phagocyted by dendritic cells, carried to lymph nodes, and stimulated by cytokines such as eosinophils and neutrophils to be presented to Naive T cells. Specific pathogen T cells can be directly stimulated in some drug antigens and migrate to the target organ. When re-exposed to the drug antigens, specific pathogenic T cells will be activated and secrete cytokines such as perforin, granzymes, and granulysin to damaged tissues. This reaction will cause clinical symptoms such as maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson Syndrome (SSJ), toxic epidermal necrolysis (TEN), acute generalized pustular exanthematous (AGEP), pustular exanthema, and eczema.[4]

The results of this study indicated that of 200 drug eruption patients, mostly were female in 101 patients (50.5%) and ages ranging from 19 – 65 years (adults), being the most affected age group in 178 patients (89%). These results were similar to the study from Farshchian et al.[10], which said that the number of women who experienced drug eruption was 194 patients (63%) compared to men, which were 114 patients (37%) with an average age of 35.2 ± 16.8. Another study by Garg et al.[11] also stated that there were more adults than children and

Table 3 Clinical Features with Suspected Drug Type Cases

Drug Type	Clinical Features								TOTAL	%
	Urticaria	Angioedema	Erythroderma	Maculopapular	Fixed drug eruption	AGEP	DRESS	SJS/ TEN		
Antibiotic									85	36.48
Ciprofloxacin		1		2				1	4	1.72
Ceftriaxone				1					1	0.43
Cotrimoxazole			1	13	2			7	23	9.87
Cefadroxil				9		2	1	1	13	5.58
Cefixime				2		1		1	4	1.72
Ampicillin								1	1	0.43
Amoxicillin			1	3		1		3	8	3.43
ATD	1		1	11	2		1	3	19	8.15
Streptomycin								1	1	0.43
Moxifloxacin				1					1	0.43
Erythromycin				1					1	0.43
Thiamphenicol		1							1	0.43
Meropenem			1						1	0.43
Clindamycin				1			1		2	0.86
Amoxiclav								1	1	0.43
Levofloxacin								1	1	0.43
Minocycline				1					1	0.43
Clofazimine				1					1	0.43
Chloramphenicol						1			1	0.43
Analgesic and NSAID									86	36.91
Mefenamic Acid					1			1	2	0.86
Methampyrone								2	2	0.86
Piroxicam				1					1	0.43
Paracetamol			1	22	3	3	2	37	68	29.18

Table 3 Continued

Drug Type	Clinical Features								TOTAL	%
	Urticaria	Angioedema	Erythroderma	Maculopapular	Fixed drug eruption	AGEP	DRESS	SJS/ TEN		
Meloxicam				1	2			1	4	1.72
Ibuprofen			1	2					3	1.29
Hufagesic								1	1	0.43
Na-Diclofenac		1		1	1			1	4	1.72
Ketolorac				1					1	0.43
Antiretroviral									25	10.73
Evafirenz				6					6	2.58
Nevirapine				5				2	7	3.00
Lamivudine				4	1			2	7	3.00
Tenofovir				1					1	0.43
Duviral				1				1	2	0.86
Abacavir								1	1	0.43
Emtricitabine				1					1	0.43
Anticonvulsant									15	6.44
Phenytoin			1	1				1	3	1.29
Lamotrigine								1	1	0.43
Carbamazepine				3				8	11	4.72
Others									22	9.44
Allopurinol							1	1	2	0.86
Pseudoephedrine								1	1	0.43
Amlodipine				1					1	0.43
Metoclopramide			1						1	0.43
Hydrea				1					1	0.43
Fluconazole				1					1	0.43
Guaifenesin								1	1	0.43

Table 3 Continued

Drug Type	Clinical Features								TOTAL	%
	Urticaria	Angioedema	Erythroderma	Maculopapular	Fixed drug eruption	AGEP	DRESS	SJS/ TEN		
Chloroquine								1	1	0.43
Alprazolam				1					1	0.43
Procardio				1					1	0.43
Amiodarone				1					1	0.43
Simvastatin				1					1	0.43
PTU				1					1	0.43
NPTU				1					1	0.43
Ranitidine				1					1	0.43
Captopril				1				2	3	1.29
Methotrexate				1					1	0.43
Lansoprazole				1					1	0.43
Betahistine mesylate				1					1	0.43

Note: ATD = Anti-Tuberculosis Drugs; NSAID = Non-steroidal Anti-Inflammation Drugs; PTU = Propylthiouracil; NPTU = Non-Propylthiouracil

older people. Most of the patients with drug eruption were young, of the age group 20–39 years. This is in contrast to the research of Talib et al.[12] in Malaysia, which stated that men are more dominant in 69 subjects than women in 65 subjects, with an average age of 47 years.

Genetics and variability in the number of male and female patients in a hospital or polyclinic may be factors that can affect the prevalence of drug eruption patients.[13] Children are probably less frequent in having some allergic reactions, possibly owing to immaturity of the immune response and lower drug consumption. However, the prevalence in elderly patients increases up to 30%, being more severe, probably due to comorbidities and multiple consumption of medication.[14]

Other studies explained that several factors linked with growing age can contribute to an increase in the risk of ADRs, such as drug metabolism changes, frailty, multimorbidity, geriatric syndromes, cognitive and sensory impairment, and polypharmacy. Conditions affecting cognition are also crucial in terms of potential patient errors or noncompliance with treatment recommendations. Functional deficits and cognitive impairment, which are characterized by memory loss, decline in intellectual function, impaired judgment, and language, can have a practical impact on pill container management and decision-making skills. Older people frequently need many medications to treat multiple diseases. According to international figures, more than 60% of the elderly are taking five or more medications at the same time. The higher the number of drugs prescribed, the greater the risk of drug reactions and interactions.[15]

This study's most common clinical appearance of drug eruption was maculopapular in 90 people (45%). This was similar to the study of Janardhan et al.[16] in India, which mentioned that maculopapular was the most common clinical picture of drug eruption, with 171 cases out of 481 patients. The study of Patel et al.[17] in India stated the same: out of 3671 drug eruption patients, maculopapular was the most clinical picture in 1189 cases. In contrast to the study by Beniwal et al.[18], they reported that out of 200 patients, fixed drug eruption was the highest clinical picture in 82 cases. On the other hand, SJS/NET became the second most common clinical picture of drug eruption in this study, with 44 people (28%). Talib et al.[12] conducted a study with similar results.

Maculopapular has been identified as the most common clinical manifestation of an ADR. It can happen with almost any medicine. In fact, the majority of commonly used medications cause cutaneous reactions of more than 1%. Polypharmacy, immunosuppression, concurrent infection, systemic autoimmune illness, a high number of secondary conditions, and extreme age are all risk factors for maculopapular. The amount of concurrent medications a person takes raises their risk of maculopapular, which is most likely related to pharmacological and metabolic interactions. Maculopapular is becoming more common as prescription drug use and polypharmacy grow.[19]

The reasons for medication allergies vary greatly and differ depending on the time, location, and type of research presented. The frequency of drug use is closely related to the high prevalence of drug allergies.[20] In this study, the highest class of drugs that caused drug eruption was analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), which were consumed alone or with other drugs (86 cases). The most common type of drug was paracetamol in 68 patients (29.18%). Then, antibiotic drugs (85 cases) were followed, with the most common type of drug being cotrimoxazole in 23 patients (9.87%). Analgesic and NSAIDs are commonly used and available without a prescription all over the world It became the most suspected causative eruption drug due to often used in the treatment of mild pain or fever to more severe symptoms, for example, in the treatment of rheumatoid arthritis.[21-23]

This study, in line with Jung et al.[24] reported that NSAIDs and acetaminophen were the main causative agents in drug eruption cases. It also aligns with Ben Fadhel et al.[25] that NSAIDs were involved in 51.2%, antibiotics in 24.4%, and other analgesics in 19.5%. But, in contrast with the study of Qayoom et al.[26] in India reported that from 75 patients, antibiotics were the leading cause of drug eruption, with quinolone being the most dominant in 28 cases. Ofloxacin was the most common drug in the quinolone group. Among the NSAIDs, piroxicam was the most commonly reported, while phenytoin was the most dominant in the anticonvulsant group.

