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Original Research

LONGER LAG TIME IN EARLY-STAGE RETINOBLASTOMA

Anindya Citra[1], Budi Utomo[2], Hendrian Dwikoloso Soebagjo[3,4]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Doctoral Medical Sciences Program, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

ABSTRACT

Retinoblastoma is a rare neoplasm disease that occurs in children, generally under the age of two. Retinoblastoma is more prevalent in developing countries and is often associated with a late diagnosis. Such delays can lead to a poor prognosis. The time from the appearance of symptoms of retinoblastoma (onset) to the time of diagnosis is called lag time. Early diagnosis of retinoblastoma by paying attention to factors such as age, clinical symptoms, and laterality can help improve retinoblastoma survival rates, especially in developing countries. The purpose of this study was to analyze the relationship between the lag time to the stage of retinoblastoma patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. This study was a retrospective analytical observational study using secondary data from retinoblastoma patients at the Ophthalmology Outpatient Unit at Dr. Soetomo General Academic Hospital, Surabaya, from January 2014 to December 2018. The data were analyzed using Kendall's tau-C test. No significant correlation was found between lag time and stage (p = 0.339). Patients with International Retinoblastoma Staging System (IRSS) I stage had the longest lag time (on average 28 months), and patients with stage IVB had the shortest lag time (on average four months). There was no correlation between lag time and retinoblastoma stage. However, there was a trend of patients with early stages delaying hospital visits, while patients with advanced stages in earlier to the hospital.

Keywords: *Retinoblastoma; lag time; IRSS stage; disease; neglected disease*

Correspondence: Anindya Citra, Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. E-mail: anindya.citra-2017@fk.unair.ac.id

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Highlights:

1. Patients with IRSS I stage have the longest lag time than IVB stage.
2. Lag time is no significant with stage retinoblastoma.

INTRODUCTION

Cancer is the prominent cause of death in children. In high-income countries, the survival rate of cancer in children reaches 80%. Concurrently, in low and middle-income countries, the survival rate is only 25% (Kellie & Howards 2008). The most frequent cancer for children is retinoblastoma (Mattosinho et al. 2019). Retinoblastoma can be found in 1 out of 20,000 live births (Dimaras et al. 2012). Retinoblastoma causes account for 2% of all cancer in children. The disease is mainly found in children under five years old, with a five-year survival rate of approximately 94% (Hewitt et al. 2003).

The most common symptoms linked to Retinoblastoma are leukocoria and squint eyes (Mattosinho et al. 2019). Symptoms during the intraocular stage are more difficult to recognize. As the disease progresses, the tumor in the eye worsens (Ortiz & Dunkel 2015). Cases in developing countries are primarily at the extraocular stages due to metastasis, subsequently causing mortality (Navo et al. 2012).

Retinoblastoma is often associated with a late diagnosis, which causes delays that may lead to a poor outcome (Brasme et al. 2012). The interval between the first appearance of symptoms and the time of diagnosis is called lag time. Based on research conducted in China, the duration of lag time in extraocular tumors is more significant than in intraocular tumors. Furthermore, extraocular tumors are related to unfavorable prognoses (Chang et al. 2006, Gao et al. 2016). These tumors can cause various complications, from vision loss to death (Shields & Shields 1993).

Retinoblastoma is more prevalent in children living in developing countries (Chintagumpala et al. 2007). The incidence of retinoblastoma accounts for the highest mortality rate in Taiwan due to a high number of parents stalling or denying therapy (Chang et al. 2006). Meanwhile, retinoblastoma's incidence in Indonesia is still unknown due to the lack of epidemiology research regarding this disease. Early diagnosis of retinoblastoma by noting factors such as age, clinical symptoms, and laterality can help improve the survival rate of retinoblastoma, especially in developing countries (Maki et al. 2009, Naseripour et al. 2009). This study aimed to find the relationship between lag time and stage in retinoblastoma patients.

MATERIALS AND METHODS

This study was a retrospective analytical observational study using secondary data. The inclusion criteria were retinoblastoma patients at the Ophthalmology Outpatient Unit in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2014 to December 2018. Lag time data was categorized into 5 groups; ≤1 month, >1 month - 6 months, >6 months - 12 months, >12 months - 24 months, and >24 months. The stages were grouped based on IRSS staging; groups I, II, III-A, III-B, IV-A, and IV-B. The correlation between lag time and staging was statistically analyzed using Kendall's Tau-c.

RESULTS

A total of 42 medical records were collected from the Ophthalmology Outpatient Unit. Out of those, 11 medical records had insufficient data, while 2 medical records were later diagnosed not as retinoblastoma. These data did not meet the criteria for sample inclusion. Therefore, the samples that fit the inclusion criteria were 29 samples. Subjects consisted of 14 males and 15 females. The average age of the subjects was 34.59 months (range 4 - 83 months). These patients originated from several regions in East Java and East Indonesia. As shown in Figure 1, no remarkable differences in cases are found in each region. The highest number of patients came from Gresik, Probolinggo, and East Kalimantan.

Table 1. Distribution of lag time and staging of retinoblastoma patients

Parameter	Frequency	Percentage (%)
Lag time		
≤1 month	3	10.3
>1 – 6 months	9	31.0
>6 – 12 months	7	24.1
>12 – 24 months	6	20.7
>24 months	4	13.,8
IRSS staging		
I	3	10.3
II	6	20.7
III A	10	34.5
III B	6	20.7
IV A	0	0
IV B	4	13.8
Total of patients	29	100

Table 1 shows the frequency of patients based on lag time and staging. The shortest lag time was found in patients with a lag time of ≤1 month with an occurrence of 10.3%, while the longest lag time was found in patients with a lag time of 1-6 months and 31.0% of incidents. The average lag time in this study was 11.45 months (ranging from 1-36 months). The average duration of lag time for IRSS stages I, II, III-A, III-B, and IV-B were 28.0, 6.0, 12.4, 10.8, and 4 months, respectively. Most patients were categorized into stage III-A (34.5%), followed by stages II and III-B with 20.7%.

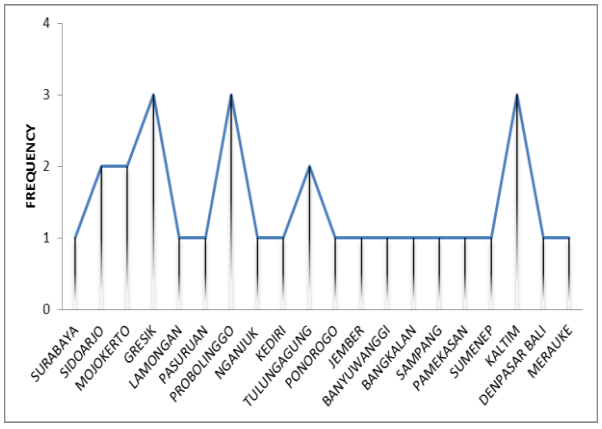

Figure 1. The frequency of cases per region in Dr. Soetomo General Academic Hospital

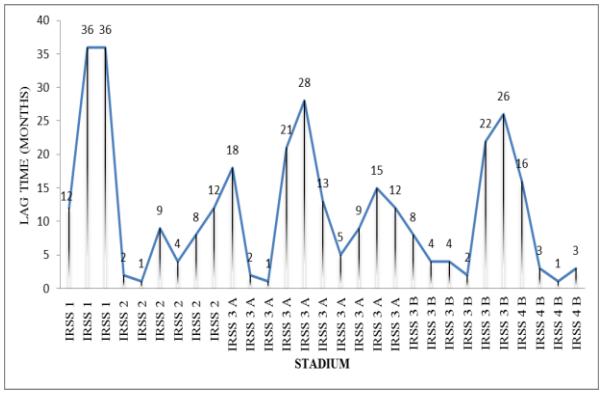

Figure 2. Lag time and stage of each retinoblastoma patient based on IRSS staging

Figure 2 illustrates the lag time and stage of each patient. The highest lag time duration was found in patients with stage IRSS I. Meanwhile, the shortest lag period was found in patients with stage IV-B. The correlation between lag time and the stage was tested using Kendall's Tau-c test. In this study, the result showed p=0.339, r=0.134, which indicated no relationship between lag time and stage.

DISCUSSION

Leukocoria is an early symptom most commonly found in retinoblastoma patients. Leukocoria is an abnormal white reflex in pupils that occurs due to light reflection from retinal lesions. Besides leukocoria, the second most frequent early symptom in retinoblastoma is strabismus (Balmer & Munier 2007). Retinoblastoma can precipitate strabismus if a mass interferes with vision (Murthy et al. 2004). Strabismus is the misalignment of the eyes. In most people, unevenly aligned eyes are visible, making them easy to detect (Helveston 2010).

In this study, 28 children (96.6%) out of 29 children with retinoblastoma had an early symptom of leukocoria according to their anamnesis. The other patient came in with an early symptom of no response to light. Research in India found that the frequency of leukocoria was as much as 98% (Sahu et al. 1998), 87% in Ghana (Essuman et al. 2010), 50% in Singapore (Aung et al. 2009), and 65% in America (Butros et al. 2002). Meanwhile, strabismus was found in 9 retinoblastoma patients (31%) in this study, as compared to research in Iran with an incidence of 28.2% (Naseripour et al. 2009), 6.6% of the incident happened in Singapore (Aung et al. 2009), and 26% in America (Butros et al. 2002). There were no recorded data regarding the type of strabismus in this research. Another study found that exotropia was the most common type of strabismus in retinoblastoma patients. At the same time, it was also found to be the most prevalent type (67%), followed by esotropia (13%), and combined with vertical strabismus (10%) (Fabian et al. 2017). Exotropia was also the most frequent (62%), followed by esotropia (28%), and an alternate exotropia/ esotropia type (10%) (Fabian et al. 2018).

In low-income countries, retinoblastoma can occur accompanied by apparent extraocular symptoms (Chantada et al. 2006). In some patients, advanced symptoms appear in the period from the first appearance of the symptoms to the time of diagnosis. Proptosis (44.8%) and red eyes (37.9%) were symptoms that were often found when patients visited the Ophthalmology Outpatient Unit at Dr. Soetomo General Academic Hospital. This finding was comparable to a study of 23 patients in Ghana, which found 34.8% proptosis and 21.7% red eyes (Essuman et al. 2010). All patients with proptosis have extraocular tumors, while those with red eyes can have both intraocular and extraocular tumors. One patient from our study initially came in with an intraocular tumor, decided not to undergo eye enucleation, and tried alternative treatments. When the patient returned to the hospital a few months later, the patient's tumor had progressed to proptosis. The tumor protruded outside the eyeball, a similar finding reported in Reddy's research (Reddy & Anusya 2010).

IRSS staging was used to classify stages of intraocular and extraocular retinoblastoma (Chantada et al. 2006). Patients with enucleated eye were grouped into stage I category, retinoblastoma patients who had been enucleated and followed by chemotherapy were grouped into stage II, retinoblastoma patients with tumors that had metastasized out of the eyeball were grouped into stage III-A, retinoblastoma patients with metastasis to lymph nodes into stage III-B, patients with hematogenous metastasis stage into IV-A, and patients with metastasis to brain tissue were grouped into stage IV-B.

IRSS is a staging system created in 2006, covering the entire stage of retinoblastoma, unlike Reese-Ellsworth (Reese & Ellsworth 1963) and Murphree's IIRC, which can only be used for intraocular retinoblastoma (Dimaras et al. 2015). In addition, IRSS also considers tumor extension or metastasis along with a response to therapy into stage classification (Chantada et al. 2006). Therefore, this staging system is the most appropriate classification for the data in the medical records at Dr. Soetomo General Academic Hospital.

Our study found no significant correlation between lag time and the stage (p=0.339), although we noted that patients with IRSS stage I had a significantly longer average lag time than those in IRSS stage IV-B. Therefore, there was a tendency for the early stage to be presented late, while the advanced stage had the earliest presentation. This study's results followed a study by Posner et al. (2017). Meanwhile, Faranoush et al. (2014) found a significant link between lag time and IIRC tumor grouping. Another study found a link between lag time and mutated retinoblastoma (IRSS stage IV) (Rodrigues et al. 2004). It can be assumed that other factors were involved beyond this research's scope. Parents' awareness and knowledge of this disease, the doubts and fears in undergoing enucleation or exenteration, and economic difficulties may contribute to the lag time (Xiao et al. 2019). The laterality of the disease was found to have an effect in the relationship between lag time and disease staging but only found in patients with bilateral retinoblastoma.

In this study, there was no correlation between lag time and staging in unilateral disease. Another factor taken into consideration was the family's socioeconomics. However, socioeconomic factors were found not to correlate with lag time, but there was a relationship between socioeconomic factors and the advanced disease (Ramirez-Ortiz et al. 2014).

Strength and limitation

This study might not be perfect due to the small number of samples. Also, some medical records contained a lack of information required. The medical record data were taken only from the Ophthalmology Outpatient Unit at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. In addition, the stage used was only IRSS due to a lack of data to classify according to the Reese-Ellsworth classification.

CONCLUSION

No correlation between lag time and retinoblastoma stage was found in this study. However, this study could reveal a trend where patients of stage I demonstrated the longest lag time duration, and the shortest duration of lag time was demonstrated by patients with the most advanced staging of IRSS.

Acknowledgment

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

All authors conceived the idea of the study, analysis data, study design. Ac revised the manuscript. BU and HDS have final content.

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Original Research

THE EFFECT OF DICLOFENAC SODIUM ON CALLUS FORMATION IN WHITE MALE RAT (*Rattus norvegicus*) CRURIS FRACTURE HEALING

Herry Wibowo[1], Prihartini Widiyanti[2]
[1]Physiology Laboratory, Department of Biomedicine, Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia
[2]Biomedical Engineering Study Program, Department of Physics, Faculty of Science and Technology, Universitas Airlangga/Institute of Tropical Disease, Universitas Airlangga, Indonesia

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac sodium, are standard treatments to relieve pain associated with bone fractures. The bone healing process consists of four stages: inflammation, soft callus formation, complex callus formation, and bone remodeling. Previous studies mentioned that intake of NSAIDs (sodium diclofenac) could inhibit the bone healing process. This study examined the effect of diclofenac sodium intake on callus formation in fracture healing. In this study, thirty-six rats (Rattus Norvegicus) with fractures were used and divided into two groups, namely 18 rats for the control and 18 rats for the treatment group. In the treatment group, each rat was given 1.8 mg sodium diclofenac/150 grams of body weight per day. In the control group, each rat was given CMC-Na 0.5% with equal volume as diclofenac sodium in the treatment group. After 28 days, all the rats were stunned until dead, and the diameter and strength of their calluses were measured. In the treatment group with diclofenac sodium1.8 mg/ 150 grams BW/ 28 days after the tibia bone callus was pressed using the Shimadzu tool, the lowest callus strength was found to be 56.500 N, and the highest callus strength was 59.000 N. The lowest callus diameter in the treatment group was 4 mm, the highest was 5 mm. In the control group, the lowest callus strength was 76 N, and the highest callus strength was 77 N. The lowest callus diameter in the control group was 6 mm, and the highest was 8 mm. The strongest callus in the treatment group was found in the ^{sixth} observation, with a value of 59 N and a diameter of 4 mm. In the control group, the highest callus strength was 77 N, with a diameter of 7-8 mm. These measurements were found on the 5^{th}, 7^{th}, 8^{th}, 9^{th}, 16^{th}, and 17^{th} observations. Diclofenac sodium with a dose of 1.8 mg/150 grams of body weight could decrease the callus quality parameters, such as callus strength and diameter on fracture healing.

***Keywords**: Bone fracture; sodium diclofenac; Rattus norvegicus; callus strength; callus diameter*

Correspondence: Herry Wibowo. Laboratory of Physiology, Department of Biomedicine, Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia. Email: drherrywibowo@staff.ubaya.ac.id

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Highlights:

1. Sodium diclofenac is one of NSAID a common treatment to relieve pain associated with bone fractures.
2. Sodium diclofenac with a some dose of body weight could decrease the callus quality on fracture healing.

INTRODUCTION

In daily practice, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain due to fractures (Akman et al. 2002). In America, more than 35 million NSAIDs are prescribed each year, and more than 1% of the population in America uses NSAIDs. In Australia, more than 20% use NSAID drugs as anti-pain and anti-inflammatory drugs.

Bone fracture cases usually happen with pain. Thus, NSAIDs, such as diclofenac sodium, relieve pain, heat, and swelling through prostaglandin synthesis inhibition (Maroon et al. 2010). The oral application of diclofenac sodium significantly extends the fracture healing period (Bissinger et al. 2016).

Prostaglandins are formed mainly in the fracture site in the inflammation and soft callus formation stage. They are formed in the healing process, stimulate osteoclast accumulation, and increase activity (Lisowska et al. 2018). Cyclooxygenase (COX) is a rate-limiting enzyme that converts arachidonic acid to prostaglandin H2 as the precursor of several molecules, including prostaglandins, prostacyclin, and thromboxanes (Moro et al. 2017). Diclofenac sodium intake inhibits the cyclooxygenase enzyme. In a previous study, NSAID intake interfered with fracture healing (Suhana 2002). NSAID was caused by the disruption of osteoclast and osteoblast activities which decreased callus quality and fracture healing. Mefenamic acid intake for handling pain associated with fracture inhibited prostaglandin synthesis (Kress et al. 2016).

Tissue damage and hematoma are present in the fracture site. Prostaglandins are formed in the inflammation stage (Phase II). They are also secreted in the soft callus stage (Phase III). The prostaglandins increase osteoclast activity and stimulate new osteoclast accumulation. Dead bone tissue is cleaned from the fracture site and followed by new blood vessel formation, osteoblast placement, active substance release, and new bone matrix formation. Osteoblast activity is preceded by osteoclast activity, and if there is a disturbance in osteoclast activity, osteoblast activity is disturbed, too (Shapiro et al. 2014).

Diclofenac sodium intake inhibits osteoclast activity. It can disturb the osteoblast placement. This study observed the effect of diclofenac sodium intake on callus formation in fracture healing and proved that diclofenac sodium intake could decrease callus quality (diameter and strength) of cruris fractures in rats. The significance of this study was related to the scope of the role of diclofenac sodium in bone healing. Therefore, this study focused on diclofenac sodium's physiological and pharmacologic role in bone healing.

MATERIALS AND METHODS

Data from experimental research on the effect of diclofenac sodium on callus quality on fracture healing of male white rat cruris were the result of measuring the strength and weight of tibia bone callus in experimental animals were measured using Shimadzu and Spencer's Dissecting microscope. The data were described and processed using the SPSS 10.0 program. Group 1 received treatment with diclofenac sodium 1.8 mg/200-grams BW/ day for 28 days. Group 2 was the control group.

Table 1. Descriptive data of callus strength (N) and callus diameter (mm) from the treatment group and control group

	Treatment group	Control group
Lowest callus strength	56,500 N	76,000 N
Highest callus strength	59,000 N	77,000 N
Mean of callus strength	57,556	76,556
Standard deviation of callus strength	0,684	0,379
Lowest callus diameter	4,000 mm	6,000 mm
Highest callus diameter	5,000 mm	8,000 mm
Mean of callus diameter	4,556	7,333
Standard deviation of callus diameter	0,511	0,594

Table 1 explains that the lowest callus strength measured in observations made in the treatment group was recorded at 56.5 N, while in the control group was recorded at 76 N. In the observations to measure the highest callus strength recorded in the treatment group, it was 59 N. In contrast, in the control group, the highest strength was recorded at 77 N. The data for the lowest callus diameter in the treatment group was recorded at 4 mm and the control group was 6 mm. In contrast, the highest callus diameter observed in this study obtained 5 mm in the treatment group and 88 mm in the control group. In this study, diclofenac sodium concentration was the free variable. Callus diameter and strength were the bound variables. The control variables were the animal type, gender, physical condition, and animal care. The body weight of the animals was the moderate variable.

The treatment and care of each rat were carried out in a 30x20x15 cm cage. The cage was made from plastic and closed by woven wires. Each cage had husk bedding. Every day, the husks were replaced to keep the cages clean. Thirty-six rats were randomly allocated into two groups: group 1 as the treatment group and group 2 as the control group, with 18 rats in each group.

The intake of 1.8 mg sodium diclofenac/150-grams of body weight per day (Reynolds 1993) was performed in the treatment group, while the control group was treated with CMC-Na 0.5%. Diclofenac sodium was given by sonde by using a size 8 nasogastric tube. The sonde was inserted through the rat’s mouth to the stomach. The drug solution volume given to each animal was 2 ml (Donatus & Nurlaila 1986).

All thirty-six rats were stunned with an ether solution in a hood. Anesthesia was performed with a titration method. The anesthesia began 2 minutes after the rats closed their eyes and slowed their movements. Then, the factorization and immobilization of one side of its lower limbs were performed.

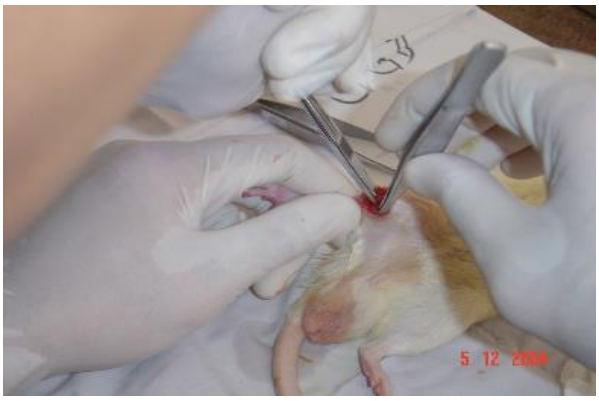

Figure 1. Fracture making process of the tibial bone of the rat

After factorization, group 1 was given 1.8 mg sodium diclofenac/150-grams daily by sonde. The duration of the intake was 28 days. Group 2 was treated with a placebo solution of CMC-Na 0.5% using sonde with the same volume as the diclofenac sodium in group 1. On day 28, all rats were sacrificed with stunning (inner anesthesia) until the rats died. Furthermore, the diameter of each callus was measured in millimeters with a dissecting microscope Spencer® type 501909 manufactured by American Company Instrument Division Buffalo, New York, USA. The strength of each callus was measured with Shimadzu Autograph in newtons (N). The Ethical Committee had approved this protocol of the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia.

RESULTS

The callus strength was calculated using a three-point bending test to find the perpendicular load. The lowest callus strength in the treatment group was 56.5 N, while the control group was 76 N. The highest callus strength in the treatment group was 59 N, while the control group was 77 N. The average callus strength of the treatment group and the control group were 57.556 N and 76.556 N, respectively (Figure 2). The standard deviations of callus strength in the treatment and control groups were 0.684 and 0.379.

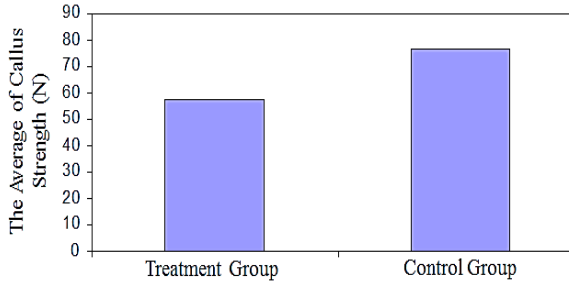

Figure 2. The results of callus strength

The callus diameter was obtained by measuring the distance between two calli through their center.

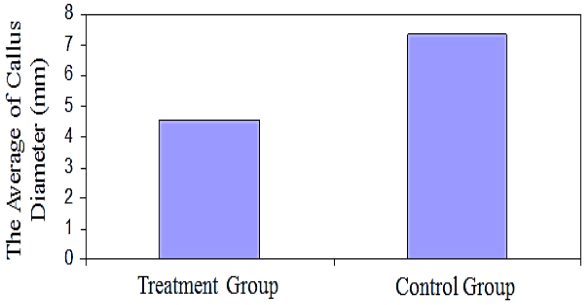

Figure 3. The average callus diameter

The lowest callus diameter in the treatment group was 4 mm and the control group was 6 mm. The highest callus diameter in the treatment group was 5 mm, and the control group was 8 mm. The average callus diameter of the treatment group was 4.556 mm, while the control group was 7.333 mm. The standard deviations of callus diameter in the treatment and control groups were 0.511 and 0.594, respectively.

A homogeneity test was performed to test whether the variance of the sample was different. This test was carried out by using Levene's test, and the result was shown that the body weight of the rats in the treatment and the control groups was homogeneous ($p>0.05$). A normality test was performed to observe whether the data were normally distributed. A normality test on callus strength and diameter was performed using the Kolmogorov-Smirnov test. The Kolmogorov-Smirnov test showed that the callus strength data were normally distributed because the probability value was more than 0.01, while the callus diameter data were not normally distributed because the probability value was less than 0.01.

A t-test was performed to determine whether the sample's average was different. There was no difference between the body weight of the rats in the treatment group (diclofenac sodium) and that in the control group (no diclofenac sodium). That could be seen from the significance level t-test of 0.411, which was more significant than the tolerance for error ($\alpha=0.05$). The callus strength data was normally distributed so that the t-test could be performed. According to the t-test result, the significance level was less than 0.01, which concluded a significant difference between the average callus strength of the treatment group and the average callus strength of the control group. According to the test, the Z calculation was more significant than the Z table, with a 1% error. It was concluded that there was a significant difference in the average callus diameter between the treatment and control groups due to the intake of sodium diclofenac.

DISCUSSION

In a previous study, the intake of NSAIDs interfered with the fracture healing process through disturbance in osteoclast and osteoblast activities (Suhana 2002). This method impacts this research on the mechanism of NSAIDs interference to fracture healing. NSAIDs act by inhibiting the production of PGs. PGs participate in inflammatory responses and increase osteoclast and osteoblast activity, bone resorption, and new bone formation (Harder & An 2003). Another study was performed using Wistar-strain rats with transverse osteotomy on the left proximal tibial bone (Beck et al. 2003). The rats were divided into four groups, with ten rats in each group. Group 1 was the control group, group 2 was treated with tramadol (20 mg/kg BW/day), and group 3 was treated with diclofenac sodium(5 mg/kg BW/day) for seven days and continued for 14 days without any drug intake. Group 4 was treated with diclofenac sodium(5 mg/kg BW/day) for more than 21 days. On day 21, the rats were sacrificed, and each leg was examined under an X-ray. Their tibial bones were examined under a CT scan, the three-point bending method, and histology.

The previous study showed that the rats in group 3 experienced inhibition of fracture healing compared to the rats in group 2 and the rats in the control group. Fracture healing was evaluated through bone density and bone strength parameters. The highest bone strength was obtained from group 1 and the control group. The rats that received diclofenac sodium therapy (group 3 and group 4) had lower bone density levels, bone strength, and stiffness than those that received tramadol therapy (group 2). The study concluded that diclofenac sodium significantly inhibited fracture healing in rats.

The effect of diclofenac sodium on the union of tibial fractures in rats was also performed (Akman et al. 2002b). In the study, there were three groups: a control group, a group with an intake of 1 mg/kg BW/day, and a group with an intake of 2 mg/kg BW/day. Closed diaphyseal fractures were performed on the right tibial bone of rats. Then, clinical, radiological, and histological tests were conducted after the second week, the fourth week, and the sixth week. At the end of the second week, the clinical test showed a difference between the treatment and control groups. The control group produced a more stable callus.

Diclofenac sodium triggers changes in bone metabolism and fracture healing because diclofenac sodium affects the healing inflammation phase (Zhou et al. 2018). By inhibiting cyclooxygenase, diclofenac sodium decreases the first synthesis of the inflammation mediator (Pratiwi & Kertia 2019), including prostaglandin, which is responsible for chemotaxis in the first phase of fracture healing. It also decreases the cell number in the fracture site, absorbs the tissue again, and allows the modification of the number of cells for callus formation (Santos et al. 2017). As the cause of prostaglandin inhibition and thromboxane synthesis, NSAIDs could affect neoangiogenesis, resulting in lower oxygen allocated to the mesenchymal cells. In the healing process, there is a tendency to differ between chondroblast and fibroblast, which are responsible for extracellular matrix synthesis. Thus, the immature and less mineralized bone callus will be produced (Painter et al. 2006).

Systemic and non-systemic factors that affected bone remodeling were explained in the literature (Painter et al. 2006). One of the most critical factors in bone healing is several pharmacological agents. Steroids, chemotherapy drugs, and some antibiotics have been reported to affect bone healing negatively. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs for pain relief and inflammation. However, they have also been found to have the potential to delay and inhibit fracture healing (Pountos et al. 2008). NSAIDs affect the osteoblastic cell cycle and cell death. A study showed that osteoblastic density was significantly decreased in groups exposed to diclofenac sodium compared to the control group (Hadjicharalambous et al. 2021). The osteoclastic densities were found to be statistically significantly higher in a group exposed to diclofenac sodium than in the control group ($p< 0.05$). The osteoblastic densities showed a statistically significant decrease in groups with exposure to diclofenac sodium compared to the control group ($p< 0.05$).

In this study, the intake of diclofenac sodium diminished the callus quality. These results were observed by examining callus strength and diameter in male Wistar rats. Based on the result of the t-test, the Z calculation was more significant than the Z table, with a 1% error level. There was a significant difference in the average callus diameters between the treatment and control groups due to diclofenac sodium intake. The callus diameter and callus strength decreased in line with the theory that the intake of NSAIDs could delay bone regeneration by inhibiting the prostaglandin at an early stage of healing as relevant to the findings of the delay of callus maturation (Krischak et al. 2007). One of the shreds of evidence was confirmed by the study result that diclofenac sodium with an intake of 1.8 mg/150- grams could decrease the quality (diameter and strength) of fracture healing callus. This finding could strengthen the theory about the effect of diclofenac sodium on the bone mechanism to guide the usage of medicament wisely and gain the best healing action.

Strength and limitation

The study focuses on an important clinical question regarding the effect of NSAIDs on the healing process of bone fractures, which has potential implications for patient care.The study used a controlled experimental design with a treatment and control group, which allows for comparison and identification of the effect of diclofenac sodium on fracture healing.

CONCLUSION

Diclofenac sodium at a dose of 1.8 mg/200g could reduce the callus strength and diameter as indicators of callus quality of fracture healing. Further research is needed to perform by involving biochemical measurement parameters and the osteocalcin levels. Osteocalcin has a role in the body's metabolic regulation to enhance osteoblasts' activity during bone healing.

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Conflict of interest

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Author contribution

HW and PW were conseptual, prepared the data analysis of the manuscript, revised, final check the manuscript and grammar.

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Original Research

RESPIRABLE DUST LEVELS, YEARS OF SERVICE, AND PULMONARY PHYSIOLOGICAL DISORDERS IN MARBLE HOME INDUSTRY WORKERS

Siti Arum Alia,[1] Noeroel Widajati,[1,2] Tri Martiana,[1] Firda Qurba Sari,[1] Abdul Rohim Tualeka[1]

[1]Department of Occupational Safety and Health, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[2]Master of Occupational Health Science Study Program, Faculty of Medicine, Universitas Gadjah Mada, Indonesia

ABSTRACT

Environmental dust in the workplace exposes the workers as they are breathing. The dust is inhaled into the respiratory tract and causes occupational diseases in the form of pulmonary function disorders. Workers in the marble industry are also prone to dust exposure. This study aimed to analyze the correlation between years of service, respiratory dust levels, and pulmonary function disorders in marble home industry workers in Tulungagung Regency, Indonesia. This study was a descriptive observational study with data from a cross-sectional technique. The population was 18 workers taken as respondents. The independent variables in this study were years of service and the level of respirable dust, while the dependent variable was the pulmonary function disorders experienced by the workers. The data were analyzed using the Correlation Contingency test. There was a close correlation between years of service and pulmonary function disorders by 0.196, indicating that the relationship between those variables was weak. The strength of the relationship between respiratory dust levels and pulmonary function disorders could not be obtained because the constant results met the threshold value. The correlation between years of service and pulmonary function disorders was weak, and the relationship between respiratory dust level and pulmonary function disorders could not be obtained.

Keywords: *Dust exposure; pulmonary disorder; occupational disease; good health and well-being*

Correspondence: Noeroel Widajati, Department of Occupational Safety and Health, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia. Email: noeroel.widajati@fkm.unair.ac.id

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Highlights:

1. The strength of the relationship between respiratory dust levels and pulmonary function disorders could not be obtained.
2. The weakness level of correlation between years of service and pulmonary function disorders.

INTRODUCTION

Based on the data from the International Labor Organization (ILO) in 2012, occupational accidents and diseases caused 2 million cases of mortality every year. The Ministry of Health of the Republic of Indonesia has noted that in 2013, every 15 seconds, one worker in the world died from a work accident, while 160 experienced work- related illness. According to data from the World Health Organization (WHO) in 2007, among all cases of occupational diseases, 30%-50% of them are pneumoconiosis. In addition, the ILO detected 40,000 new cases of pneumoconiosis or respiratory diseases every year around the world due to exposure to dust in the workplace (Abidin et al. 2015).

When humans breathe, the dust in the environment is inhaled and enters the respiratory tract. The dust will reach different target organs based on the concentration and size of the dust. Dust particles with a size of 1 micron will undergo diffusion or brown movement and settle in the alveoli. Dust particles of 1-5 microns will settle (sedimentation) in the middle respiratory tract, such as bronchiole and bronchi. Meanwhile, dust with a size of 5-10 microns will easily stick to the mucosa of the upper respiratory tract (*inertia impaction*), and rarely enter the bronchi and smaller channels. Dust particles are dangerous when they are 0.1-10 microns (Suma'mur 2009).

According to the Minister of Manpower Regulation No. 5 of 2018 concerning Occupational Safety and Health in the Work Environment, the substance of respirable particulate dust in the work environment is 3 mg/m^3. Dust levels that exceed the threshold can cause interference with lung function. Lung function disorders can occur due to exposure to dust particulates (Andersson et al. 2020, Habybabady et al. 2018), especially in obstruction or restriction, or it could be both. A person has obstructive pulmonary function disorders if the value of the forced expiratory volume in the first second (FEV1) is less than 75%, and restrictive pulmonary function disorders if the value of vital capacity (Vital Capacity/VC) is less than 80% compared to the standard value (Alsagaff et al. 2020). Several factors can affect a person's health due to dust, including dust levels in the air (Dwicahyo et al. 2019), dust properties (Cui et al. 2021), and dust size or diameter (Khan & Strand 2018, Manisalidis et al. 2020). The other common factors are dust reactivity, working weather, length of time of exposure, and individual sensitivity (Siswanto 1991).

One of the industries with the potential for exposure to dust in the workplace is the marble industry. This industry produces marble dust which contains several chemicals, such as SiO, MgO, and CaO. The marble dust also contains PM2.5 and PM10 in its chemical composition (Iqbal et al. 2022). One of the developing marble industries is located in Tulungagung Regency, Indonesia. The processing of marble stones in the home industry consists of cutting, refining, drying, caulking, heating, and polishing. Some processes that result in dust exposure include the cutting, grinding, and polishing processes because the entire production process still uses human labor, and workers risk being exposed to dust in the workplace.

The dust accumulated over a long period can cause pulmonary function disorders in workers (Oo et al. 2021). The longer the working period, the longer the period the worker is exposed to dust. This study analyzed the relationship between years of service and levels of respiratory dust and pulmonary function disorders in marble home industry workers in Tulungagung Regency, Indonesia.

MATERIALS AND METHODS

This study was descriptive-observational research with a cross-sectional technique. This research was conducted in the marble home industry in June 2019, located in the Tulungagung Regency, Indonesia. The respondents in this study were 18 workers with inclusion criteria of willingness to participate in the study, had no history of respiratory disease, were not suffering from respiratory disease, and were working when this study was taking place.

The independent variables were years of service and the level of respirable dust in the workplace, while the dependent variable was pulmonary function disorders. The data were mainly obtained through a questionnaire distributed to the respondents. The working period variable was obtained through direct questionnaires to workers. Variable levels of respirable dust were obtained through measurements using a Personal Dust Sampler conducted by officers of the East Java UPT K2 of Manpower and Transmigration Office. Pulmonary function disorder variables were obtained through measurements using a spirometer conducted by officers of the UPT K2 of Manpower and Transmigration Office, East Java, Indonesia.

Data analysis was carried out using univariate and bivariate analysis. Univariate analysis was carried out by presenting data in tabular form and percentage of data, while bivariate analysis was used to see whether or not there was a relationship between variables using the Correlation Contingency test.

RESULTS

In processing marble stone from mining, a work process cannot be avoided from exposure to dust. The processing of marble stone goes through several stages in the form of cutting, polishing, scrubbing, lathe, craft operator, finishing, and packing. The distribution of workers was based on years of service and the results of measurements of respirable dust levels.

The number of workers with a working period of ≥5 was higher (83.33%) compared to that who had <5 years of service (16.67%). Based on data on respirable dust levels, the highest level was in the cutting section work unit by1.5524 mg/m^3 (4 workers), while the work unit with the lowest respirable dust level was the packing unit (1 worker) with a value of 0.444 mg/m^3.

Table 1. Distribution of respondents based on years of service and respirable dust levels

Variable	Total	Percentage
Years of service		
≥5 years	15	83.33
<5 years	3	16.67
Total	18	100
Respirable dust level		
0.4444 mg/m^3 (Packing)	1	5.56
0.4447 mg/m^3 (Finishing)	2	11.11
0.8865 mg/m^3 (Scrub and Polish)	7	38.89
0.8877 mg/m^3 (Lathe)	3	16.67
1.0867 mg/m^3 (Craft Operators)	1	5.56
1.5524 mg/m^3 (Cutting)	4	22.22
Total	18	100

In other units, the respirable dust level of 1,0867 mg/m^3 was found in the craft operator work unit (1 worker), 0.447 mg/m^3 in the finishing work unit (2 workers), and 0.8865 mg/m^3 in the scrub work unit, and polish unit (7 workers). The measurement results of respirable dust levels in the workplace did not exceed TLV based on the Minister of Manpower Regulation No. 5 of 2018 (3 mg/m^3). Furthermore, three workers (16.67%) experienced pulmonary function disorders or abnormal lung status, while 15 workers (83.33%) had normal lung conditions. Workers with pulmonary function disorders were identified in the restrictive category and had the lowest% FEV value of 41.8.

Table 2. Measurement results of lung physiological disorders

Pulmonary Physiology status	Total	Percentage
Normal	15	83.33
Abnormal	3	16.67
Total	18	100

Pulmonary function disorders experienced by workers with a work period of ≥5 years were higher than those with a work period of <5 years. Of the 15 workers with a work period of ≥5 years (20%), they experienced pulmonary physiological disorders, while the other 12 workers did not experience pulmonary function disorders. The relationship and Correlation Contingency test results showed a correlation value of 0.196, indicating that the level of the relationship between the two was weak.

Based on the dust measurement, there were 3 workers (16.67%) with pulmonary function (restriction) disorders and respirable dust levels under the Threshold Limit Value (<3 mg/m^3) specified in the Regulation of the Ministry of Manpower and Transmigration Number 5 of 2018. A total of 15 other workers with respirable dust levels met the requirements and did not experience pulmonary function disorders.

DISCUSSION

Abnormal pulmonary function conditions or pulmonary function disorders were only found in workers with ≥5 years work period. This finding was consistent with Sudrajad's (2016) research that workers with >5 years of service had a greater risk of experiencing lung function disorders because inhaled dust particles have settled in the alveoli.

Workers working in environments with high particle levels for long periods were at high risk of developing pulmonary obstruction disorders (Grahn et al. 2021, Liu et al. 2017). The value of the Correlation Contingency test results was 0.196, indicating that the relationship between the years of service and pulmonary function disorders was weak. A study indicated no significant relationship between the years of service and pulmonary function disorders (Taruna 2015).

The relationship between the years of service and pulmonary function disorders was found weak because the length of service does not always determine whether the workers experience pulmonary function disorders. The results of the Correlation Contingency showed a positive value, indicating that the longer the years of service, the higher the risk of workers suffering from pulmonary function disorders, even though the relationship was weak.

A comparison of the measurement results of respirable dust exposure in Tulungagung marble home industry and the Regulation of the Minister of Manpower Number 5 of 2018 concerning Occupational Safety and Health at Work Environment, showed that all work units had met the specified threshold value for respirable dust of 3 mg/m^3. However, based on the results of pulmonary function measurements, some workers experienced pulmonary function disorders, even though the dust levels were below the threshold. This indicated that the respirable dust below the

Table 3. Results of correlation contingency analysis

Variable	Pulmonary physiological (restriction) disorders				Total		Contingency coefficient
	Normal		Abnormal				
	n	%	n	%	n	%	
Years of service							
≥5 years	12	80	3	20	15	100	0.196
<5 years	3	100	0	0	3	100	
Respirable dust content							
Above threshold limit value (TLV) (>3mg/m^3)	0	0	0	0	0	100	
Under threshold limit value (TLV) (≤3mg/m^3)	15	83.33	3	16.67	18	100	0.514

This indicated that the respirable dust below the threshold value still presents a high risk for workers to experience pulmonary function disorders. Although the results showed that exposure to respirable dust was below the threshold value, this fact had to be a concern because the respirable dust inhaled daily could be deposited in the lungs. Similarly, a study also found that the pulmonary function disorders occurred higher in respondents whose workplaces had exposure to respirable dust below the threshold value (Sari 2018).

Strength and limitation

The study focuses on an important topic related to occupational health and safety, specifically the impact of dust exposure on respiratory function in marble industry workers.The sample size is small, with only 18 workers taken as respondents in arble industry in Tulungagung Regency, Indonesia, which may limit the generalizability of the findingand may not be representative of other industries or locations.

CONCLUSION

The relationship between years of service and pulmonary function disorders was weak, while the relationship between respiratory dust levels and pulmonary function disorders could not be obtained because the results of measurements of respirable dust levels were constant and met the threshold value. In addition, workers should always use personal protective equipment of masks suitable for the workplace conditions and use them in any work unit location. Workers are also advised to maintain physical health with adequate rest, nutritious foods, and regular exercise.

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Conflict of interest

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Author contribution

SAA, NW, and TM - conseptual, study design, analysis data. FQS, and ART - write and revised the manuscript. NW - validation of all manuscript data.

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Original Research

PERCEPTION OF WOMEN'S EXPOSURE TO BIRTH IN THE FOREST- A CROSS-SECTIONAL STUDY ON YEI TRIBE, MERAUKE REGENCY, INDONESIA

Fenita Purnama Sari Indah[1], Riris Andriati[1], Ika Rohmawati[1], Rina Kartikasari[2], Dini Rachmaniah[2], Andiyan[2]
[1]STIKes Widya Dharma Husada, Tangerang, Indonesia
[2]Universitas Faletehan, Bandung, Indonesia

ABSTRACT

In one of the districts in Papua, namely the Merauke Regency, the maternal mortality number in 2016 reached 17 cases, 13 cases in 2017, 6 cases in 2018, 9 cases in 2019, and 7 cases in 2020. Data in 2020 showed that 4,163 of the 5,377 deliveries by health workers assistance in Merauke Regency had not been fully achieved. There were 4,098 deliveries carried out in health care facilities. This study analyzed determinant factors on perceptions of the exile women giving birth in the forest from women of Yei Tribe, Poo Village, Merauke Regency, Indonesia. This study used analytic design methods with a cross-sectional approach. The sampling was non-probability with a total sample method of 57 mothers with toddlers. Univariate analysis was used to describe the characteristics of each research variable, including respondent characteristics, mother's knowledge, the role of community leaders, and the role of husband or family, while the dependent variable was the perception of women giving birth in the forest. This study found that there was a correlation between education (p-value 0.000; OR=13.33), knowledge (p-value 0.000; OR=133.00), the community leaders' role (p-value 0.009; OR=5.00), and husband's role (p-value 0.000; OR=28.00) with perceptions of the exile women giving birth in the forest at women of Yei Tribe, Poo Village, Merauke Regency, Indonesia. Therefore, knowledge is dominant in the perceptions of exiled women giving birth in the forest.

Keywords: *Exile women; maternal mortality; maternal health; human & health*

Correspondence: Andiyan, Universitas Faletehan, Bandung, Indonesia. Email: andiyanarch@gmail.com

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Highlights:

1. The maternal mortality for women's exposed birth in the forest on Tribe Kampung Poo, Merauke Regency is higher.
2. Mother's knowledge perceptions of women's exposure to birth in the forest were more dominant than community leader's roles, husband or family roles and respondent characteristics.

INTRODUCTION

In some areas, many people choose birth attendants with non-health workers, such as TBA (traditional birth attendance), which often negatively impacts the mother and the baby. The low coverage of delivery conducted by professional health workers is one of the factors associated with maternal and infant mortality (Phiri et al. 2014, Mgawadere et al. 2017).

World Health Organization estimates that around 830 women die daily due to pregnancy complications and birth processes. According to WHO in 2016, almost all deaths occurred due to things that could not be prevented, one of which was childbirth which was carried out at home without health workers. Meanwhile, in 2013, deliveries in health facilities were 70.4%, and there were still 29.6% deliveries at home. Based on the Ministry of Health of the Republic of Indonesia, in 2014 that assistance in childbirth by competent health providers (i.e., specialist doctors, general practitioners, and midwives) had reached 87.1%, and traditional birth attendants at home performed 12.9% of birth attendants.

Some stillbirths are carried out by the mother herself or assisted by a shaman. This occurs because the role of customs and culture in the community is still typical in several regions in Indonesia. Apart from being partly due to access to unaffordable health care facilities, various other reasons, such as economic, social, and cultural factors upon the mother's choice to give birth alone or assisted by a traditional birth attendant (Chandra et al. 2019). Conceptions not administered by health workers and not carried out in health care facilities are the risk factors for maternal and child mortality in Indonesia.

The coverage of deliveries by health workers in health facilities in 2013 in Papua Province only reached 42.73%, while the national coverage showed a range of 69.99%. Data on the maternal mortality ratio in Papua is still the highest in Indonesia (305 per 100,000 live births). One of the causes of the high maternal mortality rate in Papua is birth delivery without a professional standardized process. Besides, it is also caused by unhealthy conditions of the mother, such as high bleeding during pregnancy and childbirth. In addition to maternal mortality, the same thing is also shared by infants and toddlers, whose mortality rate is still high.

In Merauke Regency, the maternal mortality rate in 2016 reached 17 cases, 13 cases in 2017, 6 cases in 2018, 9 cases in 2019, and 7 cases in 2020. In 2020, deliveries in Merauke Regency, which the health workers assist, had not been fully assisted where the target number was 5,377, but only 4,163 were achieved. Meanwhile, the Health Office in Merauke regency data presented that 4,098 of 5,377 deliveries were carried out in health care facilities.