Thus, the most clinical features of drug eruption in Dr. Hasan Sadikin General Hospital, Bandung is maculopapular and analgesics and NSAIDs drugs class, which is paracetamol, as the most suspected causative drug. There were several limitations in this study, such as the data used in this study came from secondary data, so there were some incomplete variable data, and

the causative drug data in this study were still suspicious. It also has no data about the diagnosis of each patient as the subject of this study, but it can be assumed that some drugs such as antibiotics, antiretrovirals, anticonvulsants, cardiovascular drugs, antithyroid, antifungal, antimalarial, chemotherapy were used as primary diagnostic treatment. On the other hand, the analgesics and NSAIDs group are the most often medications that caused the drug eruptions in this study and were assumed as drugs that were used both as primary and secondary diagnostic treatments. An oral provocation test, skin prick test, and other tests were needed for more accurate results about drug eruption.

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Neutrophil Lymphocyte Ratio and Mortality in Patients with Acute Limb Ischemia

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Abstract

Acute Limb Ischemia (ALI) is a sudden decrease in limb perfusion with a potential of limb loss and is an indication for immediate vascular intervention. Apart from reducing the quality of life, the mortality rate in ALI is reported to be high, i.e., around 40%. Neutrophil Lymphocyte Ratio (NLR) can be used to reflect the inflammatory process in this condition. This study aimed to assess the correlation of NLR to mortality rate in ALI Rutherford Category III patients treated in Dr. Hasan Sadikin General Hospital Bandung, Indonesia. This was a cross-sectional analytical observative retrospective study on data collected from medical records of ALI Rutherford Category III patients treated in the hospital from 2019 to 2022. Sampling was performed consecutively and data were processed using the SPSS with univariate analysis and bivariate analysis using Kendall's tau b analysis test. Results demonstrated that of a total of 46 patients, the majority were female patients (n=31) and 28 patients died. The mean NLR levels in patients who survived was 5.8, in contrast with 9.7 observed among those who died. The statistical test results showed a significant correlation between the NLR and mortality rate of ALI Rutherford category III patients ($p<0.05$), albeit weak positive correlation (r value=0.35). The higher the NLR value was, the higher the risk of death. Hence, the NLR value could be used to recognize the risk of death among these patients.

Keywords: Acute limb ischemia (ALI), NLR, mortality rate

Introduction

Acute Limb Ischemia (ALI) is defined as a sudden decrease in limb perfusion that threatens limb viability.[1,2] The Rutherford classification system categorizes ALI into stages I, IIA, IIB, and III based on clinical presentation and prognosis.[3] In Rutherford category III, irreversible tissue damage has occurred, and amputation is often necessary.[3] ALI management depends on the cause and severity. Management of Rutherford category III Acute Limb Ischemia (ALI) emphasizes that reperfusion therapy cannot restore limb function, making amputation the primary option.[4, 5] Despite adequate therapy, ALI has a high mortality rate (around 40%), often attributed to underlying vascular disorders. [6,3,5] In Dr. Hasan Sadikin General Hospital, Bandung, from 2019–2022, 187 ALI cases were reported, with 60 categorized as Rutherford III.

Neutrophil-Lymphocyte Ratio (NLR) is a simple parameter used to assess an individual's inflammatory status. An elevated NLR reflects an increasing inflammatory process and is associated with a poor prognosis.[7] Research by Nuno H. Coelho and colleagues found a positive correlation between preoperative NLR values and 30-day mortality or amputation after revascularization in ALI Rutherford grade IIa and IIb. Higher pre-revascularization NLR values are linked to increased mortality or amputation. [8,9] Besides acute limb ischemia, NLR has long been used to predict mortality and survival in various diseases, including stroke, myocardial infarction, malignancies, and more recently, predicting mortality in COVID-19 patients. [9,10] NLR, as a mortality predictor in ALI patients, offers advantages such as efficient sample collection preoperatively, simple calculation based on complete blood count upon admission, and a straightforward process without requiring

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additional analyses or reagents, making it a relatively easy, cost-effective, and rapid test. [9,10]

Given the high mortality rate among patients with Rutherford category III Acute Limb Ischemia (ALI) at Dr. Hasan Sadikin Central General Hospital, the present study aims to investigate the association between the neutrophil-to-lymphocyte ratio (NLR) and mortality. Existing literature on the correlation between NLR, as an inflammatory marker, and the severity grading of ALI remains limited. The findings of this study may contribute to improved prognostication and inform treatment decisions for patients presenting with ALI.

Methods

This study is a retrospective cohort design. Data were collected through a review of medical records of patients diagnosed with Rutherford category III Acute Limb Ischemia (ALI) at Dr. Hasan Sadikin General Hospital, Bandung. The study population comprised patients with Rutherford category III ALI treated at the same hospital. Inclusion criteria were as follows: (1) age 18 years or older, (2) confirmed diagnosis of category III acute limb ischemia, and (3) presence of comorbidities such as diabetes mellitus, heart disease, or other vascular conditions. Patients were excluded if medical records indicated signs or evidence of infection, as this could influence neutrophil-to-lymphocyte ratio (NLR) values.

The sample was obtained through consecutive sampling based on the predefined inclusion and exclusion criteria. Subjects meeting the eligibility requirements were included continuously until the end of the specified study period, ensuring that the minimum required sample size was achieved. Data were collected during each patient's hospitalization. Variables were analyzed based on their type and distribution using either the Mann–Whitney U test or the unpaired t-test, as appropriate.

The strength of correlation between variables was assessed using Kendall's tau-b analysis.

Table 1Characteristics of the Research Subjects

Characteristics	Total n=46	Alive Patients n=18	Deceased Patients n=28	p-value*
Sex				0.57
Male	15	5 (27.8%)	13 (72.2%)	
Female	31	10 (35.7%)	18 (64.3%)	
Age (year)				0.12
Mean	64	63	65	
Range	58-73	58-69	59-73	
Median	64	64	65	
Onset				
<6 hour	9	2 (22.2%)	7 (77.8%)	0.25
6–24 hour	19	10 (52.6 %)	9 (47.4%)	
24–48 hour	18	6 (33.3 %)	12 (66.7 %)	
>48 hour	0	0	0	
Comorbidity				0.25
Atrial Fibrillation	3	0 (0)	3 (100 %)	
Hypertension	14	4 (28.6 %)	10 (71.4%)	
Diabetes mellitus	12	6 (50%)	6 (50%)	
Hypercholesterolemia	11	6 (54.5%)	5 (45.5%)	
Kidney Failure	6	2 (33.3%)	4 (66.7%)	
Covid +	0	0	0	
Other disease	0	0	0	

*Uji Mann-Whitney

Table 2 Laboratory Characteristics of the Study

Characteristics	Total (n=46)	Alive Patients (n=18)	Deceased Patients (n=28)	p-value*
Hb				0.15
Mean	11.67	11.76	11.61	
Range	10.00–14.30	10.00–14.30	10.20 – 13.60	
Median	11.75	11.85	11.70	
Leukosit				0.01
Mean	13.93	10.15	16.37	
Range	2.40–29.74	2.40–21.63	4.39–29.74	
Median	11.94	9.210	15.28	
Trombosit				0.08
Mean	393.17	331.67	432.71	
Range	117–1195	117–674	148–1195	
Median	331	288	372	
Laktat				<0.01
Mean	3.76	3.64	3.84	
Range	0.80–21.50	0.80–21.50	0.80 – 21.50	
Median	1.850	1.85	2.00	
Base Excess				
Mean	- 8.66	- 0.24	-14.07	<0.01
Range	- 860–4.60	-8.60–6.50	-260.00–4.60	
Median	- 3.250	1.40	-5.85	
Ureum				<0.01
Mean	47.70	42.63	50.96	
Range	8.20–193.40	8.20–174.30	5.30–193.40	
Median	34.65	33.80	34.75	
Kreatinin				<0.01
Mean	1.60	1.46	1.69	
Range	0.45–6.17	0.45–1.40	0.34–6.17	
Median	1.02	1.01	1.10	
Neutrofil				0.03
Mean	12.75	10.35	14.29	
Range	2.45–33.90	2.45–14.24	3.62–33.90	
Median	11.92	7.84	14.30	
Limfosit				
Mean	1.96	2.16	1.82	0.04
Range	1.05-–9.16	1.05–5.98	0.62–9.16	
Median	1.87	1.94	1.50	

* Mann-Whitney

Table 3 Analysis of the Relationship Between NLR and Mortality in Rutherford Category III ALI Patients

Variable	Total (n=46)	Alive Patients (n=18)	Deceased Patients (n=28)	p*	r*
NLR				<0.01	0.35
Mean	8.4	5.8	10.1		
Range	0.5–23.3	0.45–22.92	1.54–23.29		
Median	7.0	3.89	9.71		

*Kendall's Test

Ethical approval for this study was granted by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung (Approval Number: LB.02.01/X.6.5/249/2023).

Results

As presented in Table 1, the majority of patients (67.4%) were female, with a mean age of 69 years. Among the study population, 18 patients survived or showed clinical improvement, while 28 experienced deterioration and died. The most frequent onset of symptoms occurred within 6 to 24 hours prior to hospital admission. Common comorbidities included hypertension, hypercholesterolemia, and diabetes mellitus. Comparison between the surviving and deceased patient groups revealed no statistically significant differences in age, gender, symptom onset, or comorbidities. These findings were confirmed using the Mann–Whitney U test for non-normally distributed numerical data and categorical variables ($p>0.05$).

Table 1 presents the laboratory results for patients with Rutherford category III ALI, including the mean values for various clinical parameters. A Shapiro-Wilk test confirmed that all numerical data ($n<50$) were non-normally distributed ($p>0.05$). As a result, the Mann-Whitney U test was applied to compare unmatched groups. The analysis revealed no significant differences in hemoglobin and platelet levels between the groups. However, significant differences were observed in leukocyte count, lymphocyte count, lactate levels, neutrophils, neutrophil-to-lymphocyte ratio (NLR), base excess, urea, and creatinine levels. Specifically, patients who passed away had lower lymphocyte levels and higher neutrophil levels compared to survivors.

Table 3 shows that the overall mean neutrophil-to-lymphocyte ratio (NLR) was 8.4. The mean NLR among surviving patients was 5.8, while the mean NLR among deceased patients was 10.1, indicating an elevated NLR in the latter group. A Kendall's tau-b correlation test revealed a statistically significant association between NLR and mortality in patients with Rutherford category III Acute Limb Ischemia ($p<0.05$). The correlation coefficient indicated a weak positive correlation ($r=0.2–0.4$), suggesting that higher NLR levels were associated with increased mortality.

Discussion

Acute Limb Ischemia (ALI) is a sudden decrease in arterial perfusion to the extremities, characterized by pallor, cold skin, decreased sensitivity, muscle weakness, claudication, and absence of distal pulse from the occlusion site. ALI is a medical emergency with an incidence of 3–14 per 100,000 people per year and a high rate of amputation (12–50%) and mortality (20–40%) without revascularization. The neutrophil-to-lymphocyte ratio (NLR) has been associated with specific cardiovascular disease manifestations and prognosis, but knowledge about predictive factors is still limited. [11,12]

The study included 46 patients with ALI Rutherford category III who met the inclusion criteria. The majority of patients were female, totaling 31 individuals (67.4%). This finding aligns with a study by Chihade et al., indicating a higher risk of death in female ALI patients. The prevalence of vascular disease increases in women after menopause, and their risk is determined by postmenopausal risk factors. In the United States, 67% of women have one or more major vascular risk factors at menopause, and this percentage increases with age. Hyperlipidemia, diabetes mellitus, hypertension, smoking history, and obesity are strong risk factors for developing vascular diseases. [13]

The mean age of patients in this study was 69 years, consistent with research by Daly[14]

where the average age of ALI patients was also 69 years. Another study by Kulezic et al. showed a median age of 74 years for ALI patients (IQR 66–84 years). The study found a mortality rate of 60.7%, in line with research by Sharath et al.[15] indicating a higher risk of death in patients with ALI Rutherford category III, around 20–50%. [15]

Recent studies indicate a correlation between a high neutrophil-to-lymphocyte ratio and mortality in patients with critical/acute ischemia due to the inflammatory response triggered by ischemic tissue, mediated by neutrophils. [16,17,18] Arbanasi et al. (2022) stated that increased NLR and PLR values before surgery are indicators of poor outcomes in patients with ALI Rutherford category II and III. Ergelen et al. showed that a high NLR (>6.97) is associated with increased in-hospital and long-term cardiovascular death in patients undergoing primary angioplasty. Additionally, NLR is reported as a strong independent predictor of clinical outcomes, including long-term cardiovascular mortality and morbidity after coronary artery bypass grafting and major vascular surgery. [19–21]

Spark et al. indicated that an NLR >5.25 is an independent predictive factor for all-cause mortality (HR 2.3, 95% CI 1.2–4.2; $p < 0.01$) in 149 patients diagnosed with critical limb ischemia (CLI). [22] King et al. suggested that a preoperative NLR >4 is an independent prognostic factor associated with high mortality ($p<0.05$) and low amputation-free survival ($p<0.01$) in 488 patients undergoing percutaneous intervention for femoropopliteal disease.[23] In this study, in line with previous research, the mean NLR value in the group that died or worsened after treatment was 13.75. The correlation test in this study also showed a high correlation between NLR and mortality. Thus, it can be concluded that the higher the NLR value, the higher the mortality rate.

Atherosclerotic disease and chronic inflammation are closely related, with a high white blood cell count associated with negative outcomes in patients with arterial disease. Neutrophils significantly affect the evolution of atherosclerotic plaques, while lymphopenia is a common inflammatory marker. The ratio can provide further information about the number of individual cells, neutrophilia, and lymphopenia. The inflammation imbalance expressed by neutrophils can explain different outcomes despite similar clinical presentations. Acute limb ischemia presents medical and surgical challenges, and decision-making remains difficult even after endovascular therapy. An individualized approach is needed, possibly using a more aggressive strategy for those with high initial neutrophil levels. Considering ease and cost, NLR can be used in preoperative patient stratification into risk groups, correlated with Rutherford classification, for better patient management and predictive hypothesis formation. Moreover, we consider that NLR increases clinical vulnerability to poor outcomes after revascularization, making it the first line in a series of predictable biochemical surveillance. This study suggests calculating NLR before and after thrombectomy and bypass is recommended for vascular care.

The study identified an uneven distribution of data, particularly in laboratory results between the surviving and deceased patient groups. This variability may be attributed to the relatively small sample size, indicating the need for future research with a larger cohort to enhance statistical power and generalizability.

Findings from this study demonstrated a correlation between NLR values and mortality in patients with Rutherford category III ALI. Higher NLR values were associated with an increased risk of death, emphasizing the need for timely clinical intervention. NLR may serve as a valuable tool in preoperative risk stratification, complementing the Rutherford classification to improve patient management and inform predictive modeling. Additionally, elevated NLR levels may reflect increased vulnerability to adverse outcomes following revascularization, supporting its use as an initial marker in biochemical surveillance. Further research involving a larger population and controlling for potential biases is recommended to build upon these findings and refine prognostic assessments.

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Comparison of CONUT Score, SGA Score, and GLIM Score as Gold Standard for Colorectal Cancer Patients

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Abstract

Malnutrition in colorectal cancer increases toxicity, worsens quality of life, and reduces body functions. Early identification of malnutrition is crucial to determine treatments. This study compared the Global Leadership Initiative on Malnutrition (GLIM) score as the standard nutritional status screening tool to the Controlling Nutritional Status (CONUT) and Subjective Global Assessment (SGA) scores. This study expected to identify a new nutritional status screening tool for colorectal cancer patients. This was a cross-sectional diagnostic study on 60 colorectal cancer patients treated at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia from August 16, 2022 to July 16, 2023. Results revealed that the CONUT score had a sensitivity, specificity, accuracy, and effectiveness values of 80.4%, 0.0%, 85%, and 85%, respectively, in detecting malnutrition. The SGA score had a sensitivity value of 100%, a specificity value of 21.95%, an accuracy value of 85%, and an effectiveness of 85% in detecting malnutrition. When compared with the GLIM score as the gold standard, which is assumed to have a sensitivity and specificity values of 100%, the SGA score was better than the CONUT score for detecting malnutrition in colorectal cancer patients. The SGA score is closest to the GLIM score as the gold standard for assessing malnutrition in colorectal cancer patients..

Keywords: Colorectal cancer, controlling nutritional status, global leadership initiative on malnutrition, malnutrition, subjective global assessment

Introduction

Colorectal cancer is one of the leading causes of cancer-related mortality in the United States. Each year, the American Cancer Society provides updated statistics on the incidence and mortality of colorectal cancer using data from population-based registries and the National Center for Health Statistics. In 2020, an estimated 147,950 individuals were diagnosed with colorectal cancer, and approximately 53,200 deaths were attributed to the disease. Notably, this included 17,930 new cases and 3,640 deaths among individuals under the age of 50.