Some ethnic groups in Eastern Indonesia (IBT) still have a "house of exile" culture for women giving birth. In Jagebob. District Merauke Regency, Papua, the house of exile (Tana Barambon Ambip) for women giving birth is Be'vak. This tradition applies to the tribe of Yei. Living in seclusion for women giving birth is a problematic condition compared to the current development of the modern medical world. The postpartum period for Eastern women after giving birth for 40 days in a Be'vak continues today. Mothers who have just given birth are ostracized from society and family. At the same time, their babies can only be visited by relatives closest to them and undergo some very unusual rituals for the world of health. Women who have given birth are compressed with hot water using an Eastern cloth every day with the excuse of improving blood circulation.

In addition, they also have to undergo the *Phangan* ritual (*sei*), which is the ritual of fumigating the mother and baby's bodies. The process of a fireplace is made right under the bed, then the mother and babysits or lies on it with the thought of drying the postpartum wounds. Fumigation is carried out every day for 40 days and is believed by the community to be an antidote to serious illness. This challenging process was carried out because there was fear from the parents. They thought that if the process was not carried out, the condition of the child's body would be weak and cause madness for the mother (Nina 2012, Anwar & Soerachman 2014, Setyowati 2016).

Based on the results of a preliminary study conducted in Jagebob 10 village, Merauke Regency, on April 24, 2020, to 20 mothers with toddlers, it showed that 13 mothers with toddlers still chose to give birth in the forest and were assisted by traditional healers. They preferred to give birth in the woods. This study aimed to analyze determinant factors of perceptions of the exile women giving birth in the forest in Poo Village, Merauke Regency, Papua, Indonesia.

MATERIALS AND METHODS

This study was descriptive-analytic research with a cross-sectional approach. This study used non-probability sampling with a total sampling technique. The sample was 57 Yei mothers who had toddlers in Poo Village, Merauke Regency, Papua, Indonesia.

Univariate analysis was used to describe the characteristics of each research variable. The independent variables included respondent characteristics, mother's knowledge, community leaders' roles, and husband or family roles. The dependent variable was the perceptions of the exile women giving birth in the forest. This analysis was presented in the form of a frequency distribution table. Bivariate analysis determined a correlation between the independent and dependent variables with statistical tests following the existing data scale. This study was conducted from March-early June 2021, with 57 respondents filling out the questionnaire sheets. This study was approved under decree No. 176/KEPK/FKM-UNEJ/III/2021.

RESULTS

The results of this research are univariate analysis and bivariate analysis.

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Univariate analysis

Table 1. Characteristics of respondents (n = 57)

Characteristics of respondents	Frequency	Percentage (%)
Age		
17-25 years	6	10.5
26-35 years	40	70.2
36-45 years	11	22.5
Occupation		
Housewives	6	10.5
PNS/POLRI/TNI	1	1.8
Farmer	50	87.1
Education		
Low	49	85.96
High	8	14.04
Knowledge		
Less	39	68.42
Good	18	31.58
The community leaders' role		
Less	35	61.40
Good	22	38.60
Husband's role		
Less	29	50.88
Good	28	49.12
Perceptions		
Less	42	73.68
Good	15	26.32
Total	57	100.0

Bivariate analysis

Table 2. Correlation between education with perceptions of the exiled women giving birth in the forest

Education	Perception of the exiled women				Total	
	Less		Good			
	F	%	F	%	F	%
Less	40	81.63	9	18.37	49	100
Good	2	25.00	6	75.00	8	100
Total	42	73.68	15	26.32	57	100
p-value = 0,000: OR = 13.33						

Table 2 showed that respondents with fewer perceptions of the exiled women were more common to have low education (81.63%) than respondents with high education (25.00%). In contrast, respondents with good perceptions were more common to have high education (75%) than respondents with low education (18.37%). Statistical test results showed a p-value of 0.000<0.05. It indicated a correlation between education and perceptions of the exiled women giving birth in the forest with OR=13.33 (Ha accepted).

Table 3. Correlation between knowledge with perceptions of the exiled women giving birth in the forest

Knowledge	Perception of the exiled women				Total	
	Less		Good			
	F	%	F	%	F	%
Less	38	97.44	1	2.56	39	100
Good	4	22.22	14	77.78	18	100
Total	42	73.68	15	26.32	57	100
p-value = 0,000: OR = 133.00						

Table 3 shows that respondents with fewer perceptions of the exiled women were more common to have less knowledge (97.44%) than respondents with good knowledge (22.22%). In contrast, respondents with good perceptions were more common to have good knowledge (77.78%) than respondents with less knowledge (2.56%). Statistical test results showed a p-value of 0.000 <0.05. It indicated a correlation between knowledge and perceptions of the exiled women giving birth in the forest with OR =133.00 (Ha accepted).

Table 4. Correlation between the community leaders' role with perceptions of the exiled women giving birth in the forest

Community's leader role	Perception of the exiled women				Total	
	Less		Good			
	F	%	F	%	F	%
Less	30	85.71	5	14.29	35	100
Good	12	54.55	10	45.45	22	100
Total	42	73.68	15	26.32	57	100
p-value = 0,009: OR = 5.00						

Table 4 showed that respondents with fewer perceptions of the exiled women were more common to the minor role of the community leaders (85.71%) compared to respondents with good community leaders (54.55%). In contrast, respondents with good perceptions of the exiled women were more common with community leaders' roles (45.45%) compared to respondents with fewer community leaders' roles (14.29%). Statistical test results showed the p-value of 0.009 <0.05, indicating a correlation between the community leaders' role and the perceptions of the exiled women giving birth in the forest with OR=5.00 (Ha accepted).

Table 5. Correlation between husband's role with perceptions of the exiled women giving birth in the forest

Husband's role	Perception of the exiled women				Total	
	Less		Good			
	F	%	F	%	F	%
Less	28	96.55	1	3.45	29	100
Good	14	50.00	14	50.00	28	100
Total	42	73.68	15	26.32	57	100
p-value = 0,009: OR = 28.00						

Table 5 showed that respondents with fewer perceptions of the exiled women were more common to more petite husband's role (96.55%) compared to respondents with a good husband's role (50.00%). In contrast, respondents with good perceptions of the exiled women were more common to a good husband's role (50.00%) compared to respondents with a more petite husband's role (3.45%). Statistical test results showed a p-value of 0.000 <0.05. It indicated a correlation between the husband's role with perceptions of the exiled women giving birth in the forest with OR =28.00 (Ha accepted).

DISCUSSION

The subjects in this study did not have sufficient knowledge of birth safety, affecting women to give birth in the forest temporarily. A study indicated that a pregnant woman is possessed by demons and considerably endangers society (Setyowati 2016). This perception makes them carry out delivery in the forest (temporary exiled). The lack of knowledge on childcare and pregnancy also occurred in a rural area in Ghana, where 90% of women were unable to more than four danger signs (i.e., lethargy, diarrhea, respiratory distress, and cyanosis) (Nuamah et al. 2019).

Differently in a study, a woman giving birth without professional health service assistance (homebirth) was also due to their worries about risky medical treatment that might happen (Jackson et al. 2020) and trauma of previously childbirth (LeBlanc & Kornelsen 2015). The perception of a woman on previous traumatic childbirth experience certainly impacts future delivery and can lower the need for professional health assistance (Agadjanian et al. 2016).

The role of a public figure, on the other hand, concerns a mother's decision regarding her delivery method and setting. The study's results on 30 respondents had proven the significance of public figures in maternal education concerning delivery. Besides, the study also indicated a lack of literacy among pregnant women on the importance of regular antenatal care and delivery to health workers (Permatasari & Puspitasari 2018).

Husband has also become a determinant factor in determining the way of a woman's delivery during her pregnancy. A husband (included as family-in-bound) should consider the condition of his woman and the place for delivery (Sujana et al. 2016, Ashar et al. 2019). Besides, a husband should address maternal health education that can benefit the woman's and child's health (Lewis et al. 2015, Onchong'a et al. 2016). In this situation, a study conducted in Tuatunu Village, Gerunggang District, Pangkalpinang City, Indonesia, pointed out a correlation between family support with the selection of birth attendants (p-value=0,010) (Kurrohman 2017).

Childbirth should be carried out carefully. This study addressed a significant clue for women and husbands to reconsider childcare and safety that might occur due to unhealthy and improper services. They were suggested to focus on the delivery process and postnatal care (PNC). This is significant for identifying, ensuring, and managing maternal and newborn complications during the first six weeks after birth (Habte et al. 2021).

Strength and limitation

The study addresses a significant issue of maternal mortality in a specific district in Papua, Indonesia. The study used a non-probability total sampling method, which enabled the researchers to gather data from all eligible participants. The study suggests that knowledge is dominant in the perceptions of exiled women giving birth in the forest, which can help in designing appropriate interventions to improve maternal health in the region. The sample size is relatively small, with only 57 mothers with toddlers, which may not be representative of the entire population of exiled women in the forest. which limits the generalizability of the findings to other regions in Papua or Indonesia.

CONCLUSION

73.68% of Yei Tribe women in Poo Village, Merauke Regency, had fewer perceptions of the exile women giving birth in the forest. Education, knowledge, the community leaders' role, and the husband's role correlated with the perceptions of the exiled women giving birth in the forest. Most Women in Yei Tribe, Poo Village, and Merauke Regency had less knowledge of safe childbirth, including the impact of childbirth in the forest.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

FPSI, RA, IR and DR were conseptual idea and analysis data. RK write, revised and prepared the draft of the manuscript. A was manuscript arrangement to the final content.

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Original Research

THE COMBINATION OF NLCR AND PLR ENHANCES THE SEPSIS-3 STRATEGY

Emmy Hermiyanti Pranggono[1], Endah Nurul Aini[2], Uun Sumardi[3], Yovita Hartantri[3], Adhi Kristianto Sugianli[4]

[1]Division of Respirology and Critical Care Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[3]Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[4]Department of Clinical Pathology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

ABSTRACT

According to Sepsis-3, antibiotics should be administered in the first hour of diagnosis of sepsis. Still, there is difficulty in differentiating between bacterial and nonbacterial infections and a lack of a rapid diagnostic tool to distinguish them. This study evaluated the diagnostic value of NLCR and PLR in suspected bacterial sepsis. The diagnostic value of PLR in adult bacterial sepsis patients has never been studied. This study was a retrospective study from the medical record of Dr. Hasan Sadikin Hospital Bandung. All patients at age ≥ 18 years diagnosed with sepsis based on ICD-10 code and qSOFA ≥ 2 were included. We calculated sensitivity, specificity, NPV, PPV, positive LR, and AUC of NLCR and PLR. There were 177 patients included in this study. The sensitivity of NLCR was 69.5%, specificity was 34.7%, NPV was 56.9%, PPV was 47.9%, and LR+ was 1.06, while the sensitivity of PLR was 62.2%, specificity was 38.9%, NPV was 54.4%, PPV was 46.8%, and LR+ was 1.02. We obtained cut-off values for NLCR 11.06, AUC 0.500, PLR 222.41, and AUC 0.497. The low value of AUC NLCR and PLR was due to prior antibiotic use. The combination of NLCR and PLR had higher positive LR (1.16) and specificity (54.7%), and also, according to NLCR, we had the highest sensitivity (69.5%). The combination of NLCR and PLR enhances the sepsis-3 strategy because it can be used as screening tools for bacterial sepsis, and antibiotics can also be administered in the first hour of managing sepsis, particularly in the emergency ward.

Keywords: *Bacterial sepsis; diagnostic value; infectious disease; NLCR; PLR*

Correspondence: Endah Nurul Aini, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/ Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Email: endah.na@gmail.com

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Highlights:

1. The combination of NLCR and PLR will improve the ability to distinguish infection rather than noninfection in the emergency setting for early antibiotic prescribing as well as the sepsis-3 strategy.
2. The diagnostic value of PLR in adult bacterial sepsis patients has never been studied.

INTRODUCTION

Sepsis is a severe condition of organ dysfunction resulting from dysregulated host response to infection (Singer et al. 2016). Sepsis is one of hospitalized patients' most common causes of mortality (Kumar et al. 2011). The burden of sepsis was around US$ 130 million in 100,000 patients (Purba et al. 2020).

According to Sepsis-3, broad-spectrum antibiotics should be administered in the first hour of diagnosis of sepsis (Lehman 2019). Early broad-spectrum antibacterial agents are recommended to improve survival (Dellinger et al. 2013). However, sepsis management is still challenging, particularly in distinguishing between infection of bacterial and nonbacterial (Ljungström et al. 2017).

Positive microbiological culture is the gold standard in diagnosing sepsis, although it takes time. When a patient has received antibiotics, it can lead to false negatives (Davis 2005). Moreover, bacterial sepsis is rarely proven by culture. Only 30-40% of cases are positive in blood culture (Singer et al. 2016). Therefore, simple and novel diagnostic tools are needed to help distinguish bacterial sepsis.

Recently, the neutrophil-to-lymphocyte count ratio (NLCR) has been identified as a cost-economic, simple, and fast laboratory tool which can contribute to determining bacterial sepsis (Luhulima et al. 2017). A previous retrospective study stated that NLCR was a better parameter in diagnosing bacterial sepsis compared to others, i.e., leukocyte and CRP (C-reactive protein) (de Jager et al. 2010). Meanwhile, PLR had prognostic indicators of cancer and adverse cardiovascular events, also useful systemic inflammatory markers (Shen et al. 2019). PLR also be used in predicting neonatal sepsis (Arcagok & Karabulut 2019, Can et al. 2018). The studies on the diagnostic value of PLR and NLCR are still limited, particularly in adult bacterial sepsis. Therefore, this study evaluated the diagnostic value of NLCR and PLR in suspected bacterial sepsis.

MATERIALS AND METHODS

Study design and patients

The study was conducted retrospectively from medical records in a tertiary hospital, Dr. Hasan Sadikin Hospital Bandung, West Java, Indonesia, from 1 January to 31 December 2019. This study was undergone into several steps until extracting the included data. The population of this study was the patient admitted to the hospital and diagnosed with sepsis based on the ICD-10 code. We accessed the hospital information system to achieve the list of sepsis patients according to the ICD-10 (code: A40-A41.9). We screened and included the medical record if it met the criteria as (1) adult patient (age $\geq$ 18 years), (2) quick Sequential Organ Failure Assessment (qSOFA) score $\geq$ 2, (3) performed routine blood examinations, with culture at the time diagnosis sepsis established or at the first admission with diagnosis sepsis. We excluded patients with a clinical history of HIV infection (Human Immunodeficiency Virus), hematologic disease, oncology disease, autoimmune disease, hepatic cirrhosis, invasive fungal infection, and drug-induced thrombocytopenia, and medication history of immunosuppressant.

We hand-searched the included medical record and extracted information for the demographic characteristic (age, sex), type of ward, previous antibiotic use, clinical source of sepsis, complete blood count data, and bacterial culture data. We also accessed the laboratory information system to obtain the complete blood count and bacterial culture if not present in the medical record. Bacterial sepsis was described as: (1) infection of bacteria that is defined by qSOFA $\geq$ 2 according to Sepsis-3 criteria, and (2) proven-positive culture from any suspected source of infection (blood, sputum, pus, urine, and body fluid). In this study, contaminant bacteria such as *Bacillus species* (other than *B. anthracis*), *Corynebacterium species* (other than *C. jeikeium)*, *Propionibacterium acnes*, *Clostridium perfringens*, *Coagulase-negative staphylococci* and *Viridans group streptococc*i in blood culture and sputum did not include as pathogen bacteria (Weinstein 2003).

We also examined the quality of cultured sputum from Gram stain using the Bartlett Scoring (Bartlett et al. 1998). Only epithelial cells reported below 10 per HPF were included in this study. Meanwhile, from complete blood count data, we performed calculations of NLCR and PLR. NLCR was obtained by dividing the number of absolute neutrophil counts (cells/mm^3 or uL) with the number of absolute lymphocyte counts (cells/mm^3 or uL). A value of NLCR greater than ten was considered a cut-off value for bacterial sepsis (Ljungström et al. 2017). PLR was obtained by dividing the number of platelet counts (cells/mm^3 or uL) with the number of absolute lymphocyte counts (cells/mm^3 or uL). We used the cut-off value of PLR greater than 200 for bacterial sepsis (Shen et al. 2019).

The study was authorized by the health research ethics committees of Dr. Hasan Sadikin General Hospital, Bandung, West Java No. LB.02.01/X.6.5/306/2020. No individual consent was collected since the data were derived from the hospital- and laboratory information systems.

Statistical analysis

Data on age, type of ward, previous antibiotic use, and clinical source of sepsis were summarized as frequencies and percentages. Absolute lymphocyte count, absolute neutrophil count, leukocyte, NLCR, and PLR were summarized as median (interquartile range/IQR). We performed two analyses: (1) determining the optimal cut-off value (COV) of NLCR and PLR based on this study using receiver operating characteristics curves (ROC), (2) accessing the diagnostic performance of multiple combinations between NLCR and PLR using previously reported COV and this study COV, to obtain the sensitivity, specificity, negative predictive value, positive predictive value, and positive likelihood ratio against culture among suspected bacterial sepsis.

RESULTS

We observed 566 patient records through the hospital-information system with the ICD-10 code of sepsis. This study's suspected bacterial sepsis was 31.3% (177 out of 566 patient records). The positive culture-proven among the suspected bacterial sepsis was 46.3% (82 out of 177 patient records) (Figure 1).

This study's suspected bacterial sepsis was 31.3% (177 out of 566 patient records). The positive culture-proven among the suspected bacterial sepsis was 46.3% (82 out of 177 patient records) (Figure 1).

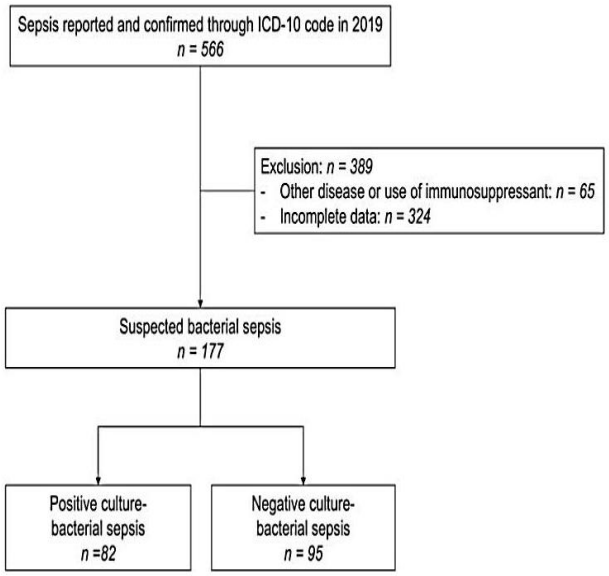

Figure 1. Flowchart of patient selection

The patients' characteristics of suspected bacterial sepsis are shown in Table 1. Admission during diagnosis of sepsis was most commonly from the emergency ward (70.7% vs. 77.9%), previous antibiotic use (34.1% vs. 35.8%), and lung mainly was the focus of infection (52.4% vs. 60%). Skin and soft tissue infection, as the focus of infection, had a chance of having positive-culture results; in contrast to gastrointestinal, which tends to be a negative-culture result in bacterial sepsis ($p<0.05$). The hematology results among positive-culture and negative-culture bacterial sepsis are shown in Table 2. Higher IQR of WBC, PLT, NLCR, and PLR was found in negative-culture bacterial sepsis.

There were 277 specimens collected from the positive-culture bacterial sepsis patients. Among this group, pus and body fluid specimens showed high positivity of culture growth, 85.7% and 55.6%, respectively. Meanwhile, blood as the primary specimen, which commonly indicates the presence of bacteremia, only showed positivity of 21.2%. We observed a discrepancy between clinical suspicion of focus of sepsis with specimens being cultured, i.e., the focus of lung infection observed in 100 patients, but the number of sputum being submitted for culture was 52 specimens (52%). Overall, the positivity of culture among all the specimens was 37.5% (Table 3).

We evaluated and calculated this study's optimal COV of NLCR and PLR. The area under receiver operating characteristics (AUROC) curves of the NLCR against culture-proven bacterial sepsis were 0.500 (0.414-0.585). Meanwhile, the AUROC of the PLR against culture-proven bacterial sepsis was 0.497 (0.412-0.583) (Figure 2). From this analysis, the optimal COV of NLCR and PLR were 11.06 and 222.41, respectively. We calculated the diagnostic performance of NLCR and PLR using different COV against culture-proven bacterial sepsis. The sensitivity of NLCR and PLR using different COV was moderate, ranging between 57.3% and 69.5%. The specificity of NLCR and PLR using different COV was low, ranging between 34.7% and 43.2%. The sensitivity and specificity of NLCR and PLR could be improved by combining two variables with optimal COV, as observed in this study (COV NLCR of 11.06 and PLR of 222.41). Using this combination, this variable's sensitivity and specificity against culture-proven bacterial sepsis were achieved at 52.4% and 54.7%, respectively. This combination also affected the improvement of PPV and LR+ (Table 4).