Malnutrition is a condition where the body experiences weight loss and a decrease in the body's working capacity, which impairs quality of life and worsens prognosis.[1] Malnutrition is a serious problem in cancer patients with a prevalence from 20% to more than 70% according to studies worldwide.[2] Malnutrition in cancer patients is caused by cancer-associated inflammatory cytokines, metabolic changes, and reduced nutrient availability, due to anorexia caused by cancer and the systemic treatment. Malnutrition in colorectal cancer can increase the risk of toxicity, worsening quality of life, and reduce body function. Approximately 10-20% of cancer patient deaths are caused by malnutrition, not the malignancy itself. Therefore, the diagnosis of malnutrition must be made as early as possible and the patient immediately receives the best treatment.[1] Nutritional status always changes over time. Therefore, it is important to assess the nutritional status of colorectal cancer patients periodically during various phases of the treatment course.[3]

Nutritional status can be evaluated using various objective and subjective measurement methods. Responding to the need for clinical nutrition assessment, in 2019, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) published

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a consensus namely the Global Leadership Initiative on Malnutrition (GLIM) as the gold standard for assessing nutritional status in adult patients.[4] This study will use the GLIM score as the gold standard in assessing the nutritional status of colorectal cancer.[5] GLIM score has the advantage of being able to completely assess various aspects of a patient. However, it also has shortcomings because it is considered impractical and there are quite a lot of criteria. Also, the degree of malnutrition in GLIM is considered more extreme because it is directly stated as moderate and severe malnutrition, there is no category for mild malnutrition. Therefore, this study investigates the alternative nutritional status screening tools that have good sensitivity, specificity, and accuracy. This study aims to compare the SGA score and CONUT score with the GLIM score to find a faster, more practical, and more accurate screening tool for assessing malnutrition in patients with colorectal cancer.

Methods

This diagnostic study utilized a cross-sectional design involving 60 colorectal cancer patients at Dr. Hasan Sadikin General Hospital, Bandung, from August 16, 2022, to July 16, 2023. The study was conducted following approval from the Health Research Ethics Committee of Dr. Hasan Sadikin Hospital (Ethical Approval Number: LB.02.01/X.6.5/49/2023). Data were obtained through medical record review, patient interviews, and physical examinations. Inclusion criteria comprised patients diagnosed with colorectal cancer, aged over 18 years, who were undergoing chemotherapy and provided informed consent to participate in the study.

The exclusion criteria were patients having malignancy other than colorectal cancer, having undergone laparotomy at the same time as surgery on other parts of the body, and having comorbidities such as diabetes mellitus, liver cirrhosis, and heart and kidney disease were excluded. Informed consent regarding the research and the patient's clinical condition was carried out to the patient or family. The patient's nutritional status is assessed using the GLIM and SGA scores. The patient's blood was taken to check albumin, total lymphocytes, and total cholesterol levels. Then, the patient's nutritional status is assessed using the CONUT score. The CONUT score consists of three assessments, namely serum albumin levels, peripheral lymphocyte counts, and total cholesterol concentrations. The research was conducted until the sample size was met. Patients with incomplete data, patients who had diseases that interfered with nutritional assessment which interfered with nutritional therapy, patients having other morbidities during treatment, and patients who died before or after surgery or chemotherapy were excluded. Data was analyzed using the 29th version of SPSS for sensitivity, specificity, accuracy, and efficacy score.

The SGA score assesses nutritional status based on the patient's medical history and physical examination. The medical history assessment included changes in the patient's weight, gastrointestinal symptoms (anorexia, diarrhea, nausea, vomiting), functional capacity, along with diseases and their relationship to nutritional needs. Physical examination was performed to evaluate subcutaneous fat loss, ankle edema, sacral edema, muscle wasting, and ascites. This assessment will divide patients into good nutrition (SGA-A), moderate malnutrition (SGA-B), or poor nutrition (SGA-C) groups.[6]

Diagnosing malnutrition using the GLIM score is carried out by examining the phenotypic and etiological criteria. An individual is categorized as malnourished if they fulfill at least one phenotypic criterion and one etiological criterion. Phenotypic criteria consisted of undesirable weight loss, low body mass index, and low muscle mass. Etiological criteria consisted of reduced food intake or impaired food assimilation, as well as assessing inflammatory conditions using blood albumin or C-reactive protein (CRP) levels. Only phenotypic criteria are used to determine severity.

Results

A total of 60 colorectal cancer patients were included in this study, with 31 males and 29 females, reflecting an almost equal gender distribution, as presented in Table 1. The average age, weight, and height characteristics of the patients are detailed in Table 2.

All of the patients who were declared as not malnourished by the CONUT score were malnourished according to the GLIM score. Moreover, all patients who were not malnourished according to the GLIM score were diagnosed as malnourished by the CONUT score. Therefore, the CONUT score had a low specificity and negative predictive value (NPV). NPV is defined as the patient who tests negative does not have the disease, while positive

Table 1 Characteristics of Colorectal Cancer Patients in Dr. Hasan Sadikin Hospital

Characteristics	Mean±SD	Median (Min.-Max.)	%
Age	51.87±12.44	51 (20–80)	-
Height	157.03±7.97	158.5 (140–172)	-
Weight	51.51±9.89	50 (29–75)	-
Male Gender	-	-	51.7%

Table 2 Cross Tabulation of GLIM and CONUT Score Results

GLIM	CONUT		Total
	Malnourished	Not Malnourished	
Malnourished	37	14	51
Not Malnourished	9	0	9
Total	46	14	60

predictive value (PPV) is defined as a person who tests positive actually has the disease. This concluded that malnourished patients assessed with the CONUT score might be misdiagnosed as not malnourished. Instead, patients without malnutrition will be misdiagnosed as malnourished by the CONUT score.

All patients who were declared malnourished by the SGA score were also declared malnourished by the GLIM score. Therefore, the SGA score had good sensitivity and Negative Predictive Value (NPV). However, a few patients who were declared malnourished by the GLIM score were also declared malnourished by the SGA score. There were 32 patients among 51 patients who were not detected as malnourished by the SGA score. Thus, the SGA score had low specificity and Positive Predictive Value (PPV).

The results of this diagnostic study are explained in Table 4. In comparison with the GLIM score as a gold standard for diagnosing malnutrition among colorectal cancer patients, the SGA score was far more superior than the CONUT score in terms of accuracy, sensitivity, specificity, and NPV. Sensitivity is defined as the ability of a test to correctly identify those with the disease (true positives), while specificity is defined as the ability of a test to correctly identify those without the disease (true negatives). Accuracy is defined as the overall correctness

Table 3 Cross Tabulation of GLIM and SGA Score Results

GLIM	SGA		Total
	Malnourished	Not Malnourished	
Malnourished	19	32	51
Not Malnourished	0	9	9
Total	19	41	60

Table 4 Diagnostic Value of the SGA and CONUT Score Compared with the GLIM Score as the Gold Standard for Detecting Malnutrition in Colorectal Cancer Patients

Diagnostic Value	CONUT	SGA
Accuracy	85.0%	85.0%
Sensitivity	80.4%	100.0%
Specificity	0.0%	21.95%
Positive Predictive Value (PPV)	72.5%	37.25%
Negative Predictive Value (NPV)	0.0%	100.0%
Likelihood Ratio	0.80	2.28

of a test, measuring how well it distinguishes between diseased and non-diseased individuals.

The CONUT score had higher PPV because the SGA score was only able to detect 19 out of 51 malnourished patients while the CONUT score detected 37 out of 51 malnourished patients according to the GLIM score as gold standard. Nevertheless, the SGA score had a higher likelihood ratio than the CONUT score which had <1 likelihood ratio.

Discussion

Colorectal cancer currently is the second leading cause of cancer deaths worldwide. Patients with colorectal cancer tend to experience high levels of malnutrition due to impaired intestinal function. such as obstruction and malabsorption.[7] This study had equal gender distribution. It shows that the incidence of malnutrition in male and female colorectal cancer patients was equal. This result follows a study by Song et al.,[8] in which the number of malnourished patients with colorectal cancer is relatively equal between male and female patients.The mean age of patients in this study was 51.87±12.44 years, which supports the observation that the incidence of colorectal cancer increases with age, particularly in individuals over 50.[9] The mean height and weight were 157.03±7.97 cm and 51.51±9.89 kg, respectively, which are consistent with the general demographic characteristics of patients in similar studies..

The lack of universal screening tools to assess nutritional status in colorectal cancer patients increased the patient's and hospital's burden. The GLIM score was issued by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) as a gold standard for diagnosing malnutrition in colorectal cancer patients.[5] GLIM proposes a two-step model. the first step is using a validated screening tool. then the second step is the assessment of the malnutrition severity level. However. the GLIM score was impractical. and it had no mild malnutrition criteria. The severity levels are divided into undernutrition and severe malnutrition. In this study. out of 60 patients. 51 patients were diagnosed as malnourished by the GLIM score.

The CONUT score had a low capability in ruling out malnourishment in colorectal cancer patients. There were 9 out of 9 patients who were not malnourished according to the GLIM score but were diagnosed as malnourished by the CONUT score. Therefore, the specificity and the NPV of the CONUT score were 0%. The CONUT score could detect 37 out of 51 malnourished patients. It had a sensitivity value of 80.4% and a positive predictive value of 72.5%.

The Controlling Nutritional Status (CONUT) score has been widely used as a nutritional assessment tool and is known to be practical and accurate. The CONUT score only focuses on assessing laboratory parameters in the patient's blood. As explained beforehand. inflammatory cytokines produced by cancer cells might reduce albumin synthesis. Hence. hypoalbuminemia often occurs in cancer patients. Peripheral lymphocytes. which play an important role in the immune response to tumors. are known to indicate a person's immunological and nutritional status. Lymphocytes create an immune response against cancer cells. so a reduction in lymphocytes results in a reduced ability to destroy tumor cells in the body. Total cholesterol concentration is known as an indicator of a patient's calorie reserves. Total cholesterol levels have been reported to correlate with cancer development because cancer tissue reduces the body's plasma cholesterol levels and caloric intake. Therefore. cancer causes hypocholesterolemia. The CONUT score results were expected to be more accurate because they directly assess the patient's blood parameters. and it is more practical to carry out because there was no need for history taking and physical examination. However. the CONUT score required expensive laboratory costs.[7]

In another way. this study found that the SGA score had 100% sensitivity and 100% Negative Predictive Value (NPV) because all significantly nourished patients diagnosed based on the GLIM score were also labeled nourished by the SGA score. However. it only had 21.95% specificity and 37.25% Positive Predictive Value (PPV) because 32 out of 51 malnourished patients were not detected as malnourished by the SGA score (Table 4).

Subjective Global Assessment (SGA) is a nutritional status screening tool that is often used worldwide. The SGA score was designed to be practical and can be filled in by the patients themselves. The SGA score was quick. easy to interpret. and did not require expensive costs. However. the SGA score had drawbacks. because it does not use laboratory tests for albumin levels or CRP levels in the blood.[10]

Previous studies also found similar results. Rosnes et al. compared the GLIM score with the PG-SGA score in 2021. The GLIM score identified

36% of the patients as malnourished and the SGA score identified 69% of the patients as malnourished.[11] Wang et al. in 2021 also found the SGA score to be similar to the GLIM score.[12]

A limitation of this study is that the severity of malnutrition based on the GLIM score was not analyzed. Additionally, factors that may influence malnutrition status, such as responses to systemic treatments and the stage of colorectal cancer, were not controlled in the inclusion and exclusion criteria. Future studies should explore these factors in greater detail, particularly focusing on the SGA scoring system as an alternative tool for detecting malnutrition in colorectal cancer patients..

This study concluded that the SGA score outperformed the CONUT score when compared with the GLIM score as the gold standard for diagnosing malnutrition in colorectal cancer patients. However, the SGA score demonstrated low specificity and positive predictive value (PPV). Notably, all patients diagnosed as malnourished by the SGA score were also classified as malnourished by the GLIM score. Conversely, patients classified as not malnourished by the SGA score may still be diagnosed as malnourished by the GLIM score. Therefore, patients who are not identified as malnourished by the SGA score should undergo further assessment to avoid the risk of misdiagnosis.

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Success Rate and Complications of Percutaneous Nephrolithotomy (PCNL) in Nephrolithiasis Patients

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Abstract

Percutaneous Nephrolithotomy (PCNL) is the standard management method for kidney stones due to its high success rates. This process is associated with risks, including complications such as infection and bleeding. This study aimed to evaluate the complications and success rates of PCNL in nephrolithiasis patients and provide important insights for clinical decision-making. Data were collected from patients undergoing PCNL for nephrolithiasis at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, in the form of demographic data, stone parameters, and postoperative complications. Data were then analyzed statistically to identify the associated factors. This study was conducted at the Urology Department of the hospital from January to December 2023, involving 80 nephrolithiasis cases. Predominantly, 67.5% of patients were males, with 63.7% in the age group of above 50 years. Multiple stones were the most common (55%), with stone sizes of ≥1.5 cm prevalent in 95% of cases. Left-sided stones (43.8%) were most frequent, followed by right-sided (36.2%) and bilateral stones (20%). Hydronephrosis complications were present in 36.2% of cases, with 100% stone clearance found in Guy Stone Score (GSS) grade 1 cases, while GSS grade 4 cases exhibited the lowest stone clearance rate at 45.4%. This study provided insights into nephrolithiasis demographics, stone characteristics, and postoperative outcomes. Male predominance, multiple stones, high rates of stone clearance, and postoperative complications, particularly in the Guy's score system, underscore the need for proper management strategies and further research in this field.

Keywords: Complication, nephrolithiasis, percutaneous nephrolithotomy, success rate

Introduction

Nephrolithiasis is a urological disorder potentially leading to fatal kidney failure, with a considerable morbidity rate.[1] The prevalence of this disease in the United States has risen from approximately 3% to 10% between 1980 and 2010. However, in Indonesia, nephrolithiasis affects six per 1,000 individuals, which makes the disease the third most common urological condition. Individuals aged 30 to 50 years are most vulnerable to kidney stones, with males being more affected than female.[2-3] While not all kidney stone episodes require treatment, surgical intervention is necessary when stones are symptomatic, causing obstruction, infection, or jeopardizing kidney function.

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Percutaneous Nephrolithotomy (PCNL) is the preferred method for removing kidney stones, specifically those larger than 20 mm or complex ones resistant to other treatments. [1,5-6] Despite the effectiveness, PCNL accounts for only 5% of stone-related procedures due to the invasive nature, higher complication rates, and technical demands compared to other methods, namely ureteroscopy or Extracorporeal Shock Wave Lithotripsy (ESWL). PCNL is associated with various complications ranging from mild, such as fever or nephrostomy tube leakage, to severe, including organ and pleural injuries, as well as bleeding and infection. [1,7-8]

Understanding the success rates and complications of PCNL is crucial for clinicians in selecting the appropriate surgical methods. The modified Clavien complication scale is an effective tool for assessing complex levels. Furthermore, the Guy score system aids in educating patients about stone-free rates and surgical prognosis.[9] PCNL has the highest stone-free rate and lower rates of additional

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procedures, including retreatment, compared to ESWL or other methods.[4,9] A study conducted on 174 patients in Bandung reported stone-free rates following percutaneous nephrolithotomy (PCNL) of 94.7% in the prone position and 91.3% in the supine position.[10] Another study reported stone-free rates ranging from 85% to 93%.[5] Given the variation in reported outcomes, the present research aimed to evaluate the complications and success rates of PCNL in patients with nephrolithiasis. Further investigation was considered necessary, as previous studies did not provide detailed descriptions of the success rates and associated complications.

Methods

This study is a descriptive observational design using a cross-sectional approach, with data collection and measurement conducted at a single point in time. The research was carried out at the Department of Urology, Dr. Hasan Sadikin General Hospital (RSHS), Bandung, from January to December 2023. The inclusion criteria encompassed all patients scheduled to undergo percutaneous nephrolithotomy (PCNL) who provided informed consent. Exclusion criteria included patients undergoing open surgery, individuals with radiolucent stones, pregnant women, patients with comorbid conditions or bleeding disorders, and those who declined to participate.

The minimum sample size of 72 was calculated using the formula for Estimating Population Proportion with Specified Absolute Precision. The subjects comprised all patients diagnosed with nephrolithiasis who met the inclusion criteria and were scheduled to undergo PCNL at the Hospital. The following laboratory tests, creatinine, bleeding, and clotting time, including urine culture, were conducted. Radiological evaluation was performed using various imaging modalities such as Kidney Ureter and Bladder X-ray (KUB), Intravenous urography (IVU), computed tomography intravenous urogram (CT IVU), ultrasonography, or Non-Contrast Computerized Tomography (NCCT) when necessary.