Table 1. Patient characteristics of suspected bacterial sepsis

Characteristic	Positive-culture bacterial sepsis (n=82)		Negative-culture bacterial sepsis (n=95)		Total (n=177)		p-value*
	n	%	n	%	n	%	
Age (years)							0.066
20 - 30	10	12.2	9	9.5	19	10.7	
31 - 40	8	9.8	7	7.4	15	8.5	
41 - 50	12	14.6	9	9.5	21	11.9	
51 - 60	20	24.4	36	37.9	56	31.6	
61 - 70	21	25.6	12	12.6	33	18.6	
> 70	11	13.4	22	23.1	33	18.6	
Gender							0.563
Female	45	54.9	48	50.5	93	52.5	
Male	37	45.1	47	49.5	84	47.5	
Admission during the diagnosis of sepsis							0.220
Non-intensive ward	10	12.2	13	13.7	23	13	
Intensive care unit	14	17.1	8	8.4	22	12.4	
Emergency unit	58	70.7	74	77.9	132	74.6	
Previous antibiotic used[$]							0.836
Yes	28	34.1	34	35.8	62	35	
No	24	29.3	24	25.3	48	27.1	
Unknown	30	36.6	37	38.9	67	37.9	
The focus of infection[#]							
Lung	43	52.4	57	60.0	100	56.5	0.312
Gastrointestinal	8	9.8	22	23.2	30	16.9	0.018
Genitourinary	8	9.8	5	5.3	13	7.3	0.253
Skin and soft tissue	26	31.7	13	13.7	39	22.0	0.004
Others	7	8.5	1	1.1	8	4.5	0.025

([$]), The antibiotic treatment is being given before the diagnosis of sepsis;
([#]), multiple foci of infection per patient possible; (*), significant p<0.05

Table 2. Hematology results among suspected bacterial sepsis

Hematology	Positive-culture bacterial sepsis (n=82)		Negative-culture bacterial sepsis (n=95)		p-value*
	IQR	Range	IQR	Range	
WBC (cells/uL)	10852.50	1100-51950	11400	1050-48740	0.921
ANC (cells/uL)	10880.33	754.80-44157.5	10001.90	955.5-39605.5	0.962
ALC (cells/uL)	1014.28	194.8-3146.5	1003.90	42-5977.5	0.634
PLT (cells/uL)	193250	30000-588000	212000	24000-671000	0.817
NLCR	13.93	1.97-96	24.08	1.58-98	0.992
PLR	293.6	31.89-1923.21	495.43	33.41-1619.05	0.951

abbrev: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; IQR, inter-quartile range; NLCR, neutrophil-to-lymphocyte count ratio; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell count

Table 3. The positivity of culture among bacterial sepsis patients

Type of specimen	Number of specimens being cultured	Positivity of culture	
		n	%
Blood	156	33	(21.2)
Urine	25	11	(44)
Sputum	52	25	(48.1)
Pus	35	30	(85.7)
Body fluid*	9	5	(55.6)
Total	277	104	37.5

(*), Body fluid was from pleural fluid, double lumen catheter, bullae, and cerebrospinal liquid

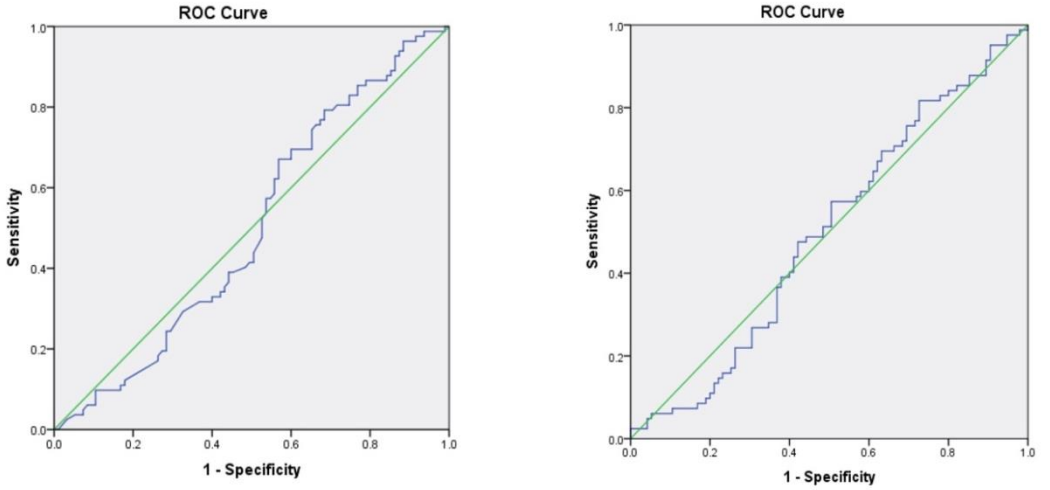

Figure 2. ROC curves of NLCR (A) and PLR (B)

Table 4. Diagnostic value of NLCR, PLR, Combination NLCR, and PLR

	Sensitivity %	Specificity %	PPV %	NPV %	LR+
NLCR > 10	69.5%	34.7%	47.9%	56.9%	1.06
NLCR > 11.06	67.1%	40%	49.1%	58.5%	1.12
PLR > 200	62.2%	38.9%	46.8%	54.4%	1.02
PLR > 222.41	57.3%	43.2%	46.5%	53.9%	1.01
NLCR > 10 and PLR > 200	52.4%	50.5%	47.8%	55.2%	1.06
NLCR > 11.06 and PLR > 222.41	52.4%	54.7%	50%	57.1%	1.16

Abbrev: NLCR, neutrophil-to-lymphocyte count ratio; NPV, negative predictive value; LR+, likelihood ratio positive; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value

DISCUSSION

Sepsis is a severe condition of organ dysfunction resulting from dysregulated host response to infection. According to Sepsis-3, broad-spectrum antibiotics should be administered in the first hour of diagnosis of sepsis (Singer et al. 2016). Early identification and management of sepsis are essential in lowering mortality (Visveswari et al. 2019). As a result, biomarkers have been developed for rapid laboratory diagnosis of sepsis (Zhang et al. 2016). NLCR and PLR are simple, fast, and cheap tools to help diagnose bacterial sepsis (Luhulima et al. 2017).

Neutrophilia and lymphopenia were both associated with bacteremia. Response of immune to infection is an increase in neutrophil count resulting from rapid movement of neutrophils from the marginated pool within the bone marrow and reduced apoptosis of neutrophils (Westerdijk et al. 2019). The lymphocyte count is also decreased by increased apoptosis of lymphocytes and migration of activated lymphocytes to inflammatory tissues (Westerdijk et al. 2019). Lymphocytes and platelet also play critical roles in the inflammatory process (Shen et al. 2019). Inflammation causes accelerated proliferation of megakaryocytes and thrombocytosis. Also, decreased lymphocytes and increased platelet were connected to aggregation and inflammation (Arcagok & Karabulut 2019). PLR also had prognostic indicators in various diseases, such as myocardial infarction, hepatocellular carcinoma, non-small cell lung cancer, and acute kidney injury (Shen et al. 2019).

We performed a diagnostic evaluation for NLCR and PLR as additional modalities for diagnosing bacterial sepsis. NLCR and PLR were found above 10 and 200 in both positive and negative culture bacterial sepsis. Previous studies have shown various sensitivity, specificity, NPV, and PPV for both NLCR and PLR. However, this study has used a similar cut of value (COV) for NLCR and PLR (Arcagok & Karabulut 2019, Ljungström et al. 2017, Luhulima et al. 2017, Mandal & Valenzuela 2018, Marik & Stephenson 2020, Zhang et al. 2016). For example, we used the COV NLCR of 10, which resulted in a sensitivity of 69.5%, and specificity of 34.7%, compared with a previous study using similar COV resulted in a

sensitivity of 64.7% and specificity of 60.8% (Ljungström et al. 2017). Other studies about the diagnostic value of PLR in adult patients were rare. PLR has been studied in neonatal sepsis. PLR value in neonates with definite early-onset sepsis had high sensitivity (91.3%) and specificity (97.6%) (Arcagok & Karabulut 2019).

The difference in diagnostic value is influenced by: (1) disease definition; (2) time of performing the gold standard test, e.g., culture; and (3) previous history of antibiotic. Different guidelines for determined Sepsis, i.e., Sepsis-2 and Sepsis-3, have resulted in different performance characteristics, as described previously. However, we consider the time of performing the gold standard and the history of antibiotics essential in this diagnostic testing. In this study, we found that antibiotic usage occurred in 35% of all subjects included, which was similar to that of previous research, which stated that 32.8% of the patients who had received prior antibiotic therapy were given antibiotics in the first hour of arrival (Abe et al. 2019). As our hospital is a tertiary hospital, we received a referral from primary and secondary care whose patients had already been given prior antibiotics.

A previous study revealed that among patients with sepsis who did not receive antibiotics, the positivity of blood culture was 50.6% and in those who were already receiving antibiotics was only 27.7%. Antibiotic therapy while obtaining blood cultures is associated with losing pathogens (Scheer et al. 2019). In this study, the positivity of the whole culture was 37.5%, and the blood culture was 21.2%. The time of performing culture was also crucial, as we found many patients whose culture was not tested, primarily in patients with lung infection (52 sputum cultures from 100 patients), but we did not explore the reason. Other potential factors may contribute: (1) inadequate sample collection, (2) patients with the chronic obstructive pulmonary disease often have squamous metaplasia of bronchial cells, (3) unidentified an-aerobic and atypical bacteria such as *Chlamydia pneumoniae, Legionella* species, and *Mycoplasma pneumoniae* (Madison & Irwin 2004).

Our study has two limitations. First, we have limited access to information about patients (the name and period of antibiotic used). Second, inadequate culture specimen and unidentified an-aerobic and atypical bacteria examination.

Despite the low-performance characteristics, we observed the additional value of the combination between NLCR and PLR in bacterial sepsis. Based on this study, most patients have been diagnosed with sepsis in the emergency ward (74.6% of all subjects), meaning sepsis treatment should be initiated in the emergency department (Hall et al. 2011).

Strength and limitation

The study provides important information on the diagnostic value of NLCR and PLR in suspected bacterial sepsis, which can aid in the early diagnosis and treatment of sepsis.The combination of NLCR and PLR had higher positive LR and specificity, which may improve the accuracy of diagnosis.The study was conducted in a single hospital, which may limit the generalizability of the results to other settings.

CONCLUSION

The combination of NLCR and PLR had higher positive LR and specificity and, according to NLCR, had the highest sensitivity. Therefore, it enhances the sepsis-3 strategy and can be implemented in emergency wards as a direct screening of suspected bacterial sepsis. This also becomes an essential tool as consideration for clinicians when providing empiric antibiotics in the first hour of managing sepsis, as well as the role of clinical pathway and antimicrobial stewardship program in the hospital.

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Conflict of interest

None.

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None.

Author contribution

EHP, ENA, US and AKS conceptualized, wrote, and revised the manuscript. YH reviewed, finalized the manuscript and managed the administration.

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Original Research

FACTORS ASSOCIATED WITH TIMELINESS OF HEPATITIS B BIRTH DOSE: A CROSS-SECTIONAL STUDY IN NORTH-WESTERN NIGERIA

Olayinka Rasheed Ibrahim[1], Rasheedat Mobolaji Ibraheem[2], Rasaki Aliu[3], Ibrahim Magaji Lawal[1]
[1]Department of Pediatrics, Federal Medical Centre, Katsina, Nigeria
[2]Department of Pediatrics, University of Ilorin Teaching Hospital & University of Ilorin, Ilorin, Nigeria
[3]Department of Pediatrics, Gombe State University & Federal Teaching Hospital, Gombe, Nigeria

ABSTRACT

No studies focused on the hepatitis B birth dose (HepB-BD) vaccine since Nigeria adopted the strategy to reduce hepatitis B viral infection. Hence, we determined the uptake of HepB-BD, factors associated with timeliness, and those that contributed to delay. This study was a cross-sectional descriptive study carried out at an immunization post in north-western Nigeria. We recruited 400 mother-infant pairs that presented for the first immunization and obtained relevant information, including socio-demographics and reasons for the delays. Of the 400 infants, 44 (11.0%) received HepB-BD within 24 hours (timeliness), 105 (26.3%) and 274 (68.5%) by day 7 and 14, respectively. Multivariate analysis showed that mothers' education (primary adjusted odds (AOR) 17, 95% CI 1.404, 204.611), secondary AOR 5.9, 95% CI 1.148, 29.895), and tertiary AOR 7.7, 95% CI 1.228, 48.545), and ^{third} born AOR 8.2, 1.625, 41.018) were associated with HepB-BD timeliness. Maternal-related factors were the commonest (129; 46.6%) for delayed HepB-BD, with maternal illness the most commonly cited reason (37; 28.7%). This study showed a deficient level of uptake of HepB-BD vaccines among infants. Factors that were associated with timeliness included maternal education and higher birth order. The commonest reason for delayed HepB-BD was maternal illness.

Keywords: *Hepatitis B birth dose vaccine; hepatitis B viral infection; hepatitis; public health; newborns*

Correspondence: Olayinka Rasheed Ibrahim, Department of Paediatrics, Federal Medical Centre, Katsina, Nigeria. Email: ibroplus@gmail.com

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Highlights:

1. Uptake of hepatitis B birth dose vaccine within 24 hours of birth is low in Katsina, north-western Nigeria.
2. The most common reason for delay presentation for hepatitis B birth dose vaccine is maternal illness.

INTRODUCTION

Viral hepatitis B is the most common chronic hepatitis of public health significance (World Health Organization 2020a). It remains a leading cause of morbidity and mortality, rivaling Tuberculosis and Human Immunodeficiency Virus in recent (World Health Organization 2007). Besides, about one-third of the world's population had at least serological evidence of hepatitis B virus (HBV) infection (Trépo et al. 2014). In 2015, 257 million people were living with chronic HBV infection, with over 800 thousand deaths from hepatocellular carcinoma and liver cirrhosis, the two most common long-term complications (World Health Organization 2007, 2020b).

Although the global burden of HBV is enormous, there are still marked variations in the prevalence; with the classification of endemicity into high, intermediate, and low risk based on the proportion of the population that tested positive for hepatitis B surface antigen (HBsAg) (Trépo et al. 2014). The prevalence of HBV infections is highly endemic in some parts of South East Asia and African countries, inclusively Nigeria, where ≥ 8% of the population are carriers of HBsAg (Alter 2003, Hou et al. 2005). A nationwide survey in Nigeria that involved children and adults (aged 2 to 90 years) showed an overall seroprevalence of 12.2% for HBsAg, with more significant variability across age groups (Nasidi et al. 2016).

In addition, studies in Nigeria showed marked variation in the prevalence among children with a range of 3.9 to 19.0% depending on the geographical locations and population of the study (Ndako et al. 2011, Ashir et al. 2010, Jibrin et al. 2014, Lawal et al. 2020). Whereas viral hepatitis B is highly endemic in Nigeria, the predominant mode of spread of the disease is vertical transmission from mothers to their children, with a lesser contribution from child to child in early childhood (Ashir et al. 2010). The impact of viral hepatitis B infection is more in children, where the propensity to progress to chronic disease could be as high as 90% for the perinatally acquired infection (Stevens et al. 1979).

A critical and most effective strategy for reducing the burden of new HBV infection to less than 90% by 2030 (World Health Organization (WHO) strategy goal towards making HBV more minor public health threat) is birth dose vaccination (World Health Organization 2016a, World Health Organization 2017). The Hepatitis B vaccine has an efficacy of 95%, and dramatically reduces the chance of mothers transmitting the disease to their children when given early. Indeed, the more tremendous success recorded in reducing the burden of viral hepatitis B in Europe, some Asian countries, and Americans was attributed to vaccination, including birth dose (Alter 2003, Álvarez et al. 2017). HBV vaccination led to a reduction from about 8.3% (regional average) to less than 1% in the Western Pacific region (Wiesen et al. 2016).

The importance of vaccines in the global eradication of viral hepatitis B made the WHO recommend that newborns receive hepatitis B birth dose (HepB-BD), preferably within 24 hours of birth (World Health Organisation 2017). This WHO position has been adopted by many countries, inclusive of Nigeria. Nigeria adopted HepB-BD in 2004 (Sadoh & Sadoh 2014). Nigeria gives HepB-BD within a designated period of 24 hours of birth. Though the HepB-BD vaccine is monovalent, it is usually given along with oral polio and BCG vaccines; both of which are allowed up to the 14th day of life; which means it may be delayed (Sadoh et al. 2013, Chido-Amajuoyi et al. 2018).

Although there is no universally acceptable definition of timeliness for the HepB-BD vaccine, WHO recommends the first 24 hours of life (World Health Organization 2007). The provision of hepatitis B birth dose reduced the chance of perinatal transmission and remained a crucial strategy in preventing HBV infection in the endemic countries (Wiesen et al. 2016).

A few years after the hepatitis B vaccine became available in Nigeria, few studies have assessed the timeliness of birth dose vaccines in Nigeria, and none focused on the HepB-BD vaccine (Sadoh & Eregie 2009; Ibraheem et al. 2019, David et al. 2020). Besides, the studies were carried out in the other regions of the country, excluding the north-western geopolitical zone, the region with the least immunization coverage (National Bureau of Statistics (NBS) and United Nations Children's Fund (UNICEF) 2018).

The Nigeria Demographic and Health Survey in 2017 indicated that the region has the least coverage for routine immunizations coverage rate of 13.7% for Pentavalent 3 (National Bureau of Statistics (NBS) and United Nations Children's Fund (UNICEF) 2018). Thus, the implementation of the HepB-BD vaccine remains unknown, mainly in the north-western geopolitical region of the country. This calls for an appraisal of the level of HepB-BD vaccine, identifying the gaps, and probably proffer solutions as the country strife to meet the global target of a 90% reduction in the burden of HBV infection by 2030.

Thus, we hypothesized that the uptake of HepB-BD was low and influenced by some local factors. Hence, we determined the timeliness HepB-BD vaccine and associated factors. We also described factors that cause the delay of HepB-BD to identify measures that may improve coverage.

MATERIALS AND METHODS

Ethical considerations

We obtained ethical approval from the Ethical Review Committee of the Federal Medical Centre, Katsina, Nigeria. We obtained informed consent from the mothers or caregivers after clearly explaining the study details to them. The confidentiality of the data was also ensured. All mothers were educated about the importance of immunization and the number and timing of each immunization appointment.

Study design and location

This descriptive cross-sectional study was conducted in Federal Medical Centre, Katsina, Katsina State, from February to July 2019. Katsina state is located in the northwest geopolitical zone of Nigeria. It lies approximately 12^{o}59 N and 7^{o}36 E. Based on the last census (2006) in Nigeria, the Katsina Local Government Area had a population size of 318,459 with an annual growth rate of 3%.

Though a tertiary health facility, the hospital provides routine immunization services in collaboration with Katsina State Primary Health Care Development Agency. The immunization post runs daily on weekdays (Monday to Friday) from 8:00 am to 3:00 pm. The average number of newborns attending routine vaccination was 141 per month (Immunization record).

Sample size estimation

We estimated the minimum sample size required for the study from the proportion formula (Kasiulevičius et al. 2006).

$$n = \frac{z^2 pq}{d^2}$$

Where:
n = minimum sample size
z = the standard normal deviate usually set at 1.96 and corresponds to a 95% confidence interval.
p = the proportion in the target population estimated to have a particular characteristic, using 53.8% obtained in a study in Northcentral Nigeria (David et al. 2020)
q =1-p
d = tolerable margin of error was set at 5%. Hence, the minimum size obtained was 381. However, 400 mothers-infants paired were recruited.

Study population

The study populations were the infants and their respective mothers/caregivers who presented at the immunization clinic for their first vaccination dose during the study period.

Study inclusion criteria

Mothers/caregivers who brought their newborns for the first round of vaccines gave consent to participate in the study.

Study exclusion criteria

Mothers/caregivers whose babies had received the first doses of vaccines (before presentation), and those whose vaccination cards could not be cited for verification.

Data collection

We enrolled every mother-baby pair who fit the inclusion criteria till the sample size was attained. A trained research assistant administered a pretested semi-structured interview-based questionnaire. The research attendant was a nursing student trained in filling the study proforma. Information obtained included the sociodemographic details of the mother-child pair presenting for vaccination, such as sex of the child, age of mother, religion, marital status, level of education, and occupation of the child's parents. We classified the socioeconomic class based on Oyedeji's socioeconomic classification (Oyedeji 1985). Details of antenatal care clinic (ANC) attendance, place of birth for the index child, and the child's birth order were also recorded.

Definition of terms

Timeliness for HepB-BD vaccine was defined as those that received the vaccine within 24 hours of birth (WHO).

Outcomes measured

The primary outcome measure for this study was the proportion of newborns that received their HepB-BD within 24 hours of life. The secondary outcomes included variables associated with the timeliness of HepB-BD and factors that contributed to the delayed HepB-BD vaccine.

Data analysis

We analyzed the data using the IBM® SPSS version 25.0 (*IBM corporation, Virginia, U.S.A.*). Parents' ages were normally distributed and expressed as mean with standard deviation (SD), while the infants' age (not normally distributed) was summarised as median with interquartile range (IQR). The categorical variables were summarized as frequency and percentage. The number of children that received the HepB-BD was expressed over the total number of children recruited to determine the proportion of children on day 1 (timeliness), day 7, and day 14. A simple odds ratio expressed the relationship between timeliness and other variables. Variables that were less than 0.02 from the odds ratio were entered into binary logistic regression and expressed as adjusted odds ratio (AOR) with a 95% confidence interval to identify factors associated with timeliness. We summarized the reason for delayed vaccination with a frequency and percent Table. A p-value of less than 0.05 was taken as the level of statistical significance.

RESULTS

The median age of the infants was 12 (interquartile range-6.25 to 17) days. The age ranges from 0 (day of birth) to 197 days. Of the 400 recruited babies, 216 were males (54.0).

The mean (SD) age of the mothers was 27.65 (5.71) years, ranging from 16 to 45 years, and the mean (SD) age of the fathers was 37.63 (7.09) years. Most mothers were married (99.8%) and from monogamous family settings (66.3%). Also, 96.5% (386) had more than three antenatal clinics (ANC) visits, and most were delivered at a government health facility (88.5%). About 50.0% of the mothers had a secondary level of education, though most were unemployed (59.0%). Table 1 also shows that most respondents were from the middle class (47.8%). Of the 400 children paired with their mothers, 135 (33.8%) were fourth born and above.

Out of 400 infants, 44 (11.0%) received hepatitis B birth dose vaccine within 24 hours of life. At the end of the first and second weeks of life, 105 (26.3%) and 274 (68.5) infants received hepatitis B birth dose vaccine, respectively (Table 2). The median (interquartile range) duration of the first dose of the Hepatitis B vaccine was 12 (6.25, 17) days (Table 2).

Factors associated with hepatitis B birth dose vaccine within 24 hours of life included a higher birth order-3rd born (odds ratio 5.906, 95% CI 1.342, 26.339). In contrast, mothers whose occupation belongs to group 2 are less likely to receive the hepatitis B vaccine within 24 hours (odds ratio 0.215, 95% CI 0.072, 0.639), as shown in Table 3.

Table 1. General characteristics of the study population

Variables		Frequency(n=400)	Percent
Mothers' age group (years)	Less than 25	168	42.0
	26 to 35	195	48.7
	36 to 45	37	9.3
Fathers' age group (years)	Less than 25	13	3.3
	26 to 35	170	42.5
	36 to 45	170	42.5
	Greater than 45	47	11.7
Marital status	Married	396	99.0
	Unmarried	4	1.0
Family type	Monogamous	265	66.2
	Polygamous	135	33.8
ANC attended	None	6	1.5
	1 to 3 visits	8	2.0
	More than three visits	386	96.5
Place of birth	Home delivery	31	7.8
	Government hospital	354	88.4
	Private hospital	15	3.8
Mothers' educational level	None	14	3.4
	Primary/Islamic	33	8.3
	Secondary	196	49.0
	Tertiary	157	39.3
Fathers' educational level	None	19	4.8
	Primary/Islamic	8	2.0
	Secondary	81	20.2
	Tertiary	292	73.0
Mothers' occupations*	Group 1	18	4.5
	Group 2	16	4.0
	Group 3	89	22.2
	Group 4	41	10.3
	Group 5	236	59.0
Socioeconomic class	Upper	112	28.0
	Middle	191	47.7
	Lower	97	24.3
Child's birth order	1st born	114	28.5
	2nd born	86	21.5
	3rd born	65	16.2
	4th and above	135	33.8

ANC-antenatal clinic; Group 1-Professional senior civil servants, large business owner and contractors; Group 2-Non-academic professionals e.g., nurses, secondary school teachers, medium size business owner, intermediate grade public servants; Group 3-junior school teachers, non-manual skilled workers such as clerks, drivers, artisans; Group 4- Petty traders, messengers, labourers; Group 5- Unemployed, students.

Mothers' age, family type, place of delivery, attendance of antenatal clinics, family socioeconomic status, and days of the weeks the infants were delivered were not associated with the timeliness of the hepatitis B birth dose vaccine (Table 3).

After controlling for confounders, multivariate analysis (binary logistic regression) showed that mothers being educated (primary- adjusted odds (AOR) 17, 95% CI 1.404, 204.611), secondary- AOR 5.9, 95% CI 1.148, 29.895), and tertiary AOR 7.7, 95% CI 1.228, 48.545). Higher birth order (3rd born AOR 8.2, 1.625, 41.018) was significantly associated with an infant receiving a hepatitis B dose vaccine within 24 hours. In contrast, mothers whose occupation belongs to group 2 are less likely to receive the hepatitis B vaccine within 24 hours (AOR 0.143, 95% CI 0.037, 0.554), as shown in Table 3.

Table 2. Hepatitis B vaccination status of the infants (n=400)

Hepatitis B vaccination status	Frequency	Percent	95% Confidence interval
Hepatitis B vaccine within 24 hours (birth dose)	44	11.0	8.0, 14.0
Hepatitis B vaccine received from day 0 to 7	105	26.3	21.9, 30.6
Hepatitis B vaccine received from day 0 to 14	274	68.5	64.0, 73.0
Median (IQR) duration (days) of first dose of hepatitis B vaccine	12.0 (6.25, 17.0)		
Range (days) of the first dose of Hepatitis B vaccine	0 to 197		

Table 3. Multivariate analysis of factors that were associated with Hepatitis B birth dose vaccination within 24 hours

Variables	N (44)	OR	95% CI	p-value	AOR	95% CI	p
Mothers' age (years)							
Less than 25	20 (45.5)	1					
26 to 35	19 (43.1)	1.252	0.644, 2.434	0.508			
36 to 45	5 (11.4)	0.865	0.302, 2.476	0.787			
Fathers' age (years)							
Less than 25	2 (4.5)	1					
26 to 35	16 (36.4)	1.750	0.356, 8.600	0.491			
36 to 45	21 (47.7)	1.290	0.267, 6.228	0.751			
Above 45	5 (11.4)	1.527	0.260, 8.958	0.639			
Family type							
Monogamous	34 (77.3)	1					
Polygamous	10 (22.7)	1.840	0.880, 3.848	0.105	2.353	0.966, 5.729	0.060
ANC attended							
None	0 (0)	1					
1 to 3 visits	0 (0)	1.615	0.627, 4.161	0.321			
> 3 visits	44 (100.0)	1.328	0.640, 2.758	0.447			
Place of birth							
Home delivery	1 (2.3)	1					
Govt. hospital	42 (95.4)	0.467	0.027, 8.015	0.599	0.437	0.023, 8.889	0.590
Private hospital	1 (2.3)	0.248	0.033, 1.863	0.175	0.270	0.031, 2.374	0.238
Mothers' educ.							
No formal educ.	3 (6.8)	1					
Primary	1 (2.3)	8.727	0.820, 92.854	0.073	16.952	1.404 204.611	0.026
Secondary	21 (47.7)	2.273	0.587, 8.806	0.235	5.859	1.148, 29.895	0.033
Post-secondary	19(43.2)	1.981	0.507, 7.747	0.326	7.720	1.228 48.545	0.029
Fathers' educ.							
No formal educ.	1 (2.3)	1					
Primary	1 (2.3)	0.389	0.021, 7.111	0.524			
Secondary	7 (15.9)	0.587	0.068, 5.081	0.629			
Post-secondary	35 (79.5)	0.408	0.053, 3.151	0.390			
Mothers' occupation.							
Group 5 ref	27 (61.4)	1					
Group 1	1 (2.3)	2.196	0.281,17.166	0.453	1.514	0.168, 13.622	0.711
Group 2	6 (13.6)	0.215	0.072, 0.639	0.006	0.143	0.037, 0.554	0.005
Group 3	9 (20.5)	1.148	0.517, 2.548	0.734	1.220	0.506, 2.938	0.658

Group 4	1 (2.3)	5.167	0.682, 39.125	0.112	5.643	0.714, 44.613	0.101
SEC							
Lower	7 (15.9)	1					
Upper	13 (29/5)	0.592	0.226, 1.550	0.286	0.607	0.139, 2.648	0.507
Middle	24 (54.5)	0.541	0.224, 1.305	0.172	0.404	0.142 1.151	0.090
Birth order							
1st born	18 (40.9)	1					
2nd born	11 (25.0)	1.278	0.569, 2.870	0.552	1.656	0.695 3.950	0.255
3rd born	2(4.5)	5.906	1.342, 26.339	0.020	8.165	1.625, 41.018	0.011
4th and above	13 (29.5)	1.760	0.821, 3.770	0.146	3.831	0.677 4.008	0.272
Birth day **							
Weekend	10 (22.7)	1					
Weekdays	34(77.3)	0.713	0.340, 1.495	0.370			

OR- odds ratio, AOR-Adjusted odds ratio; ANC-antenatal clinic; educ-education; Occup-occupation; ** days of the weeks the infants were born. Occupational classifications (Group 1-Professional senior civil servants, large business owners, and contractors; Group 2-Non-academic professionals, e.g. nurses, secondary school teachers, medium-size business owners, intermediate grade public servants; Group 3-junior school teachers, non-manual skilled workers such as clerks, drivers, artisans; Group 4- Petty traders, messengers, laborers; Group 5- Unemployed, students)

Table 4. Factors or reasons for delay in hepatitis B birth dose

Variables n=277		Frequency	Percent
Maternal-related factors n=129	Mother was sick	37	13.4
	Not aware she needs to bring the child within 24 hours for hepatitis B dose vaccine	26	9.4
	Delivered weekend	25	9.0
	Decides to come after naming ceremony	18	6.5
	Mother traveled	6	2.2
	Mother had cesarean delivery	17	6.1
Healthcare-related factors n=45	Given appointment to come later at the delivery facility	31	11.2
	Out of stock	14	5.1
Infants' factors n=29	Baby was sick	29	10.5
Others n=74	No reasons	72	26.0
	Father declined	2	0.6

Out of 277 respondents that provided reasons, maternal-related factors were the commonest (129; 46.6%) for delayed hepatitis B birth dose, with maternal illness the most commonly cited reason (37; 28.7%). Other reasons included being given an appointment to come later at the delivery facility (31; 11.2%) and baby sickness (29; 10.5%). Worthy of note is that only two fathers declined vaccination (0.6%), as shown in Table 4.

DISCUSSION

Hepatitis B birth dose vaccine remains a crucial strategy to combat the HBV infection in an endemic country like Nigeria. This study showed low uptake (11%) of hepatitis B dose vaccine based on the timeliness within 24 hours recommended by WHO. The percentage of children that received the HepB-BD vaccine was low compared with 50% and 53.8% reported in Ilorin (Ibraheem et al. 2019) and Jos (David et al. 2020), respectively in Northcentral Nigeria;. However, both studies included oral polio and BCG vaccines. The number of children that had HepB-BD based on timeliness was also far less than 62.8% of children that received the HepB-BD vaccine within 24 hours of birth among Vietnamese children (Álvarez et al. 2017) and other high-income countries (Wiesen et al. 2016, Álvarez et al. 2017). In contrast, the value obtained in this study was higher than 1.3% reported in Benin (Sadoh & Eregie 2009), south-south Nigeria, which may reflect the years apart in the studies. The Benin study was done more than a decade before the present study.

The number of children vaccinated within 24 hours was also far higher than 1.1% in the Gambia (Miyahara et al. 2016). The low value obtained in this study compared with the north-central studies may be due to the focus on the hepatitis b birth dose received within 24 hours compared with the other studies that included other vaccines (polio and BCG), both of which can be given up to 14 days after birth. Besides, the low value in this study could also reflect low coverage of immunization in north-western Nigeria, inclusive of the state where this study was conducted. Also worthy of note is the progressive increase in the number of children that received the first dose within 14 days

(68.0%), raising the possibility that a continuous schedule along with other antigens that allowed up to two weeks of life may have contributed to the delayed HepB-BD vaccine. The import of this low level of HepB-BD vaccine suggests an urgent need for a scale-up, especially if the country will meet the set global target of a reduction to 90% in the burden of new HBV infection since the vertical route remains the leading route of transmission in the country.

This study also showed that a higher birth order (3rd born) was associated with six times the likelihood of timeliness of HepB-BD vaccine compared with the firstborn. In contrast to the observation in this study, findings in the Western Region of Gambia showed that higher birth order was associated with delayed timeliness for vaccination (Miyahara et al. 2016). This finding also contradicted the observation in Ilorin, which showed that the timeliness of birth dose vaccines was unrelated to birth orders. The observation that the older birth order likely got HepB-BD within 24 hours may have reflected the maternal experience and probably improved knowledge as they gave birth to more children. Hence, they may have recognized the importance of early vaccination.

This study also showed that maternal age, place of delivery, and socioeconomic class were not related to the timeliness of the HepB-BD vaccine. In Ilorin (Ibraheem et al. 2019), place of birth (hospital delivery), and attendance at the antenatal clinic were the factors that were associated with the timeliness of birth dose vaccines. In contrast, Jos' study showed that socioeconomic status and maternal age were associated with timeliness for birth dose vaccines (David et al. 2020). In Vietnam, low birth weight, age less than 20 years, and socioeconomic status were associated with timeliness for the HepB-BD vaccine. This observation affirms the previous findings of variability in factors that may contribute to the timeliness of HepB-BD and the need to identify local factors that will help in planning and policy formation (World Health Organization 2016b, Moturi et al. 2018).

After controlling for confounders, factors associated with timeliness of hepatitis B birth dose included mothers being educated, with those with primary education 17 times more likely to bring their children for HepB-BD vaccine within 24 hours compared with those without formal education. This finding supported most studies that showed education as the key determinant of timeliness presentation for vaccination (Miyahara et al. 2016, Chido-Amajuoyi et al. 2018, Anh et al. 2019). Maternal education (at least at the primary level) has been shown to improve women's understanding and knowledge and encourage better child health care practices, including attendance at immunization clinics. We also observed that those at middle occupational levels are less likely to vaccinate their children for HepB-BD vaccine at birth. This may be related to their work because they may be busy at work while pregnant and see the delivery period as the time to rest.

The common reasons for delayed HepB-BD vaccine were maternal-related factors, with the commonest being maternal illness (13.4%). This finding differs from other parts of Nigeria, where out-of-stock (Sadoh et al. 2013, David et al. 2020) and delivery at the weekend (Ibraheem et al. 2019) were identified as the leading cause of delay in the timeliness of birth dose vaccines. The focus of attention on the sick mothers may have prevented the relatives and caregivers from remembering the newborns for vaccination. This also calls for a review of health facilities policy that allows immunization to be taken to the mothers who just delivered and afford the babies the opportunity not to miss vaccination.

Strength and limitation

The limitation of this study was being a single-center study and may not have been a reflection of the number of newborns who received HepB-BD vaccine in the state.

CONCLUSION

A very low level of HepB-BD vaccine uptake among the infants presented at an immunization post in the North-western part of Nigeria. This finding calls for urgent interventions to scale up the delivery of HepB-BD if the country meets the global goal of a 90% reduction in the new HBV infection. Factors that were associated with vaccination within 24 hours of birth included maternal education (at least primary level) and higher birth order. The most typical reason for delayed HepB-BD was a maternal illness, which calls for a review of a hospital policy that would allow birth dose vaccines to be taken to mothers in their words. By doing so, the missed opportunity can be avoided.

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Conflict of interest

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Author contribution

OKI and KMI conceptualized, wrote, and revised the manuscript. KA reviewed, finalized the manuscript and managed the administration. IML and OKI were final check.

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Original Research

8-HYDROXYDEOXYGUANOSINE URINE AND TOTAL NITRIC OXIDE SERUM IN CHRONIC KIDNEY DISEASE

Putri Aliya Ahadini[1], Mochammad Thaha[2,4], Arifa Mustika[3]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Indonesian Society of Internal Medicine

ABSTRACT

Oxidative stress is essential to chronic kidney disease (CKD). Several markers include 8-Hydroxydeoxyguanosine (8-OHdG) and Nitric Oxide (NO). Reactive oxygen species (ROS) and Reactive Nitrogen Species (RNS) increased in CKD and had a role in renal impairment progressivity. There are some controversies regarding oxidative markers in CKD patients in several studies. This study aimed to understand oxidative markers 8-OHdG and NO and explained the correlation of both markers in hemodialysis and non-hemodialysis CKD patients. Twenty hemodialysis patients and forty-nine non-hemodialysis patients were enrolled in this cross-sectional study. Urine patients were collected to measure 8-OHdG using the enzyme-linked immunoassay (ELISA) method, and NO was measured from serum patients using the Griss Saltzman method. Based on Bivariate Pearson analysis, there was no significant correlation between 8-OHdG urine and total NO serum in the hemodialysis group (p= 0,510, p>0.05) and in the non-hemodialysis group (p= 0.801, p>0,05). In this study, DNA oxidative marker, 8-OHdG, was not correlated with NO in CKD patients.

Keywords: *Chronic kidney disease; 8-hydroxydeoxyguanosine; nitric oxide; oxidative stress; life expectancy*

Correspondence: Mochammad Thaha, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. E-mail: mochthaha@yahoo.com

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Highlights:

1. Oxidative markers 8-Hydroxydeoxyguanosine and Nitric Oxide was found high in hemodialysis and non-hemodialysis chronic kidney disease patients.
2. There is no correlation between 8-Hydroxydeoxyguanosine and Nitric Oxide in hemodialysis and non-hemodialysis chronic kidney disease patients.

INTRODUCTION

Chronic Kidney Disease (CKD) is a clinical diagnosis of decreased kidney function characterized by a progressive decrease in the Glomerulus Filtration Rate (GFR). Kidney disease, including CKD, contributes to the world's diseases with a mortality rate of 5-10 million people (Luyckx et al. 2018). The global CKD prevalence is 11 to 13%, contributing to a significant cost burden on healthcare systems worldwide (Hill et al. 2016).

Oxidative stress is the primary key that causes the pathogenesis of CKD (Duni et al. 2019). Oxidative stress indicates an imbalance between pro-oxidants and antioxidants that lead to kidney damage (Ravarotto et al. 2018). Oxidative stress shows the progression of kidney dysfunction because Reactive Oxygen Species

(ROS) and Reactive Nitrogen Species (RNS) accumulation accelerates kidney damage through cytotoxic mechanisms (Duni et al. 2017).

Nitric Oxide (NO) is considered the key directly involved in oxidative stress-mediated kidney disease (Duni et al. 2019). An increase in NO is found in CKD patients due to an increase of inducible-Nitric Oxide Synthase (i-NOS) – one of the enzymes that trigger NO formation due to inflammation (Toualbi et al. 2020). Another evidence indicated that NO production is decreased in CKD, even in the early stage, due to endothelial dysfunction (Baylis 2006). NO interacts with one of the ROS, superoxide radicals ($O_2^{\cdot -}$), and induced peroxynitrites ($ONOO^-$) formation (Duni et al. 2019).

Oxidants that interact with cellular nucleic acids can cause cell death due to the inactivation of mitochondrial enzymes and directly cause DNA damage, transcription factors, and enzymes for DNA repair (Putri & Thaha 2014). Hydroxyl (OH-) targets the DNA of cells and mitochondria, causing them to contain free radicals and forming several oxidation products (Sung et al. 2013). Damage to DNA due to the accumulation of oxidants causes the emergence of oxidative stress markers, namely 8-OHdG (Putri & Thaha 2014). 8-Hydroxydeoxyguanosine is a product of DNA damage caused by oxidative stress produced by specific enzymatic cleavage following 8-hydroxylation of guanine bases (Ghanayem et al. 2017). Levels of 8-OHdG can be known through intact urine specimens without going through other metabolic stages (Sung et al. 2013).

Theoretically, there was a correlation between 8-OHdG and NO in CKD, caused by oxidative stress (Alsagaff et al. 2020). Peroxynitrite formed due to the reaction between NO and O_2 increases RNS cytotoxic. These compounds can cause oxidative DNA damage, leading to the appearance of 8-OHdG. Thus, this study aimed to prove whether there was a correlation between 8-OHdG, DNA damage marker, and NO in CKD.

MATERIALS AND METHODS

A cross-sectional study was conducted on 20 hemodialysis patients and 49 non-hemodialysis patients at Universitas Airlangga Hospital, Royal Hospital, and Premiere Hospital in Surabaya, Indonesia, and conducted in April 2017-July 2017. The Ethical Committee of Universitas Airlangga Hospital had approved this study under decree No. 187/KEP/2021. The inclusion criteria for the participants were patients over 21 years old with CKD undergoing routine treatment for more than three months at three hospitals (non-hemodialysis group); patients over 21 years old with CKD undergoing chronic hemodialysis for more than three months at these hospitals (hemodialysis group). Data were collected through blood and urine sampling. Blood serum was measured for NO, and urine sampling for 8-OHdG.

According to the manual instruction, 8-OHdG was measured in urine using the enzyme-linked immunoassay method with Bioxytech 8-OHdG-EIA (Cat. No. 21026, Oxis Health, USA). The patients were measured by Microplate Reader 680 with 96 healthy plate format (Biorad, USA). The concentration of urinary 8-OHdG was then determined by comparing the patients' optical density (OD) to the standard curve, then corrected by renal filtration rate using creatinine, then reported in units of ng/mg creatinine. Total nitric oxide was measured using the sample's nitrite and nitrate measurement approach using the colorimetric principle with the Griess reaction method. The reagent used was the Total Nitric Oxide Parameter kit (R&D Systems, USA) with catalog number KGE001. The tool used was Microplate Reader 680 with 96 healthy plate formats (Biorad, United States), and a 10 kDa ultrafilter used was Vivaspin 500 (Sartorius, Germany). Total NO serum was reported in units of umol/L.

Data were presented as mean±SD. Bivariate Pearson tests were performed to assess the correlation between variables. $P < 0.05$ following two-tailed analysis was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, New York, USA).

RESULTS

The characteristics of the patients are shown in Table 1. The age range of the study patients was 21-80 years. In both groups, most patients were between the age of 51-60. The study sample was divided into two groups: patients who did continuous hemodialysis and those who did not. Most patients in the continuous hemodialysis group were 12 males (17.39%) and eight females (11.59%). The total number of patients for the group undergoing continuous hemodialysis was 20 (29.99%). The group that did not undergo hemodialysis consisted of 27 males (39.13%) and 22 females (31.89%). The total number of patients for the group that did not undergo hemodialysis was 49 (71.01%). Thus, male patients outnumbered females in both groups.

Table 1. Patient's characteristic

Characteristic	Hemodialysis Group	Non-hemodialysis group
Age (years)	56.7±11.41	58.6±5.96
Male/female n (%)		
Male	12 (17,39%)	27 (39,13%)
Female	8 (11,59%)	22 (31,89%)
Total of sample n (%)	20 (29,99%)	49 (71,01%)
Total all patients n (%)	69 (100%)	

The mean level ± SD of 8-OHdG urine in the hemodialysis group was 4.46±3.24 ng/mg creatinine, while the mean level in the non-hemodialysis group was 10.55±6.07 ng/mg creatinine. The normality Unpaired T-Test showed that the data of the two variables in this group were not normally distributed (Sig. <0.005). The data on the non-hemodialysis group were the mean level ± SD of 8-OHdG urine was 72.65±36.79 umol/L, while the mean level of urinary Total NO serum from the patients was 61.81±61.80 umol/L. The normality unpaired t-test showed that the data of the two variables in this group were typically distributed or homogenous (Sig. >0.005). Thus, NO was found to increase, and 8-OHdG was high in both groups. Those proved the occurrence of oxidative stress in CKD patients.

Table 2. Correlation between 8-OHdG and Total NO serum of the study patients based on bivariate Pearson analysis

	Hemodialysis group	Non-hemodialysis group
Correlation coeff. (r)	-0.156	-0.037
Significance (p)	0.510	0.801

A Bivariate Pearson correlation test was performed to determine the correlation between urinary 8-OHdG and serum NO in CKD. Based on Table 2, there was no significant association between 8-OHdG with NO in the hemodialysis group (p=0.510, r=-0.156) and the non-hemodialysis group (p=0.801 r=-0.037). This uncorrelation means that 8-OHdG and NO do not affect each other's value.

DISCUSSION

We obtained that the level of 8-OHdG urines was high in both groups, particularly in the non-hemodialysis group. A previous study showed that in hemodialysis patients, 8-OHdG levels were higher than those without hemodialysis because circulating ROS increased by 14x acutely after a dialysis session (Duni et al. 2019). Meanwhile, there was also an increase in serum 8-OHdG levels in pre-HD CKD patients, not associated with eGFR (Dai et al. 2019). Therefore, the more significant rise in 8-OHdG may occur in the non-hemodialysis group, so it generally has a lower severity than the hemodialysis group with higher eGFR values.

Total NO serum was increased in both groups. A study showed an increase in total serum NO in CKD patients undergoing hemodialysis (Meenaski & Agarwal 2013). It was caused by the dialysis process, which stimulates cytokines to increase Nitric Oxide Synthase (NOS), the NO-forming enzyme. This increase triggers cytotoxic substances that are responsible for causing complications, including hypertension and nitrosative stress. Toualbi et al. (2020) explained that the increase in NO was in line with the severity, and the highest was found in a group undergoing hemodialysis.

In contrast, another study showed a decrease in NO production and NO bioavailability (Roumeliotis et al. 2020). It is due to an increase in endogenous inhibitors of NOS. A decrease in NO was also found in CKD patients undergoing hemodialysis because hemolysis can cause an increase in free hemoglobin, which has a high affinity for binding NO (Roumeliotis et al. 2020).

In this study, there was no correlation between 8-OHdG urine and total NO serum in CKD, whether in the hemodialysis or non-hemodialysis group. Meanwhile, a study indicated that NO has a particular role that can cause the appearance of 8-OHdG (Hsu & Tain 2021). The study explained that in CKD, there are inhibitors of the NO-forming enzymes that cause NOS to become uncoupled and then cause NO to meet $O_2^{\cdot-}$ so that peroxynitrite ($ONOO^-$) is formed.

Peroxynitrite is a product of RNS which has a cytotoxic effect and causes oxidative damage to DNA. One of the oxidative DNA markers is 8-OHdG. Thus, further research is required to identify and focus on other factors affecting the 8-OHdG and NO values so that more significant results were obtained.

Strength and limitation

This study has several limitations, including the number of patients in the group that did not undergo hemodialysis was twice as large as other groups. Based on the unpaired t-test analysis results, the data on urine 8-OHdG levels in both groups showed that the data variation was not homogeneous. The group of CKD patients was also not differentiated based on severity. Some of these things can affect the results of the analysis and the final results of this study.

CONCLUSION

In this study, there was no significant correlation between 8-OHdG and NO in patients with CKD. Even though 8-OHdG is widely known as a biomarker of DNA oxidative stress, its role in CKD progression is the factor that affects the value, so further research is required.

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Conflict of interest

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Author contribution

AM conceptualied the study and managed the administration. PAA collected and analyed the data, and rote the manuscript. MT validated, revised, and finalied the manuscript

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Original Research

MANAGING HUMAN RESOURCES FOR SURGE CAPACITY IN REFERRAL HOSPITALS BASED ON WHO HOSPITAL READINESS CHECKLIST FOR COVID-19

Fitri Dinia[1], Mochamat Helmi[2], Laksono Trisnantoro[1]
[1]Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia
[2]Faculty of Medicine, Universitas Tarumanegara, Indonesia

ABSTRACT

One of the components of effective disaster response management to deal with surge capacity in referral hospitals in West Kalimantan, Indonesia, was to ensure the adequacy of the number of human resources (health workers). This study was conducted to evaluate three referral hospitals and identify the role of the West Kalimantan Provincial Health Office in managing human resources for health workers facing surge capacity due to the Covid-19 pandemic. This study used Rapid Assessment Procedures with qualitative and quantitative methods. Data were collected through observation and interview by using instruments adopted from the Checklist of WHO Hospital Readiness for Covid-19. Based on the checklist, 51.1% of referral hospitals had implemented HR management regarding staff availability. However, the readiness of referral hospitals in West Kalimantan to face surge capacity had not been optimal in several key components, such as staff availability, staff mobilization and recruitment, division of staff duties, and hospital staff welfare during the Covid-19 pandemic. The role of the Provincial Health Office had not been optimal in managing HR at referral hospitals. The Provincial Health Office only played an active role at the beginning of the Covid-19 pandemic, especially for the provision of volunteers. Meanwhile, in the second year of the Covid-19 pandemic, the role of the Provincial Health Office had decreased, especially in the staff availability and training at the referral hospitals. Therefore, the role of the West Kalimantan Provincial Health Office in HR management at the referral hospitals was highly not dominant (17.78%). The central government should regulate the authority of the Provincial Health Office as the leading sector in all types of referral hospitals to integrate all potencies and human resources of local governments to maximize HR management in referral hospitals to face surge capacity due to the increased cases of Covid-19.