Data collection involved obtaining relevant demographic and clinical information from medical records, including age, gender, stone size and location, comorbidities, intraoperative findings, postoperative outcomes, and complications. Stone size and location were assessed through radiographic imaging and classified using the Guy's Stone Score (GSS). Postoperative evaluation was conducted using a kidney, ureter, and bladder (KUB) X-ray on the first postoperative day. Stone clearance was defined as residual fragments smaller than 4 mm, along with the absence of significant hematuria, and indicated eligibility for nephrostomy tube removal within 48 to 72 hours after the procedure. Foley catheter removal was considered if no urinary leakage was observed from the nephrostomy site after 48 hours postoperatively. Ethical approval for this study was obtained from the Health Research Ethical Committee of Dr. Hasan Sadikin General Hospital, Bandung (Approval Number: DP.04.03/D.XIV.6.5/28/2024). Data processing included verification, coding, entry, sorting, and normalization. Key variables such as age, gender, GSS score, postoperative stone clearance, and operation duration were analyzed. Statistical analysis was performed using SPSS version 22 to identify factors associated with the success of PCNL (stone-free rate) and related complications.

Results

This study examined patient characteristics, including gender, age, stone count, size, location, and the presence of hydronephrosis. The research was conducted over a one-year period, from January to December 2023, at the Department of Urology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung. The study sample comprised 80 individuals diagnosed with nephrolithiasis who underwent PCNL within the specified timeframe and met the predetermined inclusion and exclusion criteria. The table below presents the general characteristics of the study population.

From January to December 2023, a total of 80 nephrolithiasis cases at the Department of Urology, Dr. Hasan Sadikin General Hospital, Bandung, met the inclusion criteria and did not fulfill the exclusion criteria. Among these cases, the majority of patients were male, accounting for 54 individuals (67.5%), while 26 patients (32.5%) were female. The age distribution showed that most patients were over 50 years old, comprising 51 individuals (63.7%). This was followed by 21 patients (26.3%) aged between 40 and 49 years, and 3 patients (3.8%) aged between 18 and 29 years.

The data also showed that the most common stone count was multiple stones, which suffered

Table 1 General Characteristics of the Research

Variables	n (%)	Mean
Gender		
Male	54 (67.5)	(-)
Female	26 (32.5)	
Age		
18-29 Years	3 (3.8)	
30-39 Years	5 (6.2)	
40-49 Years	21 (26.3)	52.85
>50 Years	51 (63.7)	
Stone Count		
Single	36 (45)	
Multiple	44 (55)	
Stone Size		
<1.5 cm	4 (5)	
≥1.5 cm	76 (95)	
Stone Burden	88.196	
Stone Location		
Right	29 (36.2)	
Left	35 (43.8)	
Bilateral	16 (20)	
Hydronephrosis		
Present	29 (36.2)	
Absent	51 (63.8)	
Body mass index		
Underweight	2 (1.3)	23.57
Normoweight	49 (61.3)	
Overweight	24 (30.1)	
Obesity	5 (6.3)	
Stone Composition		
Urea		31.52
Creatinine		2
Calcium		5.015
Phosphate		5.60
Uric Acid		5.67

Table 2 Postoperative Success by Comparing GSS with Stone Clearance

Grade	n (%)	Stone Clearance
1	19 (23.8%)	100
2	30 (37.5%)	66.67
3	20 (25%)	85
4	11 (13.8%)	45.45

by 55%, equivalent to 44 patients. The majority, approximately 95% or 76 patients, had stone sizes ≥1.5 cm. The most common stone location detected in 43.8% or 35 patients was on the left side, followed by the right side, suffered by 36.2% or 29 individuals, and bilateral by 20% or 16 recorded cases. In this research, approximately 36.2% or 29 patients reportedly suffered from hydronephrosis complications. The Postoperative success was examined by comparing the GSS with stone clearance, as shown in Table 2.

Urea shows the highest mean concentration at 31.52, indicating its significant presence in the stone. Uric acid and phosphate have relatively similar mean concentrations of 5.67 and 5.60, respectively, suggesting their notable contribution to the stone's makeup. Calcium has a mean value of 5.015, reflecting its importance in stone formation, while creatinine has the lowest mean concentration of 2.

This study revealed that all patients with GSS grade 1 achieved a 100% stone clearance rate. In contrast, the lowest stone clearance rate, at 45.45%, was observed in patients with GSS grade 4. Postoperative complications were systematically classified using the Clavien-Dindo grading system, a widely accepted tool for evaluating surgical complications. The distribution of these complications is detailed in Table 3, offering a comprehensive overview of postoperative outcomes among the study cohort.

According to Table 3, the majority of postoperative complications were classified as Clavien Grade I, particularly among patients with a GSS of 2, representing 37.5% of the cases. Additionally, 1.25% of patients with GSS grade 1 experienced Clavien Grade III complications. No postoperative complications were recorded under Clavien Grades II or IV.

Discussion

Age is a significant factor in the incidence of nephrolithiasis, with global data indicating the highest prevalence among individuals aged 50 to 60 years, particularly in males.[5] This trend aligns with the findings of the current study, where 63.7% of patients were over the age of 50. The increasing incidence in older age groups may be influenced by occupational factors and lifestyle choices, such as dietary habits, fluid intake, and physical activity levels. However, obesity (BMI≥30 kg/m^2) significantly increased the incidence of nephrolithiasis in the elderly, possibly due to

Table 3 Clavien Scale[11]

Grade	Description
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens: antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. Includes wound infections opened at the bedside.
2	Requiring pharmacological treatment with drugs other than those allowed for Grade 1 complications. Includes blood transfusions, antibiotics, and total parenteral nutrition.
3	Requiring surgical, endoscopic, or radiological intervention.
3a	Intervention under regional/local anesthesia.
3b	Intervention under general anesthesia.
4	Life-threatening complication requiring intensive care/intensive care unit (ICU) management.
4a	Single organ dysfunction.
4b	Multi-organ dysfunction.
5	Patient demise.

Table 4 Postoperative Complications According to the Clavien Scale

Guy Score	Clavien I	Clavien II	Clavien III	Clavien IV
Guy Score 1	22.5% (18)	-	1,25% (1)	-
Guy Score 2	37.5% (30)	-	-	-
Guy Score 3	25% (20)	-	-	-
Guy Score 4	13.75% (21)	-	-	-

heightened levels of uric acid nephrolithiasis in obese individuals. While most patients had a normal BMI, approximately 36.25% had a BMI above the normal range, suggesting a correlation between BMI and nephrolithiasis occurrence. Increased excretion of calcium, oxalate, and uric acid in urine raises the risk of calcium kidney stone formation, as shown by the biochemical profile in this research. [12]

The gender disparity in nephrolithiasis is significant, with a prevalence two to three times higher in men than in women globally.[12] This trend is consistent with the research findings, including investigations conducted in Korea and NHANES data from the United States. However, the prevalence gap between men and women tends to be narrowing over time, with continuous increases observed in females across various analyses and annual cycles.[12] The research findings contributed to this understanding, focusing on a stable male prevalence, but a rising occurrence in females, particularly among those below 60 years. The role of estrogen in reducing kidney stone recurrence in postmenopausal women shows the importance of hormonal factors in nephrolithiasis development. [13]

This research also elaborated on the distribution of stone characteristics, with multiple stones being the most prevalent (44%) and the majority of cases having stone sizes ≥1.5 cm. Compared with a study conducted by Alasker et al.,[15] the mean stone size was 12.2±9.91 mm.[14] In terms of laterality, left-sided stones were more frequently observed than right-sided ones, consistent with findings by Saeed et al.,[16] who reported that 55% of patients had stones on the left side and 45% on the right.Furthermore, hydronephrosis was identified in 36.25% of the patients in this study, reflecting the impact of obstruction caused by nephrolithiasis.. Four patients had bilateral stones.Kidney and ureteric stones were the most common cause of hydronephrosis. Fifty-four percent of adult hydronephrosis patients were caused by kidney and ureteric stones.[17] Stone clearance rates varied across GSS grades, with GSS grade 1 cases possessing a 100% stone clearance rate. However, the lowest, approximately 45.45%, was observed in GSS grade 4 cases, showing the influence of stone complexity on treatment outcomes.

The adoption of standardized assessment systems, such as GSS and S.T.O.N.E. nephrolithometry, was crucial for predicting

treatment outcomes and guiding patient counseling. These systems facilitated uniform reporting and comparison between different surgical methods and institutions.[13] Despite the significance of stone complexity in treatment outcomes, no significant relationship was found between stone complexity and postoperative complications, in line with previous research findings.[18] Further investigation into the predictive value of assessment systems and the impact on treatment outcomes must be conducted to enhance clinical decision-making in nephrolithiasis management.

Thomas et al. reported that GSS had suitable reproducibility with ideal inter-rater agreement. Several research have reported a strong correlation between GSS and stone-free rates. The research reported 81%, 72.4%, 35%, and 29% success rates for GSS 1, 2, 3, and 4, respectively. Other investigations reported stone-free rates ranging from 93.9% to 100%, 85.71% to 97%, 90.17% to 100%, and 60% to 77.77% for GSS 1, 2, 3, and 4. Overall success rates ranging from 62% to 97.73% had been reported in different investigations validating the GSS.[19]

In a retrospective research by Kumsar et al. that compared GSS and S.T.O.N.E., stone-free rates of 90%, 96%, and 34% were obtained in the GSS 1, 2, and 3 groups, respectively. Some investigations have also found GSS based on CT scans to be effective in predicting the success rates of PCNL. Okhunov et al. recently introduced the STONE score, which was validated by retrospective research in predicting PCNL success rates. Additionally, this was supported by only one prospective investigation. [19]

Labadie et al. conducted a retrospective comparative analysis and reported that low GSS and STONE scores were significantly associated with stone-free rates (p=0.002 and 0.004). Furthermore, both systems also correlated with blood loss and length of hospital stay. The assessment systems had effective predictive value for stone-free status. [20,21]

This research reported that most cases experienced postoperative complications at the Clavien I scale, especially 37.5% of GSS 2. Meanwhile, 1.25% of GSS 1 experienced postoperative complications on Clavien III scale. No cases of postoperative complications at the Clavien II or IV scales were found. According to Shaheem et al., [22] complications after PCNL measured based on the significantly modified Clavien Dindo scale were associated with GSS and STONE scores of p-value=0.007 and 0.005, respectively.

Thomas et al. reported no significant association between GSS and complications following PCNL. Similarly, Noureldin et al. found that neither the GSS nor the STONE score correlated with intraoperative complications. In contrast, Vicentini et al. demonstrated a significant association between GSS and post-PCNL complications. Furthermore, Singla et al. identified only a weak correlation between all three assessment systems (GSS, STONE, and CROES) and the modified Clavien-Dindo classification of complications.[19,22]

GSS is a simple and reliable tool for predicting success rates. It is mainly used in kidney, ureter, bladder (KUB), and intravenous urography (IVU) films to predict success rates after PCNL. The GSS and STONE scores effectively predicted stone-free (SF) status (AUCs: 0.68, 0.72) and correlated with perioperative complications. Overall complication rates (modified Clavien) were lower compared to Thomas et al. and Okhunov et al.[23] CROES PCNL showed 75.5% SF and 20.5% complication rates, with 3.1% requiring transfusions.

Lojanapiwat et al. reported that GSS based on KUB and intravenous urography was a valuable tool in predicting outcomes and complication rates after PCNL through the upper pole. Direct success rates, operation time, tubeless or uncomplicated procedure rate, and major complications differed significantly in each GSS group.[24]

In conclusion, this study observed a male predominance among PCNL patients, accounting for 67.5% of the study population, with the majority of cases occurring in individuals over the age of 50. Most patients presented with multiple stones, typically measuring ≥1.5 cm in size. Left-sided stones were more frequently encountered than right-sided or bilateral stones. Postoperative complications were common, with the majority classified as Clavien grade I, indicating predominantly minor surgical outcomes.

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CASE REPORT

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A Case Study of Psoriasis Vulgaris After COVID-19 Vaccination in Saudi Arabia

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Abstract

Since the COVID-19 vaccines have been approved, worldwide reports of adverse events have been reported. Although a few cases of Psoriasis vulgaris have been reported after COVID-10 vaccination, there is currently limited evidence to establish a direct relationship between the vaccine and this condition. A 27-year-old Saudi woman, previously healthy and had no medical issues, reported skin lesions on her lower legs, which she noticed ten (10) days after receiving the first dose of the Pfizer COVID-19 vaccine. The patient had no prior history of such lesions or any family history of psoriasis. Joint pain was not observed. A diagnosis of psoriasis vulgaris was made, and the patient was treated with Daivobet® cream, urea cream 10%, and full-body NB-UVB light therapy three times a week for up to two months. The patient's condition improved partially. This report presents the first known case of psoriasis vulgaris after the COVID-19 vaccine in the Middle East. Further research is needed to fully understand this connection. The study emphasizes the significance of a thorough medical history and evaluation for precise diagnosis and treatment.

Keywords: COVID-19, drug-related side effects and adverse reactions, SARS-CoV-2, vaccines, vulgaris

Introduction

Psoriasis is a chronic, inflammatory skin condition caused by the immune system. This condition can significantly negatively impact a patient's overall quality of life.[1] The WHO classified this disease as a non-curable, chronic disease with no typical clinical presentation in 2016.[2] There are several clinical classifications of psoriasis, and different subtypes include plaque, flexural, guttate, pustular, and erythrodermic. Plaque psoriasis is the most widespread type of psoriasis, which is distinguished by well-defined salmon pink plaques with silvery-white scale, sometimes in an asymmetrical pattern, and affecting the extensor surfaces, notably the elbows and knees, trunk, and scalp.[3] Skin scaling is the most common symptom of psoriasis, followed by itching and erythema. Fatigue, swelling, burning, and bleeding are also reported in some cases.[4] Psoriasis can affect people of any age, and there is no significant difference in the prevalence or incidence of psoriasis between males and females.[5] The prevalence of psoriasis varies across countries, and its rate ranges from 0.33% to 0.6% in different races, estimated to be around 125 million people worldwide.[6]

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In Saudi Arabia, the prevalence of psoriasis is 5.7%.[7] Individuals with psoriasis are reported to be more likely to have obesity, cardiovascular disease, non-alcoholic fatty liver disease, diabetes, and metabolic syndrome than the general population.[8] In addition, mental health issues, including anxiety and depression, are higher among patients with psoriasis than in the general population.[9]

It is widely believed that psoriasis results from genetic and environmental factors. Various triggers, such as stress, skin injuries, infections, medications, or vaccination, can exacerbate the condition.[10,11] The relationship between vaccines and psoriasis onset or flare-up has been described previously, including psoriasis triggered by influenza (H1N1), pneumococcal pneumonia, tetanus-diphtheria, and yellow fever vaccines.[11,12]

Several COVID-19 vaccines have recently proven their effectiveness and safety in trials; some vaccines have been authorized to be used to prevent COVID-19 infection.[13] COVID-19 side effects have been reported, with pain at the injection and headaches as some of the common ones.[14,15] However, rare adverse events, including cutaneous side effects related to the COVID-19 vaccine, have also been reported, including the exacerbation of psoriasis plaque.[16] While data on the safety of COVID-19 vaccines in patients with psoriasis is limited, previous studies reporting flare-ups and new onsets of psoriasis after the COVID-19 vaccination have been reported.[16,17] According to the Center for Disease Control (CDC) Vaccine Adverse Events Reporting System (VAERS) data, the occurrence of psoriasis after the administration of the COVID-19 vaccines is around 244 cases of a total of 207,302 COVID-19 vaccine adverse effects (0.11%).[18] Reports on the flare-up and new onset of psoriasis post-COVID-19 vaccination in the Middle East and Saudi Arabia are limited. Therefore, this study aimed to present the case of a female patient who developed psoriasis vulgaris after receiving COVID-19 vaccination.

Case

A 27-year-old female patient from Saudi Arabia with no previous health issues reported skin lesions on her lower legs about 10 days after receiving the first dose of the Pfizer COVID-19 vaccine. The patient's condition worsened over time, with the emergence of scalier beefy red lesions that spread to her trunk and caused itching. The patient had no family history of psoriasis or similar lesions and did not experience joint pain on physical examination. Blanchable erythematous papules and plaques with silvery-white dry scaling of various sizes were present on her trunk, legs, and hands (Figure 1).

Some of her nails had pitting, but her joints were not affected (Figure 2). Blood test results were normal. Punch Skin biopsy revealed focal parakeratosis with entrapped neutrophils.