***Keywords**: Covid-19; surge capacity; health policy; health system; public health; virus*

Correspondence: Fitri Dinia, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. Email: byan.adzra15@mail.ugm.ac.id

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Highlights:

1. Managing human resources for surge capacity in three referral hospital at West Kalimantan was evaluated.
2. Availability, mobilization and recruitment, duties division, and hospital staff welfare are the reasons for referral hospitals in West Kalimantan are not optimal to face surge capacity during the Covid-19 pandemic.
3. Provincial Health Office role had not been optimal in the HR management at referral hospitals during the Covid-19 pandemic.

INTRODUCTION

In December 2019, a new cluster of pneumonia outbreaks was found caused by strains of a newly identified β- coronavirus in Wuhan, China (Adhikari et al. 2020, Alhazzani et al. 2020). The Covid-19 pandemic is included in the biological disaster category because the concept of handling this pandemic is the same as disaster management (World Health Organization 2020). Effective disaster management can be implemented by improving the intensity of coordination and communication, eliminating ego-sectoral attitudes, and involving competent human resources (Ariyanto 2018, Firmansyah et al. 2020). The

government has made an effort to reduce the rate of the further spread of Covid-19 infection by issuing several guidelines, policies, and regulations to suppress the spread of infection and reduce mortality and morbidity due to Covid-19. The Health Office of the Province of West Kalimantan, Indonesia, to implement the regulation of the Ministry of Health, has set as many as fifteen hospitals as referral hospitals in West Kalimantan to provide Covid-19 services.

The increase in new infection, death, and recovered cases related to Covid-19 is sufficiently essential for local governments and health service providers, including policymakers in the health sector, to develop mitigation strategies in preparing for a possible surge in the number of Covid-19 patients (Kucharski et al. 2020). One of the components for effective disaster response in dealing with surge capacity in the health sector and medical services is to ensure the adequacy of the number of human resources for health workers, proper conditions, and meet the appropriate qualifications (Aziz et al. 2020, Rodriguez-Llanes et al. 2020, Al Mutair et al. 2020, Melnychenko 2020).

In the case of Covid-19 in West Kalimantan, human resources (abbreviated as HR) for health workers were certainly limited when many medical staffs and health workers were infected with the virus, so the need for human resources for health workers was greater. As of October 30, 2020, the West Kalimantan Provincial Health Office reported that as many as 440 health workers in West Kalimantan were exposed to the virus due to fatigue and the large number of patients who had to be treated. This condition has caused the temporary closing of the referral hospitals and the recruitment of volunteers to cover the shortage of human resources.

Effective and efficient health management still becomes a challenge at the local government level, especially at the Health Office. Generally, the West Kalimantan Provincial Health Office plays a significant role in implementing regulations for health sector programs/ activities at the regional level. To support the HR of health workers in overcoming limitations and achieving these targets, the Health Office can provide health programs for staff training and planning along with their main task and function in terms of coping with the pandemic (Djalante et al. 2020).

The experience of Covid-19 pandemic management in 3 countries, i.e., Austria, Italy, and Romania, revealed that weaknesses were found at the level of a human resource management system of health workers in hospitals. No other area has revealed the need for a European and trans-sectoral governance approach to the policy, management, and HR planning of health workers for migrant situations in getting long-term care due to Covid-19 (Kuhlman et al. 2020). Covid-19 makes the HR management of health workers in hospitals have a highly vital role because it requires considerable human resources care for Covid-19 patients (Chersich et al. 2020).

We noticed that there was a necessity to evaluate and solve problems in the readiness and management of health workers at the West Kalimantan referral hospital through Provincial Health Office policy in facing surge capacity due to Covid-19. Until now, there has been no policy prepared by the West Kalimantan Provincial Health Office to support the readiness to manage human resources for health workers to face potential surge capacity.

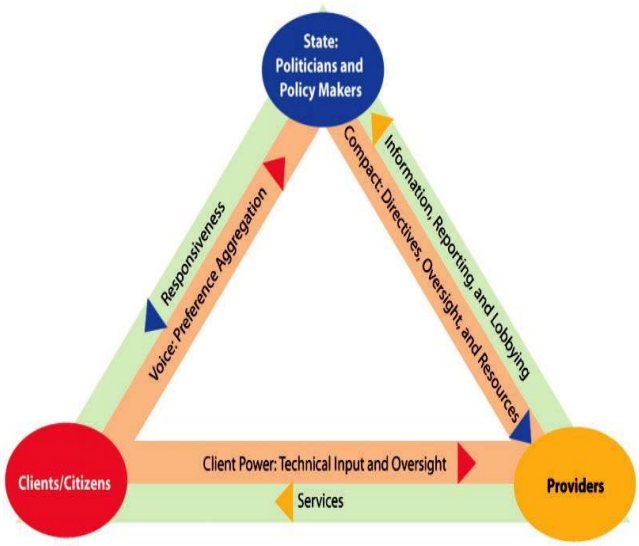
Rationale

The Indonesian government has tried to reduce the rate of further spread of Covid-19 infection by issuing several guidelines, policies, and regulations to suppress the spread of infection and reduce mortality and morbidity due to Covid-19. West Kalimantan had a risk category for increasing Covid-19 cases from day to day and had entered the red zone category (especially Pontianak city). In this regard, the Ministry of Health of the Republic of Indonesia has designated 132 hospitals spread throughout Indonesia as referral hospitals for the control of certain emerging infectious diseases, spread across 34 provinces.

The selection of referral hospitals that the Governor of West Kalimantan had determined was considered to have the capacity and ability to provide care for patients with certain emerging infectious diseases, such as the availability of human resources for health workers for special pulmonary health services with pulmonary disease specialists, internal medicine specialists, and surgeons, as well as appointed visiting doctors for pulmonary services at the hospital. Along with the increasing number of cases, whether it was a new infection, deaths, or recovered cases, some speculations required estimation of when and how many cases would be the turning point of the Covid-19 pandemic in Indonesia (Kucharski et al. 2020, Zulisda 2020). This prediction was important for local government and health service providers, including policymakers in the health sector (especially the West Kalimantan Provincial Health Office), to develop mitigation strategies in preparing for the possible surge in the number of Covid-19 patients in the region (Kucharski et al. 2020).

The West Kalimantan Provincial Health Office appealed to all referral hospitals to be able to handle the surge in patients properly, especially related to the existence of unusual or highly specialized medical service technicalities. This was relevant to the Covid-19 pandemic situation caused by a new Coronavirus strain, which required complex clinical treatment. Another problem was that West Kalimantan has a fairly large area, and the uneven distribution of health workers (only focused on the Pontianak City area) caused fears of a surge in Covid-19 patients in the area outside Pontianak.

Human resource management for health workers is increasingly being recognized as an important factor in the performance of the health system. However, conceptually and practically, it is still poorly understood and often unclear and competing with each other about what its role is and how to overcome its weaknesses (Brinkerhoff & Bossert 2013). In the health sector, HR management of health workers is largely treated more or less explicitly as a set of tasks or functions that are assumed to be carried out by or under the direction of the Ministry of Health (Brinkerhoff & Bossert 2013).



Source: World Bank (2004, 2007), Brinkerhoff & Bossert (2013)

Figure 1. The theory of human resource management for health workers of the world bank

The building block model of the World Health Organization (WHO) health system embodies the role of the Ministry of Health by labeling one of the blocks as 'leadership and governance' (Brinkerhoff & Bossert 2013). The three actors in governance shown in Figure 1 include States, Healthcare Providers, and Clients (citizens) based on the World Bank's work on service delivery and accountability.

The conceptualization of the tasks/functions of HR management for health workers is not sufficient to discuss the number of HR actors in the health system, the distribution of roles and responsibilities among HR health workers, as well as the ability and willingness of health workers to fulfill their roles and responsibilities (Brinkerhoff & Bossert 2013). Good management of human resources for health workers is defined as a system of values, policies, and institutions where the community manages economic, political, and social issues through the government, private and civil sectors (Manafi et al. 2019). Human resource governance for health workers is the most important component of good governance for human resources for health workers because the governance of the health system is committed to protecting and improving human health (Pyone et al. 2020).

MATERIALS AND METHODS

Design of the study

This study used the Rapid Assessment Procedures (RAP) design developed by Scrimshaw and Hurtado (Scrimshaw & Hurtado 1998). RAP is a qualitative research method as a combination of data collection techniques. This study was conducted from November 2020 to May 2021. Data were obtained from the formal and informal (casual) methods, such as interviews and a checklist adapted from WHO. The subjects in this study were three directors of referral hospitals in West Kalimantan Province, Indonesia, and three policy stakeholders in West Kalimantan Provincial Health Office, which were determined based on the purposive sampling technique. Data analysis was carried out by narratively presenting data from the results of the checklist distribution and the results of interviews. This study was conducted with the approval of the Research Ethics Commission of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada under decree Number KE/FK/0084/EC/2021, and the informed consent approved by the informants/research subjects had also been submitted.

Table 1. List of research subjects

No.	Names of hospital	Research subject	Amount	WHO checklist	Deep interview
1.	West Kalimantan Provincial Health Office	Head of Health Office (Stakeholder)	1	√	√
		Head of Health Services (Stakeholder)	1	√	√
		Head of Referral Health Services and Health Crisis (Stakeholder)	1	√	√
2.	Dr. Soedarso Hospital	Director	1	√	√
3.	Sultan Syarief Moh Alkadrie Hospital	Director	1	√	√
4.	Tanjungpura University Hospital	Director	1	√	√

Table 2. Hospital characteristics based on HR data for health workers and availability of beds for covid-19 patients

Names of hospital	Type	Number of health workers	Availability of ICU beds for Covid-19 + suspect patients	Number of ICU beds filled with Covid-19 positive patients + suspect	ICU drill (%)	Availability of ICU beds for Covid-19 + suspect isolation patients	Number of ICU beds filled with positive Covid-19	Number of bedrooms filled with suspect	Insulation drill (%)
Dr. Soedarso Hospital	A	448 people	12	10	83.33	85	59	8	78.82
Sultan Syarif Moh Alkadrie Hospital	B	314 people	2	1	50	20	9	2	55
Tanjungpura University Hospital	C	210 people	0	0	0	9	9	0	100

Source: Pontianak city COVID-19 handling acceleration task force team in 2021

Research context

The characteristics of referral hospitals in West Kalimantan included several components, namely the number of health workers, the availability and number of ICU beds for Covid-19 and suspected patients, and ICU BOR and isolation BOR.

RESULTS

WHO checklist results on referral hospitals

Based on the WHO checklist on referral hospitals, the total distribution value of the categories "implemented," "in progress," and "not yet implemented" was 45, with a total frequency of 100%. HR management that had been implemented was 44.4% (20 items/points in the checklist), 4.4% was “in progress” (2 items/points in the checklist), and 51.1% had not been implemented (23 items/points in the checklist). This figure showed that referral hospitals had not been able to fully implement the management of hospital human resources, especially health workers. Thus, referral hospitals in West Kalimantan were not yet ready to face surge capacity due to Covid-19.

In general, as many as 82.2% indicated the absence of the role in terms of recruitment and management of health workers in type A and C referral hospitals in the West Kalimantan Provincial Health Office to face surge capacity. On the other hand, the West Kalimantan Provincial Health Office played a major role in type B referral hospitals with a percentage of 17.8%.

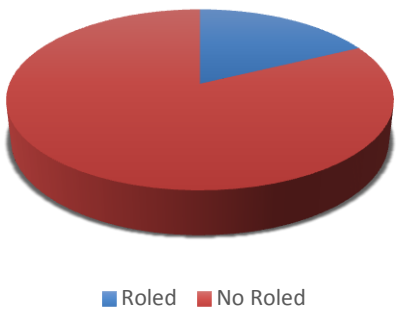


Figure 2. Percentage of evaluation of the role of the West Kalimantan Provincial Health Office in HR management at Covid-19 referral hospitals

The previous data had addressed that referral hospitals could not fully implement HR management based on the 2020 WHO checklist. The West Kalimantan Provincial Health Office also did not play an optimal role in HR management at Covid-19 referral hospitals, especially in facing surge capacity.

WHO checklist results on the role of referral hospitals

Many West Kalimantan Health Office policies had not been implemented, with a cumulative average percentage of 48.8%. This indicated that the influence and role of the West Kalimantan Health Office in referral hospitals were low. However, there were 35.7% of health office policies had been implemented well, including estimating and monitoring the attendance of referral hospital staff on a regular basis and identifying the minimum needs that include health care personnel and other hospital staff to ensure the operational adequacy of a particular hospital department, engaging in the recruitment and training of additional staff (i.e., retired staff, military reserve personnel, affiliates/students, and volunteers) as needed, providing training in areas that could potentially increase clinical demand, including emergency and intensive care to ensure adequate staff capacity and competence, and ensuring the provision of vaccines to all HR (health workers) at the hospital.

DISCUSSION

The role of the health office in hospital HR management to deal with surge capacity

In this study, the hospital readiness checklist for Covid-19 was used to observe the HR management at referral hospitals and the role and policies of the West Kalimantan Provincial Health Office. Since the beginning of the Covid-19 pandemic, the Provincial Health Office did not have a whole policy on referral hospitals. According to the results of the WHO checklist on staff contact, attendance monitoring, and staff leave policies at referral hospitals, there was no policy from the West Kalimantan Provincial Health Office. Based on the information, staff contact information, attendance, and leave or permission were regarded as internal issues (for the hospital only). The Provincial Health Office could not provide intervention, while the Covid-19 pandemic had caused a surge in the capacity of West Kalimantan Province referral hospitals.

During this emergency condition, the Provincial Health Office could not take part in setting an emergency plan to provide food, drink, and shelter/space for referral hospital personnel. The Provincial Health Office did have an emergency plan to deal with surge capacity due to Covid-19. However, the emergency plan was only in the form of providing food for referral hospital personnel, although not routinely. In addition, the Provincial Health Office did not play a role in prioritizing staffing requirements and distributing personnel at referral hospitals during the Covid-19 pandemic. The policy was internal to the hospital, and the Provincial Health Office could not regulate hospital personnel management. The staffing requirements were adjusted to the needs and regulations of the hospital, while the Provincial Health Office only provided an appeal.

The absence of involvement of the Provincial Health Officer in the management of health workers in referral hospitals was due to the existence of a law issued by the central government. Supposedly, the West Kalimantan Provincial Health Office, as the government's organizer in the regional health sector, can also help referral hospitals face surge capacity together with the Provincial and Regional Governments. The need for support and coordination between the central and local governments in handling Covid-19 was evidenced by a study, where the hospital services that the Ministry of Health appointed were not still sufficient to serve the increasing number of patients (Dewi & Setiyaningsih 2020).

Management of human resources for health workers at referral hospitals in West Kalimantan Province to face surge capacity

The availability of staff is an essential factor to complement the limited number of health workers in dealing with the situation of a surge in the number of patients due to Covid-19 at the West Kalimantan referral hospital. This conception also followed the

findings in the study of Utami et al. (2021). However, the study used the concept of surge capacity and ICS (Incident Command Systems) to deal with and anticipate the surge in Covid-19 patients. In this study, we recommended that staff contact in referral hospitals should also be the one who holds the critical information in mitigating HR management in referral hospitals. 66.7% of contact renewals had been carried out in type A and B hospitals, while 33.3% were in the process of being implemented in some type C hospitals.

Furthermore, referral hospitals in West Kalimantan had never identified the minimum need for health service personnel in other hospitals. The referral hospital only calculates its HR needs to ensure the adequacy of staff operations and never asks for help from other hospitals if there is a staff shortage. The shortage of health workers was also caused by some of the staff being infected with Covid-19. We highlighted the importance of maintaining and stabilizing the availability of health workers in the hospitals, especially the referral hospitals because health workers are prominent elements in all types of health events (Akbar et al. 2020, Rosita & Simamora 2021). According to Hersche et al. (1999), this is included in the hospital's preparedness phase in dealing with disasters.

Based on the theory of hospital preparedness (Russo et al. 2015), hospitals also need to ensure the appropriateness of the plan to the state regulations and its accordance with the standards set by accrediting organizations, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Comprehensive Covid-19 planning can also help the hospital plan for other emergency situations. Similarly, some possible treatments, such as preparing more wards and medical facilities, medicine, diagnostic tools, and Personal Protective Equipment, are other ways of facilitating hospitals to face emergencies (Djalante et al. 2020).

In disaster management, hospitals need adequate human resources, including personnel who are trained in emergency and disaster preparedness and have the relevant management skills (Wahyuni et al. 2020). Volunteers' increased knowledge and skills are beneficial for themselves and the process of interacting with the environment related to disaster management (Quyumi & Alimansur 2020), especially in handling and treating Covid-19 patients, which have different treatment characteristics from other patients (Pashar et al. 2020). Disaster emergency preparedness in the health sector involves a logical process, with activities ranging from policy formulation to ongoing monitoring and evaluation (Wahyuni et al. 2020).

In managing human resources in hospitals, task shifting or task sharing is one of the strategies related to the redistribution and stabilization of human resources. Task transfer is the transfer of autonomy in carrying out clinical actions from someone with higher qualifications to someone with lower qualifications. In contrast, the division of tasks is a form of cooperation and collaboration between several people with the same or lower qualifications to share clinical responsibilities while prioritizing communication, education, and training to maintain the quality of service provided. Moreover, patients who are already in the ICU who need equipment and prompt handling, especially patients with Covid-19 who are admitted into the ICU, are in more critical condition and greater need of extreme supportive treatment, such as mechanical ventilation, compared to patients in other hospital locations (Sen-Crowe et al. 2020). Certainly, competence and level of knowledge are important. However, in conditions of limited medical specialist resources, task division methods are preferable to ensure patient safety (Rosen et al. 2018). The ideal task-sharing process includes the training, implementation, monitoring, and evaluation phases (Figure 4).

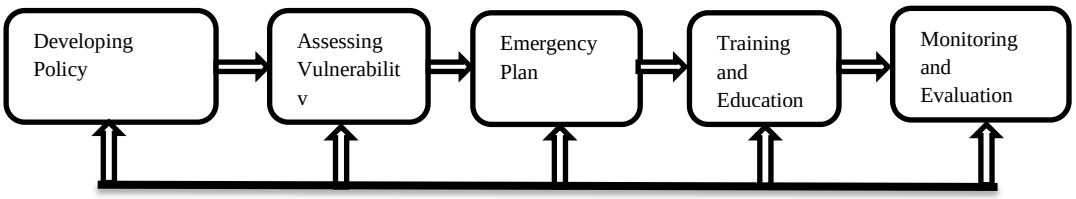


Figure 3. Process in health sector disaster emergency preparedness (WHO-WPR, 2006)

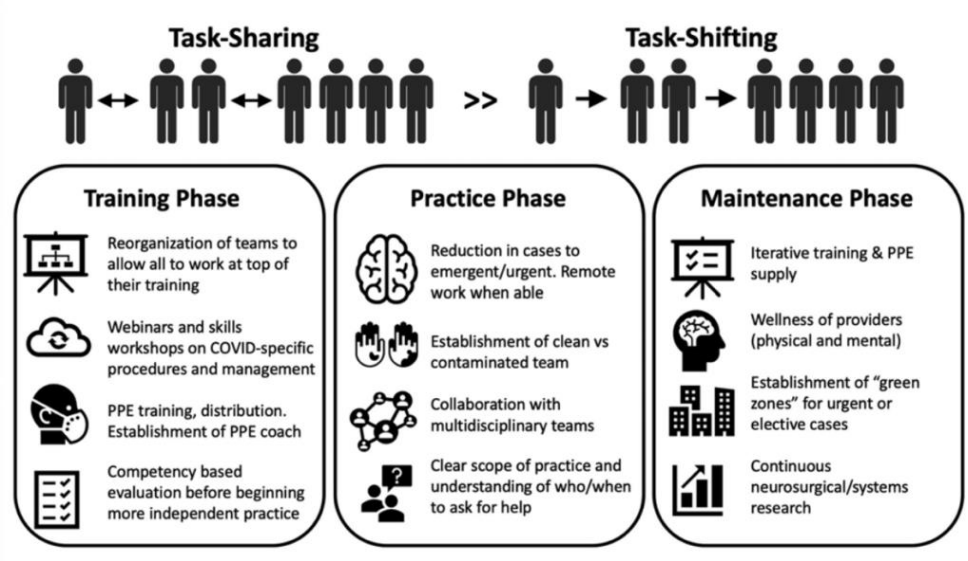


Figure 4. Task shifting process (Raams et al. 2018)

Figure 5. Disaster management cycle (World Health Organization 2020)

The previous management of human resources is expected to be in accordance with the disaster management cycle. When a disaster occurs, there will always be a chaotic situation that can disrupt the patient handling process and result in non-optimal results. With a good disaster plan, chaos will still occur, but efforts can be made to keep the time as short as possible, so services can still be carried out according to the standards set. In addition, mortality and morbidity can be reduced to a minimum (Garcia et al. 2017), especially during a pandemic (Figure 4).

The WHO restructuring in March 2019 recognized the need to strengthen critical health security responsibilities in responding to health crises and helping other countries prepare for health security. This issue is considered very important, so there is a new structural pillar in the organization, the emergency preparedness division, which reports directly to the Director-General. This will support countries in preventing and mitigating the impact of epidemics and other health crises (Simatupang 2017). In this study, we found systematic and strategic disaster management to handle and control the emergency situation in health cases. The human resource was the major factor that should receive an evaluation, and the hospital managers need to regularly evaluate the ratio of hospital staff and number of patients (Figure 5).

Strength and limitation

The study does not provide a detailed analysis of the reasons for the suboptimal readiness of referral hospitals and the limited role of the Provincial Health Office.

Further studies may be needed to investigate these issues in more detail.The study addresses an important issue related to disaster response management in West Kalimantan, Indonesia, during the Covid-19 pandemic. The study utilizes a checklist adopted from the WHO Hospital Readiness for Covid-19, which ensures the validity and reliability of the data.The study highlights the role of the Provincial Health Office in managing human resources in referral hospitals and provides recommendations for improvement.

CONCLUSION

Based on the study, almost all referral hospitals had implemented human resource management for health workers. Some managerial points had not been fully implemented, such as identification of minimum staff requirements for operational adequacy, insurance issues, temporary licensing related to additional staff and volunteers, cross-sectional health services and training, identifying domestic support for staff, and not yet providing staff with psychosocial support teams. This study recommended that the local government quickly build a system of providing health workers with an integrated data information system with all existing health organizations and health education institutions in West Kalimantan. Besides, the Provincial Health Office was expected to recruit human resources to carry out special supervision in each referral hospital to monitor and ensure the hospital's readiness for a health disaster such as Covid-19.