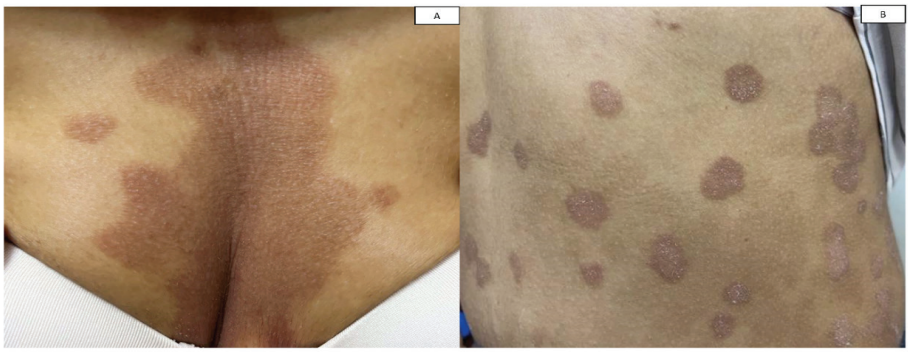

Figure 1 Several Blanchable and Well-Defined Borders Papules and Plaques are Observed on the (A) Chest, (B) Abdomen, And (C) Leg. These areas also have dry, silvery-white scaling of various sizes. The patient has developed clearly defined papules and plaques with redness and dry scaling on their upper extremities. Nail pitting (D) has been observed on some of the fingernails

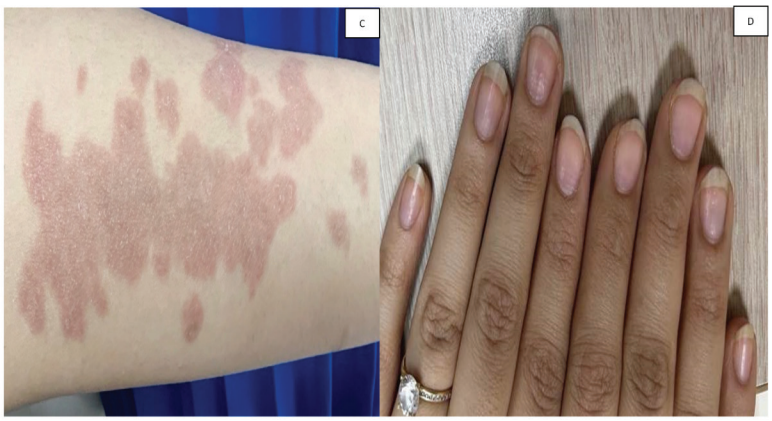

Figure 2 Well-defined Erythematous Papules snd Plaques With Dry Scaling sre Found Over the Upper Extremities (c); Nail Pitting Appears in Some of the Patient's Fingernails (d)

The patient was diagnosed with plaque psoriasis and was treated with Daivobet® cream and urea cream 10%. Full-body narrowband ultraviolet B (NB-UVB) light therapy was administered three times a week for up to two months. The patient reported a partial resolution of psoriasis during her outpatient clinic visits, with most of the lesions disappearing.

Discussion

This report describes a case of a 27-year-old Saudi female patient, previously healthy and free from any medical complaints, with a chief complaint of skin lesions on her lower legs after receiving the first dose of Pfizer COVID-19 vaccine. Later the patient was diagnosed with psoriasis vulgaris. It is imperative to thoroughly analyze this case report due to the insight it provides into a potentially uncommon adverse event that may occur subsequent to receiving the COVID-19 vaccination. Comprehending such incidents is critical for healthcare professionals in order to promptly identify and manage analogous cases. Moreover, it underscores the significance of surveillance and communication regarding adverse events in order to bolster the safety of vaccines and instill public trust in vaccination initiatives.

In this case report, we diagnosed an adult patient with de novo psoriasis vulgaris. The condition appeared ten (10) days after receiving COVID-19 vaccine. Psoriasis cases resurfacing after immunization have been documented, despite the rare occurence. Previous studies have reported psoriasis symptoms in people aged 65 to 89 following COVID-19 vaccination (Table 1).[16,17,19]

These studies suggest that aging may contribute to a weakened immune system, leading to susceptibility to inflammation and infectious diseases as the protective immunity deteriorates over time. [20] However, this present study represents the first case report of de novo psoriasis in adult non-psoriatic patients following COVID-19 vaccination in Saudi Arabia. In this study, the brand of the vaccine received Pfizer. However, other studies reported different brands of COVID-19 vaccine, including Pfizer, AstraZeneca vaccine, and mRNA-1273 vaccines. Unlike most other reported studies, in the case of this study, the patient's symptoms started to appear after the first dose of the vaccine. The patient was diagnosed with a new onset of psoriasis, like previous studies conducted in India, Vietnam, and the United States. However, due to geographical differences, there is not enough evidence to suggest a correlation between the vaccine and any skin condition. Psoriasis is an immune-mediated inflammatory skin disease affected by several triggers comprising a combination of immune, genetic, and environmental factors.[3,21] Accordingly, the Pfizer COVID-19 vaccine, which targets the immune system, has an associated potential trigger with the new onset of psoriasis, as reported in three previous studies.[12,17,19] Unfortunately, there is no well-understood pathophysiology for new-onset psoriasis following vaccination. However, the increase of interleukin-6 (IL-6) and T-helper17 (Th17) cells after COVID-19 mRNA vaccinations has been shown to play an essential role in the pathogenesis of the disease [22]. Similarly,

Table 1 Summary of Cases Reported in the Literature Review

Study	Nagrani et al.[16] (2022)	Wei et al.[14] (2022)	Tran et al.[17] (2021)	
No. patients	1	1	2	
Gender	Male	Male	Male	Female
Age	65	89	51	68
Type of vaccines	Oxford-AstraZeneca /Covishield)	mRNA-1273 vaccine	AZD1222 vaccine	mRNA-1273 vaccine
Vaccine shot to observe symptoms	2	2	1	3
Days of onset	10	24	7	30
Physical finding	scaly erythematous papules and plaques over the trunk and extremities	Scalp, torso, arms, legs 60% BSA.	blanchable erythematous demarcated papules and plaques with silvery-white dry scaling were found on his scalp, legs, and hands. Some of his nails had onycholysis and subungual hyperkeratosis	erythematous demarcated papules and plaques and scaling on trunk and extremities with mild onycholysis
Type of lesions	new-onset of plaque psoriasis	new-onset of plaque psoriasis	new-onset of plaque psoriasis	new-onset of plaque psoriasis
Treatment	Apremilast (10 mg on a day one, increased to 30 mg twice daily by day 7), antihistamines and emollients	Ixekizumab Acitretin 25 mg.	Topical calcipotriol/ betamethasone antihistamines.	
History of COVID	Unknown	No	No	No
Medical history	No	No	Hypertension was a 35-pack-year smoker, and drank alcohol occasionally	Hypertension

previous studies show a significant increase in the production of IL-6 and, in turn, the cellular development of Th17 following BCG, tetanus-diphtheria, and influenza vaccines.[23] In addition, a prominent study area showed that innate and adaptive immune systems are thought to be at the root of the psoriasis pathogenesis.[24] It shows a complicated interaction between dendritic cells, T cells, and keratinocytes, which explains the underlying cause of psoriasis, with the IL-23/Th17 axis being the central driver of immune activation, chronic inflammation, and keratinocyte proliferation.[25]

Based on the severity classification of the patient's psoriasis, it is considered a mild to moderate case. The chosen treatment options include Daivobet® cream, which is a topical corticosteroid (betamethasone dipropionate 0.5 mg/g), combined with a topical vitamin D3 analog (calcipotriol 50 µg/g) for four (4) weeks. Additionally, applying urea cream 10% as a moisturizer and undergoing a full-body NB-UVB light therapy three times a week for up to 2 months is recommended. However, there are currently no recommendations for treating psoriasis that appears specifically after COVID-19 vaccination.

Sharing information about COVID-19

vaccination and its impact on dermatological features across regions is paramount. Our observations indicate psoriasis may be a potential clinical manifestation following the COVID-19 vaccine. Nevertheless, the limited data availability for this association necessitates further research for comprehensive exploration of this condition. Further research is crucial to gain a comprehensive understanding of the potential risks and contradictions associated with the COVID-19 vaccine.

In conclusion, the first known case report of psoriasis vulgaris occurring after receiving the COVID-19 vaccine in the Middle East is presented in this case study. Further investigation is necessary to determine any potential connection. This study emphasizes the significance of a comprehensive medical history and assessment for precise diagnosis and treatment.

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