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Conflict of interest

None.

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Author contribution

FD- conceptualized, collected and analyed the data,
MH- wrote, and revised the manuscript.
FD and L- reviewed, finalized check analysis data and grammar.

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Original Research

A FIRST STEP TO NOVEL APPROACH FOR TREATING ALKALI INJURY OF THE CORNEA: EFFECT OF PLATELET RICH FIBRIN LYSATES ON CULTURED RABBIT (*Oryctolagus cuniculus*) LIMBAL STEM CELL PROLIFERATION EXPOSED TO SODIUM HYDROXIDE

Wahyu Endah Prabawati[1,3],Gatut Suhendro[1], Endang Retnowati[2]
[1]Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Mitra Sehat Mandiri Hospital, Sidoarjo, Indonesia.

ABSTRACT

Chemical injuries of the eye produce extensive damage to the ocular surface and limbal stem cells, resulting in permanent unilateral or bilateral visual impairment. Alkali injuries occur more frequently than acid injuries. Platelets are a rich source of potential wound healing, promoting polypeptide growth factors. This study aimed to investigate the effect of platelet-rich fibrin (PRF) lysates on limbal stem cell proliferation, which was exposed to sodium hydroxide that resembled limbal stem cell deficiency due to chemical trauma. Confluent rabbit (Oryctolagus cuniculus) limbal stem cells wounded using 20µL of 0.00625 M sodium hydroxide (pH 13) were treated with platelet-rich fibrin lysates (PRF) (0, 5, and 10%). PRF lysates were prepared from peripheral rabbit blood according to Choukroun's method without using anticoagulant and foreign factors for platelet activation. The proliferation of limbal stem cells was measured by a 3-(4,5-dimethylthiazol-2-yl)-2.50 diphenyl tetrazolium bromide (MTT) colorimetric assay at 24, 48, and 72 hours after exposure to sodium hydroxide. Proliferation significantly increased limbal stem cells with PRF lysates 5% ($p<0.01$) and 10% ($p<0.01$) group compared with the control (PRF 0%). There was no significant difference between PRF lysates of 5% and 10% ($p>0.01$). The highest proliferation of limbal stem cells was found in the PRF lysates 5% group after 48 hours (100.24%). PRF stimulated limbal stem cell proliferation in chemical trauma caused by the sodium hydroxide model. PRF repaired the limbal stem cell niche and influenced the limbal stemness. The present findings warrant further research on PRF as a novel alternative treatment for limbal stem cell deficiency.

Keywords: *Platelet-rich fibrin lysates; limbal stem cells; limbal stem cells deficiency; proliferation; sodium hydroxide*

Correspondence: Wahyu Endah Prabawati. Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: prabawati_endah@ymail.com

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Highlights:

1. Sodium hydroxide causing platelet rich fibrin stimulates limbal stem cell proliferation in chemical trauma.
2. Limbal stem cell niche and influences limbal stemness was repaired by Platelet Rich Fibrin.

INTRODUCTION

Limbal stem cell deficiency is related to the destruction of limbal stem cells or insufficient stromal microenvironment to support stem cell function. Limbal stem cell deficiency is characterized by intrusion of conjunctival epithelial cells, which have goblet cells on the cornea, neovascularization, chronic inflammation, and persistent epithelial defect. The most common etiology of limbal stem cell deficiency is chemical trauma. According to several studies, the ratio of the relative frequencies of acids and alkalis as the causative agents of chemical injury ranges from 1:1 to 1:4. Currently, no medical treatment is available to restore limbal stem cells after acute inflammation and inciting event control (Anderson et al. 2001, Kocaba et al. 2016).

Regeneration of limbal stem cells is regulated by microenvironment/niche through interaction between mesenchymal cells, cytokine, oxygen, nutrient, and growth factor. The growth factor is important in maintaining the deficiency of limbal stem cells and promoting the proliferation of limbal stem cells. Platelet is the main source of growth factors which has a role in tissue regenerate-platelet-rich fibrin. It is a new revolution in the platelet therapy concept (Castro-Muñozledo 2015, Freire et al. 2014, Naik et al. 2013).

Platelet-rich fibrin was first published in France by Choukroun et al. study in 2001 (Naik et al. 2013). Platelet-rich fibrin becomes more frequently applied in order to support the wound healing process because it has many advantages compared to the PRP, such as the simple and effective collecting process, no added substances from the outside to activate the platelets, arrested platelets into the fibrin network, and support for hemostasis, cell migration, and proliferation. Platelet-rich fibrin is obtained from the blood without anticoagulant and centrifuged just once to obtain the PRF matrix. The platelets in the fibrin fiber network were activated to release growth factors without additional components, such as bovine thrombin and calcium chloride (Nguyen et al. 2016).

Many growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF-β are released from PRF. Recently, studies have demonstrated that PRF has a very significant slow, sustained release of key growth factors for at least one week and up to 28 days, which means that PRF could stimulate its environment for a significant time during wound healing (Wu et al. 2012). Platelet-rich fibrin is applied in many clinical trials, but the mechanism of PRF to wound healing has not been studied much. This research was conducted to evaluate the effect of PRF on the proliferation in cultures of rabbit limbal stem cells exposed to sodium hydroxide.

MATERIALS AND METHODS

This study was an in vitro experimental study in cultured rabbit limbal stem cells exposed to natrium hydroxide and treated with platelet lysates. All rabbits were cared for following the procedures and designs approved by the animal experimentation ethics (no.771-KE) committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia. This study aimed to investigate the difference in limbal stem cell proliferation exposed to natrium hydroxide resembling the limbal stem cell deficiency model caused by chemical trauma. This study was a true experimental study using a posttest-only control group design due to the presence of intervention, control, replication, randomization, and observation after intervention only. Experimental units were divided into three different intervention groups which were then evaluated 24, 48, and 72 hours after the intervention. First was the control group without PRF, the second was the intervention group with PRF of 5%, and the third was the intervention group with PRF of 10%. The independent variables of this study were PRF lysates and observation time. The dependent variable of this study was limbal stem cell proliferation.

RESULTS

This study used passage 5 for limbal stem cell culture with viable cell count 77% (1,62 x 10^6 cell/mL) and total cell count 2.09 x 10^6 cell/mL. Cell surface marker identification used CD45, p63, CD 73, CD 90, and CD 105 in the population of limbal stem cells isolated from the limbus. CD 73, CD 90, and CD 105 were positively expressed on limbal stem cell culture and negatively expressed for CD 45. It indicated that the limbal stem cell culture population was true limbal mesenchymal stem cell. p63 was also positively expressed, showing that the population was a limbal epithelial stem cell. The ratio of limbal mesenchymal and limbal epithelial stem cells was 1: 1.005. Natrium hydroxide exposure used 20 µl of 0.00625 M in every well and caused less than 50% limbal stem cell damage.

PRF effect was evaluated by assessing cell viability using an MTT assay. MTT assay result was a percentage of the viable cell. Proliferation was highest in group II (PRF 5% intervention) in 48 hours of observation. Mean of viable cells percentage on control group in 24, 48, 72 hours observation were a (79.73 $\pm$ 14.23)%, (74.60 $\pm$ 25.00)%, and (62.7 $\pm$ 12.40)%. Mean of viable cells percentage on group with PRF 5% in 24, 48, 72 hours observation were (90.74 $\pm$ 6.22)%, (100.24 $\pm$ 14.88)%, and (93.61 $\pm$ 13.35)%, respectively. Mean of viable cells percentage on group with PRF 10% in 24, 48, and 72 hours observation were respectively (89.17 $\pm$ 8.42)%, (100.17 $\pm$ 19.72)%, and (92.50 $\pm$ 16.30). There was a significant difference between group II (PRF 5%) and group III compared with group I (control) ($p<0.01$). There was no significant difference between group II (PRF 5%) and group III (PRF 10%). Statistically, there was no significant difference between the time of observations ($p>0.01$).

Table 1. Percentage of viable cells among various groups

Group	Time (hour)	n	Percentage of the viable cell (%)	
			Min.	Max.
Group 1 (control)	24	8	60.58	103.31
	48	8	14.55	89.85
	72	8	47.38	78.02
	Total	24	14.55	103.31
Group II (PRF 5%)	24	8	70.21	120.53
	48	8	77.00	115.24
	72	8	77.68	116.41
	Total	24	70.21	120.53
Group III (PRF 10%)	24	8	78.22	102.37
	48	8	80.88	134.02
	72	8	66.91	116.61
	Total	24	66.91	134.02
Total	24	24	60.58	120.53
	48	24	14.55	134.02
	72	24	47.38	116.61
	Total	72	14.55	134.02

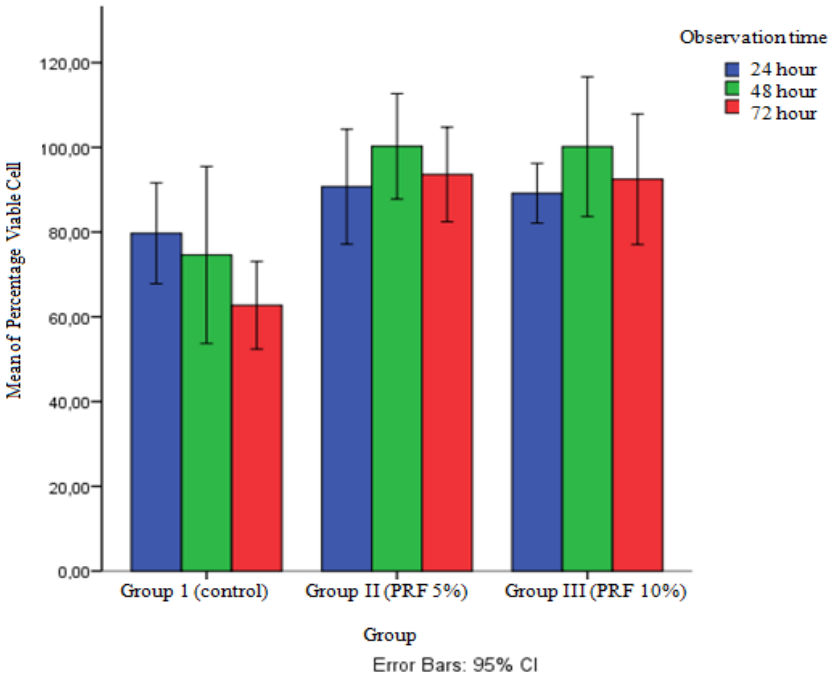

Figure 1. Mean of viable percentage cells among various groups

Note: The results are expressed as the mean of percentage viable cell + SD. The results had statistically significant differences concerning control ($p<0.01$) (two-way ANOVA), and significant differences concerning control ($p<0.01$) (Post Hoc Tukey HSD)

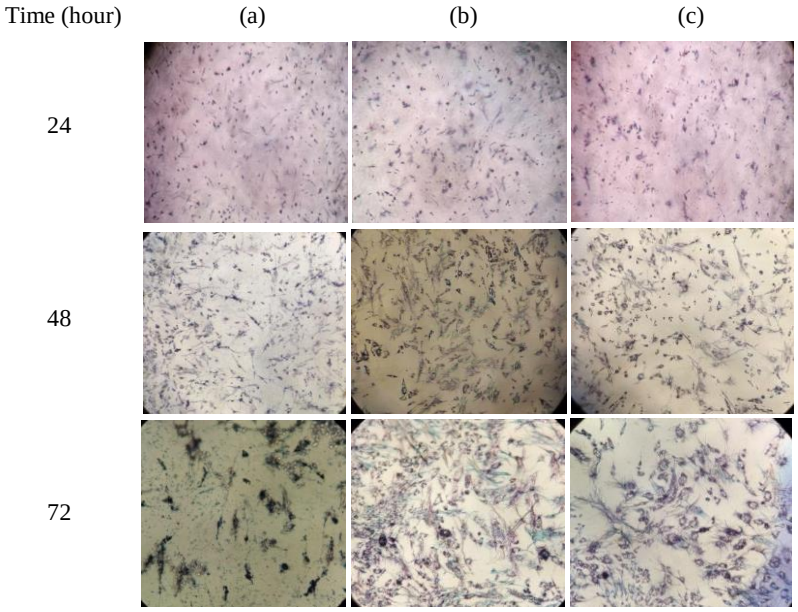

Figure 2. Limbal stem cell was exposed to sodium hydroxide and incubated for 24, 48, and 72 hours. Limbal stem cell was exposed to sodium hydroxide (a), sodium hydroxide and treated by PRF 5% (b), to sodium hydroxide and treated by PRF 10% (c).

DISCUSSION

Homeostasis of corneal epithelium is essential for maintaining a healthy ocular surface and for corneal transparency and accurate vision. Continuous renewal epithelium is provided by a population of adult stem/progenitor cells residing in the limbus, the transitional zone between the vascular conjunctiva and the avascular transparent cornea. Limbal stem cells require a particular environment to retain their stem cell properties (Sacchetti et al. 2018). The environment is provided by the stem cell niche in which signaling from adjacent cells, as well as properties of the basal membrane, are believed to play a role in the maintenance of their 'stemness'.

When limbal stem cells are depleted below a certain threshold, a clinical sign of limbal epithelial stem cell deficiency (LSCD) appears, causing gradual vision loss. LSCD occurs due to disease or damage to the limbal stem cell population. Deficiency can arise from injuries, including chemical or thermal burns. In this study, limbal stem cell damage was less than 50% after being exposed to 20 µl of 0.00625 M sodium hydroxide with pH 13 (Kadar et al. 2013). This study differed from the prior one by Pattamatta et al. (2009), which used 0.5 µl of 0.1 M sodium hydroxide. A preliminary study used 0.5 µl of 0.1 M sodium hydroxide, and all limbal stem cell cultures were damaged. The hydroxyl ions rapidly penetrated the eye, causing saponification of cellular membranes with massive cell death and partial hydrolysis of corneal glycosaminoglycans and collagen.

Platelet-rich fibrin described by Choukroun is a second-generation platelet concentrate consisting of a 3-D polymerized autologous fibrin matrix incorporating platelets, growth factors, cytokines, circulating stem cells, and a small number of leukocytes, which have key roles in homeostasis and wound healing. The intrinsic incorporation of these factors within this scaffold allows their progressive and controlled release as the fibrin mesh degrades. PRF releases autologous growth factors gradually, resulting in a stronger and more durable effect of proliferation, differentiation, migration, and matrix synthesis by binding to specific cell-surface-receptor (Cakmak et al. 2017).

In this study, the PRF 5% group had the highest proliferation rate within 48 hours of observation. Increasing proliferation in 48 hours of observation was related to the population doubling time on stem cell culture. The previous study showed that the human corneal epithelial cell line population doubling time was 45 and 42 hours (Fan et al. 2011). The PRF optimum concentration was limited, while studies on prior platelet products PRF had been widely conducted. In the previous study, the optimum concentration of PRP varied from 50% to 10% or less than 1%. Soffer et al. (2003) considered 0.5-1% as the optimum concentration for cellular proliferation and mineralization rates. However, Freire et al. (2014)

found that 50% PRP was the optimum concentration for osteoblast proliferation.

On the other hand, 10% PRP was sufficient to induce marked cell proliferation of MSC derived from adipose tissue. In addition, 5% PL is considered the optimum concentration for MSC and DPSCs proliferation and osteogenesis (Saeed et al. 2017). In this study, the cell proliferation rate was measured by MTT assay. MTT protocol includes a liquid handling step to solubilize formazan precipitates during an assay, thus making the protocols less convenient (Saeed et al. 2017).

In the previous study, the potential function of PRF in wound healing was investigated on Human Gingival Fibroblasts (HGFs) for cell proliferation and migration, which provided evidence for PRF use in periodontitis treatments. The results showed that PRF promoted the proliferation and migration of HGFs (Nguyen et al. 2016).

PRF is rich in various growth factors, including transforming growth factor-beta 1 (TGFβ-1), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF), fibroblast growth factor, epidermal growth factor (EGF), and hepatocyte growth factor. It promotes the movement, proliferation, and differentiation of stem cells, neovascularization, and collagen synthesis. IGF prevents cells from undergoing apoptosis, VEGF stimulates vasculogenesis and angiogenesis, and EGF function in cell proliferation and differentiation (Duan et al. 2017).

In this study, PRF increased limbal epithelial stem cells and limbal mesenchymal stem cells. There was a positive expression of mesenchymal and epithelial surface markers. Cell surface marker identification used CD45, p63, CD 73, CD 90, and CD 105 in the population of limbal stem cells, which were isolated from the limbus. CD 73, CD 90, and CD 105 were positively expressed on limbal stem cell culture and negatively expressed for CD 45. It indicated that the limbal stem cell culture population was a true limbal mesenchymal stem cell. p63 was also positively expressed and it showed that the population was also a true limbal epithelial stem cell. The ratio of limbal mesenchymal stem cell and limbal epithelial stem cell was 1: 1.005 (Mark et al. 2013, Nakatsu et al. 2014). A previous study reported that MSCs supported the survival, growth, and proliferation of various types of cells, such as hematopoietic stem cells, hepatocytes, cardiac progenitor cells, neural stem cells, neurons, and Schwann cells. Hu et al. (2012) demonstrated that MSCs had the same effect on corneal limbal epithelial cells. Several reports previously described the favorable effect of MSC transplantation after ocular surface destruction may be partly attributed to the proliferation of endogenous corneal cells evoked by MSCs.

Strength and limitation

The study addresses a significant clinical problem, which is chemical injuries to the eye resulting in permanent visual impairment. The study investigates a potential novel treatment option using platelet-rich fibrin (PRF) lysates to promote limbal stem cell proliferation and repair the limbal stem cell niche. The study uses a reliable method to assess cell proliferation, the MTT colorimetric assay. The study includes a control group and multiple treatment groups with different concentrations of PRF lysates.The study did not include a detailed analysis of the mechanism by which PRF lysates promote limbal stem cell proliferation. The study did not investigate the long-term effects of PRF lysates on limbal stem cell proliferation or potential adverse effects.

CONCLUSION

PRF promotes increasing proliferation in cultured limbal stem cells exposed to natrium hydroxide that resembled deficient limbal stem cells caused by alkali trauma through repairing niche limbal stem cell conditions. PRF is expected to benefit limbal stem cell regeneration, especially in limbal stem cell deficiency caused by alkali trauma.

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Conflict of interest

None.

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None.

Author contribution

WEP and AM conceptualized, wrote, and revised the manuscript. MT collected and analysis data, finalized the manuscript.

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Original Research

ELEVATED SERUM TRANSAMINASE (SGOT/SGPT) AND SEPSIS IN BURN PATIENTS IN A TERTIARY HOSPITAL, SURABAYA, INDONESIA

Iswinarno Doso Saputro[1], Lobredia Zarasade[1], Rifqi Kurniawan[2]
[1]Department of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Resident of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Burns trigger hypermetabolic stress reactions that cause inflammatory responses. When there is a sustained or increased hypermetabolic reaction, the inflammatory response can be life-threatening, such as sepsis, and significantly impact hepatic metabolic function. After burns, varying degrees of liver injury are usually associated with burn severity. This study determined the correlation between elevated serum transaminases (SGOT/ SGPT) and sepsis in burn patients at a tertiary hospital of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 1, 2018, to December 31, 2020. This was a descriptive-analytic study with a retrospective cohort design. The data in this study included the demography of burn patients, causes of burns, inhalation trauma, burn severity, increased serum transaminase (SGOT/SGPT), mortality, and sepsis. This study found that the correlation between elevated serum transaminases (SGOT/SGPT) and sepsis was determined using the Spearman-Rho Rank statistical test. Burn patients with sepsis in the hospital were dominated by males (65.2%) and mostly aged 26-55 years (69.6%). The flame was found to be the highest cause of burns (80.4%), burn area above 20% (91.3%), the highest level of severity was major burn (91.3%), and no inhalation trauma (54.3%). In this study, there was an increase in SGOT of 69.6% and SGPT of 78.3%, with a mortality rate of 39.1%, with average inpatient days of 24 days. The correlation test between elevated serum transaminase (SGOT) and sepsis showed an insignificant relationship ($p = 0.065$, $p > 0.05$) with a correlation coefficient of 0.200. In contrast, the correlation between elevated serum transaminase (SGPT) and sepsis was significant ($p=0.006$, $p<0.05$) with a correlation coefficient of 0.296.

Keywords: *Burns; elevated of SGOT/ SGPT; sepsis; medicine*

Correspondence: Iswinarno Doso Saputro, Department of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: iswinarno.doso@fk.unair.ac.id

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Highlights:

1. There is no correlation between the increase of SGOT and sepsis.
2. Correlation between the increase of SGPT and sepsis was significant founded.

INTRODUCTION

Burns are body skin damage caused by heat or cold trauma (*frostbite*). The causes are fire, hot water, electricity, chemicals, radiation, and cold trauma (*frostbite*). This damage may include subcutaneous tissue (Ministry of Health 2019).

The leading cause of death in burn patients is multiple organ dysfunction syndromes (MODS) (Li et al. 2021). It is also a direct response to sepsis. It is also found in all patients admitted to the intensive care unit, where there has been a slight improvement in the survival of patients with sepsis over the last few decades, so various efforts have been made to increase the speed of diagnosis and shorten the treatment period for sepsis (Greenhalgh 2017).

Previous studies had shown that burns produced a hypermetabolic stress reaction that caused an inflammatory response. When there was a sustained or increased hypermetabolic reaction, the inflammatory response could be life-threatening, and this had a significant impact on the metabolic function of the liver. After burns, the degree of liver injury varies with the severity of the burn. A study by Borah et al. (2017) found a strong positive correlation between liver enzymes and the degree of burn injury. The immediate increase in liver enzymes after burns may be due to the formation of hepatic edema, which leads to cell damage and the release of liver enzymes.

Previous studies had shown that burns produced a hypermetabolic stress reaction that caused an inflammatory response. When there was a sustained or increased hypermetabolic reaction, the inflammatory response could be life-threatening, and this had a significant impact on the metabolic function of the liver. After burns, the degree of liver injury varies with the severity of the burn. A study by Borah et al. (2017) found a strong positive correlation between liver enzymes and the degree of burn injury. The immediate increase in liver enzymes after burns may be due to the formation of hepatic edema, which leads to cell damage and the release of liver enzymes.

Aminotransferases or transaminases are a group of enzymes that catalyze amino acids and oxoacids by transferring amino groups (Esani 2014). Aspartate aminotransferase (AST), formerly called glutamate oxaloacetate transaminase (GOT), and alanine aminotransferase (ALT), formerly called glutamate pyruvate transaminase (GPT), are the most clinically significant aminotransferases. The main clinical application of measurement of serum AST and ALT is the detection and diagnosis of the differential etiology of liver disease. Liver cell injury manifests by increased serum transaminase activity before clinical signs and symptoms (i.e., jaundice) appear. Relative elevations of AST and ALT are hallmarks of viral, toxic, or non-ethanol-induced acute hepatitis. Similar serum transaminase levels under these conditions are thought to be caused by the cellular release of only cytoplasmic enzymes associated with reversible liver cell damage (Walker et al. 1990).

Aspartate transaminase or aspartate aminotransferase (AST) catalyzes the reversible transfers of amino groups between aspartate and glutamate (Jansen et al. 2020, Sookoian & Pirola 2012). It is also an essential enzyme in amino acid metabolism. AST is found in the liver, heart, skeletal muscle, kidneys, brain, and red blood cells. Serum AST levels, serum ALT (alanine transaminase) levels, and their ratio (AST/ALT ratio) are commonly measured clinically as biomarkers for liver health (Giannini et al. 2005).

This study determined the correlation between elevated serum transaminase (SGOT/SGPT) and sepsis in burn patients.

MATERIALS AND METHODS

This study was an observational analytic study with a retrospective cohort design. The data were obtained from patients' medical records in a tertiary hospital of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, for the period January 1, 2018, to December 31, 2020, which met the inclusion criteria of all burn patients who were treated with sepsis and had complete medical records with exclusion criteria of patients with electrical burns, history of comorbidities in the liver and patients who did not have a complete medical record. The sampling used in this study was the total sampling method. Data collection from the patients' medical records had been approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, No. 0536/LOE/301.4.2/VIII/2021.

The data included patients' characteristics (gender and age), degree of burn severity, burn area, causes of burns, inhalation trauma, increase in serum transaminase (SGOT/SGPT), an average of inpatient days, and mortality in injured burn patients. Data on the increase in serum transaminase SGOT and SGPT were tested for correlation with sepsis using the above variables. The correlation with sepsis was determined using the Rank Spearman-Rho statistical test. All data obtained were presented in tabular form.

RESULTS

As many as 276 patients and 86 (31.2%) patients met the inclusion criteria; 46 patients were found with sepsis (American Burn Association Sepsis Criteria), while 40 patients did not have sepsis. Data were processed statistically with SPSS 25 version and displayed in tabular form.

Table 1. The sex distribution of burn patients with infection

Sex	n=46	Percentage (%)
Male	30	65.2
Female	16	34.8

It was found that the number of male burn patients who experienced sepsis was 30 patients (65.2%), while female patients were only 16 (34.8%).

Table 2. Age distribution of burn patients with infection

Age (year)	n=46	Percentage (%)
0-5	1	2.2
6-11	2	4.3
12-16	3	6.5
17-25	9	19.5
26-35	11	23.9
36-45	12	26.1
46-55	4	8.7
56-65	1	2.2
>65	1	2.2

The data in Table 2 indicate that the most of the burn patients were in early adulthood, ranging from 36-45 years, as many as 12 patients (26.1%), while the most minor group with one patient each (2.2%) is the group of 0-5 years old, 55-65 years old, and >65 years old.

Table 3. Distribution of etiology/causes of burns in patients

Etiology	n=46	Percentage (%)
Scald	8	17.4
Fire	37	80.4
Thermal contact	1	2.2

The causes of burns in burn patients with sepsis were a fire in 37 patients (80.4%), scald in 8 patients (17.4%), and thermal contact in 1 patient (2.2%).

Table 4. Classification of the severity of burns in the patients

Burn area	n=46	Percentage (%)
< 20%	4	8.7
> 20%	42	91.3

In this study, there were 4 patients (8.7%) with burn area <20% and 42 patients (91.3%) with burns above 20%, as shown in Table 4. This classification is according to ANZBA 2016.

Table 5. Classification of burn area in patients

Severity of burn	n=42	Percentage (%)
Minor	0	0
Moderate	4	8.7
Major	42	91.3

The severity of burn patients, according to the American Burn Association in 2007, was divided into 3. In this study, we found four patients (8.7%) with moderate burns and 42 patients (91.3%) with significant burns (Table 5).

Table 6. Burn patients with inhalation trauma

Inhalation trauma	n=46	Persentase (%)
Yes	21	45.7
No	25	54.3

In this study, 21 patients (45.7%) had inhalation trauma, and 25 (54.3%) did not experience inhalation trauma.

Table 7. Burn patients with increased SGOT

Increase SGOT	n=46	Percentage (%)
Yes	32	69.6
No	14	30.4

In this study, there were 32 patients (69.6%) with elevated SGOT and 14 patients (30.4%) without non-increased SGOT (Table 7).

Table 8. Burn patients with increased SGPT

Increased SGPT	n=46	Percentage (%)
Yes	36	78.3
No	10	21.7

It was found that 36 patients (78.3%) had increased SGPT and ten patients (21.7%) did not have increased SGPT (Table 8).

Table 9. The mortality rate in burn patients with sepsis

Mortality	n=46	Percentage (%)
Yes	18	39.1
No	14	60.9

The mortality rate of patients with sepsis showed that 18 patients (39.1%) died, and 28 patients (60.9%) survived (Table 9).

Relationship between increased serum transaminase (SGOT and SGPT) and the incidence of sepsis

The analysis was carried out using the Spearman-Rho Rank test. The test was stated to have a significant relationship if the p-value <0.05 (Table 10). Statistical tests of the relationship between increased serum transaminase (SGOT) and sepsis using Rank Spearman-Rho obtained a sig/p-value of 0.065, and the relationship between increased serum transaminase (SGPT) and sepsis using Rank Spearman-Rho obtained a sig/p-value of 0.006.

Table 10. Spearman-Rho SGOT rank correlation test results

Correlations				
			Sepsis	SGOT
Spearman's Rho	Sepsis	Correlation Coefficient	1.000	.200
		Sig. (2-tailed)	.	.065
		n	86	86
	SGOT	Correlation Coefficient	.200	1.000
		Sig. (2-tailed)	.065	.
		n	86	86

DISCUSSION

There were 276 patients, with 86 patients (31.2%) included in the inclusion criteria and 190 patients (68.8%) in the exclusion criteria (electrical injury, patients with liver disorders/diseases, incomplete data), where 46 patients (53.4%) were septic, and 40 patients (46.6%) were not. Gomez et al. (2009) conducted an autopsy study on the causes of the death in burn patients in 2009 and found that 60% of deaths were caused by infectious complications and MODS.

Table 11. Spearman-Rho SGPT rank correlation test results

Correlations				
			Sepsis	SGOT
Spearman's rho	Sepsis	Correlation Coefficient	1.000	.296
		Sig. (2-tailed)	.	.006
		n	86	86
	SGOT	Correlation Coefficient	.296	1.000
		Sig. (2-tailed)	.006	.
		n	86	86

The percentage of burn patients who experienced sepsis was dominated by male patients (65.2%). As some studies found that estrogen in women increased immune function (Angele et al. 2014, Taneja 2018), it was plausible that males dominated the infection in burn patients. In this study, the highest incidence was at the age of 26-55 years as many as 32 patients who were in early adulthood to late elderly (productive age).

The causes of burns in sepsis patients in most studies included a fire in as many as 37 patients (80.4%), eight patients with scald (17.4%), and one patient with thermal contact (2.2%). Data of the Ministry of Health, Indonesia, showed that burn cases treated at RSCM from 2012 to 2016 were mostly caused by fire as much as 53.1%, followed by water/scald (19.1%), electricity (14%), thermal contact (5%), and chemical contact (3%). The majority of the burn patients were males (62.8%), comprising 58 patients, while the female ones were 37.2% (32 patients). This was following data released by the American Burn Association in 2017, where 67% of burn patients were males and 33% females, while the highest incidence was at the age of 26-55 years, with as many as 32 patients.

The results of this study indicated that the highest percentage of the severity of burns accompanied by sepsis was in the degree of significant burn amounted to 41 patients (91.3%) with the highest burn area > 20%. The study by Dvorak et al. (2021) stated that patients with a burn area greater than 20% had an increased risk of sepsis and death since the extensive burns caused substantial damage to the skin and could inhibit the ability of the skin as a major barrier to infection.

In this study, from 23 patients with inhalation trauma, 21 patients (91.3%) had sepsis, with a mortality rate of 30.4% for patients with inhalation injury. Inhalation trauma increased 10% to 20% of morbidity and mortality in burn patients, and inhalation trauma has also been an independent predictor of mortality in burn patients. Inhalation trauma also causes increased bronchial blood flow delivering activated polymorphonuclear leukocytes and cytokines to the lungs, which potentiates the inflammatory response. The loss of bronchial epithelium and ROS (Reactive Oxygen Species) results in the loss of plasma proteins and fluids from the intravascular space into the alveoli and bronchioles. Transvascular protein shift causes exudate and blockage formation within the airways, leading to alveolar collapse or complete occlusion of the airways, increased blood flow to the injured lung segment, and decreased ventilation of the collapsed segment to ventilation-perfusion mismatch as the primary mechanism of hypoxemia after trauma. Inhalation. Atelectasis, immune system dysfunction, and mechanical ventilation predisposed to pneumonia, a common complication of inhalation injury (Walker et al. 2015).

The average lengths of stay of burn patients with sepsis who met the inclusion criteria in 2018, 2019, and 2020 were 25, 23, and 30 days, respectively, with the average length of stay for sepsis patients in 2020 was 21 days, hence the average length of stay of burn patients with sepsis at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, for period January 1 2018 to December 31, 2020 was 24 days.

Relationship between increased serum transaminase (SGOT and SGPT) and the incidence of sepsis

The increase in SGOT with sepsis did not have a significant relationship, where the p-value was 0.065 (p-value > 0.05). There was a significant relationship between the increase in SGPT with a p-value of 0.006 (p-value < 0.05) and a correlation coefficient of 0.296, which was positive for both aminotransferases in the liver. However, SGOT is also obtained differently in the heart, skeletal muscle, kidney, brain, and red blood cells, and SGPT has low concentrations in skeletal muscle and kidney, so elevated serum levels of SGPT are more specific for liver damage. In the liver, SGPT is only localized in the cell, whereas SGOT is found in the cytosol (20%) and mitochondria (80%). (Costa et al. 2021).

In this study, data on SGOT and SGPT were obtained in the second-week observation because serum SGOT, SGPT, and ALKP peaked during the first-week post-burn and approached the normal range of 3-5 weeks post-burn. If the damage persisted or sepsis occurred, the enzymes increased (Jeschke et al. 2007). This indicated continued damage, and most of the burn patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, were diagnosed with sepsis in the second week. The level of SGOT and SGPT increased slightly < 5 times the normal value, where an increase in SGOT in 46 septic patients was found to be a mild increase (<5 times the normal value) in 31 patients, and a mild increase in SGPT value (<5 times the normal value) in septic patients was found in 32 patients. To distinguish whether the increase in serum transaminases was caused by sepsis or other diseases, it was necessary to carry out various investigations. Costa et al. (2021) stated that a minimal or mild increase in serum aminotransferase was the most common biochemical change encountered in daily clinical practice, and additional investigations needed to be carried out to determine the cause of the increase in serum transaminase whether the cause was extrahepatic or intrahepatic.

Alcohol abuse and, to a lesser extent, drug-induced liver injury are frequently associated with mild aminotransferase abnormalities, and causality should be ruled out clinically. In the western world, chronic viral hepatitis, autoimmune hepatitis, and hereditary hemochromatosis are the most common causes of mild aminotransferase changes (Angganis et al. 2018). Investigations to rule out the above patient causes need to be performed (HBsAg, anti-HCV, ANA test), and if none of the above diseases is found, attention should be paid, to whether the patient suffers from Nonalcoholic Fatty Liver Disease (NAFLD) or steatohepatitis which is also frequently encountered in clinical practice.

In acute liver damage, the patient's pharmacological history is essential. All drugs that have been given are considered again, and the risks and benefits of administration are considered. Suspicion of NAFLD is raised in the presence of conditions associated with metabolic syndrome and insulin resistance (elevated body mass index, diabetes, hyperlipidemia, hypertension), although this disease can occur in patients without associated factors (Costa et al. 2021).

Strength and limitation

The study was conducted at a tertiary hospital, which is a specialized center for burn management, increasing the reliability of the data collected.It included a large sample size, increasing the statistical power of the results.

CONCLUSION

Even though this study used secondary data (medical records), which could have indirectly affected the results, we found that the increase in SGPT and sepsis had a significant correlation with a p-value of 0.006 (p-value <0.05) with a correlation coefficient of 0.296. At the same time, there was no correlation between the increase of SGOT and sepsis (p = 0.065, p> 0.05). Future studies should be conducted to involve different comorbidities, so the effects of the existing comorbidities can be minimized.

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Conflict of interest

None.

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None.

Author contribution

FPSI, RA, IR and DR were conseptual idea and analysis data. RK write, revised and prepared the draft of the manuscript. A was manuscript arrangement to the final content.

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Original Research

COGNITIVE, MOTOR, AND LANGUAGE ASSESSMENT IN CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS

Putu Indah Budi Apsari[1], I Nyoman Supadma[2], Ketut Dewi Kumara Wati[3], I Wayan Dharma Artana[3]
[1]Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universitas Warmadewa, Bali, Indonesia
[2]Famili Husada Hospital, Bali, Indonesia
[3]Department of Child Health, Universitas Udayana/ Sanglah Hospital, Bali, Indonesia

ABSTRACT

The cognitive, motor and language aspect of HIV-infected children is an important issue affecting their quality of life. The capute scale, divided into Cat and Clams scores, is commonly used to assess children's cognitive, motor, and language functions. This study assessed Cat and Clams' scores of HIV-infected children. We performed Cat and Clams assessment on 136 children consisting of 68 HIV-infected children and 68 normal children as control aged 0-36 months. The Capute scale examined both groups at the first meeting (first month), and for the rest six months, we evaluated the progress of cognitive, motor, and language development. In the first meeting, we found that HIV-infected children had significantly low capute scores than the control group. The sixth-month Capute score in HIV-infected children was also significantly lower than the control group. HIV-infected children had lower Capute scores than normal children.

***Keywords**: HIV; child; virus; CAT/CLAMS*

Correspondence: Putu Indah Budiapsari, Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universitas Warmadewa, Bali, Indonesia. Email: putuindah51@yahoo.com

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Highlights:

1. HIV-infected children had lower capute scores than normal children.
2. HIV child age range 12-24 months almost suffer delayed speech, and were in suspect criteria was founded.

INTRODUCTION

According to World Health Organization (2022), children with HIV infection risk developmental and behavioral challenges. Worldwide, AIDS currently accounts for 3% of deaths in children under five years of age—and 6% of those in sub-Saharan Africa, where AIDS has become one of the major killers of young children. One in seven people dying of HIV-related illness worldwide is a child under 15 years old. Most of these children acquire HIV from their HIV-infected mothers during pregnancy, birth, or breastfeeding. With successful antiretroviral interventions, the risk of mother-to-child HIV transmission can be reduced to 2%. However, such interventions are still not widely accessible or available in most resource-limited countries, where the burden of HIV is highest. An estimated 1,500 children get newly infected with HIV every day. The number of children receiving ART increased from about 75,000 in 2005 to almost 200,000 in 2007.

HIV infection adversely affects growth, morbidity, mortality, and neuro-development (Wedderburn et al. 2019). The virus can enter the central nervous system (CNS) during pregnancy, resulting in neuronal injury in the developing brain (Rie et al. 2007). This neuronal injury causes progressive encephalopathy in children. Delays are seen in cognitive, language, and motor

functions (Rie et al. 2007). The prevalence of these delays may be as high as 60% (Baillieu & Potterton 2008, Rie et al. 2007). HIV-associated central nervous system (CNS) diseases are prevalent in countries with limited treatment resources. Notably, in these parts of the world, perinatally infected children and adolescents show significantly impaired neurocognitive performance compared to the uninfected population (Weber et al. 2017). Clinical features include loss or failure to achieve appropriate developmental milestones, impaired brain growth, and global or selective impairments in cognitive, language, motor, attention, behavior, and social skills that may affect day-to-day functioning (Walker et al. 2013).

Clinically and immunologically, stable HIV-infected children had more frequent behavioral problems and lowered developmental and cognitive scores than established childhood norms (Nozyce et al. 2006). Some degrees of cognitive decline may present even in the early and asymptomatic stages of HIV infection. The benefits of antiretroviral treatment for cognitive performance can be detected after only a few weeks of follow-up. Supadma et al. (2020) stated a positive correlation exists between CD4 and Capute score of HIV children.

Andrade et al. (2012) stated that HIV infection in children could cause brain damage in the form of neurocognitive disorders. Younger HIV+ children also have lower scores in various domains of development while still having the most significant potential for benefit from early intervention (McHenry et al. 2018). Untreated HIV infection in children was associated with the development of cognitive, motor, language, and psychological impairment. Early developmental delays in language and cognitive abilities can affect various daily life functions (Levy 2018). Early identification and intervention can prevent cognitive and language impairment.

A capute scale is a screening tool that is widely used to evaluate developmental milestones, such as cognitive, language, and visual-motor, first published by Capute and Biehl in 1973 and revised by Capute and Accardo in 1978. Capute scale consists of two examinations: the cognitive adaptive test (Cat) and the clinical linguistic and auditory milestone scale (Clams). Differential performance on the significant development streams (motor, language, problem-solving, and adaptive) can be used to formulate and confirm neurodevelopmental diagnoses.

The Capute Scales are composed of CAT and CLAMS, an easy and practical screening neurodevelopmental assessment test for HIV-infected children in an outpatient setting. With the ease of this test, we could incorporate it into routine practice and early detect children with delayed development who benefited from the early stimulation program (Vanprapar et al. 2005). This study assessed cognitive, motor, and language development in HIV-infected children compared to HIV-negative children using Capute scales.

MATERIALS AND METHODS

The study was conducted in Sanglah Hospital and Werdhi Kumara kindergarten in Bali, Indonesia, from December 2013 to May 2014. The prospective cohort analytical study recruited children aged 0-36 months as participants. The target populations were HIV–infected children and normal children. The status of HIV-infected children was assessed using medical records and confirmed diagnosis by several examinations that met the criteria of HIV infection. The control group was defined by no record of HIV infection and another comorbid disease. The inclusion criteria were children aged 0-36 months in stable clinical conditions whose parents or guardians were willing to participate by signing informed consent and filling out the questionnaires. Exclusion criteria were children with co-morbidities disease, loss to follow-up, or their parents refusing to participate. We targeted 68 subjects per group selected by consecutive sampling.

HIV subjects and normal subjects were tested by Cat and Clams score of HIV-infected children compared to normal children. The research sample was followed for six months to assess the probability differences between the first examination and the upcoming six months examination result.

CAT/ CLAMS is a 100-item scale administered in a standardized manner in two parts and is obtained through observation (CAT) and parenteral report (CLAMS). CAT consists of visual-motor problem-solving items that are performed directly with the child. CLAMS item consists of language acquisition. A score was derived for CAT and CLAMS separately. CAT/ CLAMS score is the numerical average of the two, converted to a developmental quotient (DQ) by dividing the total score by the chronological age in months and multiplying by 100. The DQ of 85 to 125 is normal, 70 to 85 is borderline, and under 70 is delayed. Cat and Clams score between HIV- infected group and the normal group was tested by independent

t-test. The Mann-Whitney U test tested Cat and Clams scores between the first and six months of examination. This study was approved by the Ethics Committee of the Research and Development Unit, Universitas Udayana/Sanglah Hospital, Bali, Indonesia.

RESULTS

A total of 136 subjects were selected, consisting of 68 samples in the HIV-infected group, and 68 samples were selected as the control group. Based on the characteristics of both sexes in HIV and control groups, it was found that 54.5% of the sexes in the HIV group were mostly male as many as 37 patients, while 55.9% of the control group was mostly female, with as many as 38 patients. The average age of both groups was 21 months old, while the age range in both groups was mostly 12-24 months old. There were 30 patients in the HIV group undernourished (44.1%) and three patients malnourished (4.4%), but the control group was almost in good nutrition. Besides, family income in the HIV group was lower than in the control group. In socioeconomic grouping, 25 patients had a low economic state (36.8%), and 39 had a medium economic state (57.4%). In the control group, the patients were predominantly of medium-high socioeconomic status. We found no difference in parents' educational levels between groups. There were 68 subjects with HIV. The characteristics of subjects in the infected group are shown in Table 2. HIV groups were mostly 31 males aged 12-24 months (48.4%). There were 39 patients in the asymptomatic stage (57.4), while 14 patients were in the mild stage (20.6%), 13 patients in the moderate stage (19.1%), and two patients in the severe stage (2.9%), but all patients were in stable condition as they were treated with antiretrovirals.

Table 1. Characteristics of subjects

Subject characteristics	HIV group n = 68	Control group n = 68
Gender, n (%)		
Male	37 (54,5)	30 (44.1)
Female	31 (45)	38 (55.9)
Age (Month), Mean (SD)	21.3 (8.9)	21.7(8.9)
Range of age (n%)		
0-12 Months	14 (20.6)	17 (25.0)
12-24 Months	31 (25.6)	33 (48.5)
24-36 Months	23 (33.8)	18 (26.5)
Nutritional state (n%)		
Normal	35 (51.5)	68 (100)
Undernourished	30 (44.1)	-
Malnourish	3 (4.4)	-
Family income (n %)		
< 1 Million IDR	28 (41.2)	0 (0)
1-2.5 Milion IDR	32 (47.1)	30 (44.1)
2.5-5 Milion IDR	8 (11.8)	38 (55.9)
Socio-economic state (n%)		
Low	25 (36.8)	0 (0)
Medium	39 (57.4)	34 (50)
High	4 (5.9)	34 (0)
Mother educational level		
Elementary School	1 (1.5)	1 (1.5)
Junior High School	20 (29.4)	20 (29.4)
Senior High School	41 (60.3)	41 (60.3)
Vocational Degree	4 (5.9)	4 (5.9)
Bachelor Degree	2 (2.9)	2 (2.9)
Father educational level		
Elementary School	3 (4.4)	3 (4.4)
Junior High School	21 (30.9)	21 (30.9)
Senior High School	40 (58.8)	40 (58.8)
Vocational Degree	3 (4.4)	3 (4.4)
Bachelor Degree	1 (1.5)	1 (1.5)

Table 2. Characteristic of HIV infected children

Characteristic	Frequency (%)
Gender	
Male	37 (54.5)
Female	31 (45.5)
Age	
0-12 month	14(20.5)
13-24 month	31(45.5)
25-36 month	23(33.8)
Stage of infection	
Asymptomatic	39 (57.4)
Mild	14 (20.6)
Moderate	13(19.1)
Severe	2 (2.9)
Developmental state (6 months examination)	
Mental retardation	1 (1.5)
Delayed speech	2 (2.29)
Normal	40 (58.8)
Suspect	25 (36.8)
Clinical manifestation	
Gastro-Intestinal Tract (diarrhea)	2 (2.9)
Gastro-Intestinal Tract (vomiting)	1 (1.5)
Upper Respiratory Infection	17 (25)
Skin Hyperpigmentation	1 (1.5)
No Complaint	42 (61.8)
Wasting syndrome	5 (7.4)

Table 3. The result of the CAT/CLAMS examination in the HIV group

Developmental State	First examination				6th-month examination			
	CAT		CLAMS		CAT		CLAMS	
	70-85	85-120	70-85	85-120	70-85	85-120	70-85	85-120
Mental retardation (n)	1	0	1	0	1	0	1	0
Delayed speech (n)	1	1	3	0	1	1	2	0
Normal (n)	0	40	0	3	0	6	0	42
Suspect (n)	25	0	49	0	59	0	24	0

Table 4. The result of the CAT/CLAMS examination in the control group

Developmental State	First examination				6th-month examination			
	CAT		CLAMS		CAT		CLAMS	
	70-85	85-120	70-85	85-120	70-85	85-120	70-85	85-120
Normal (n)	0	62	0	64	0	68	0	68
Suspect (n)	6	0	4	0	0	0	0	0

Table 5. The difference in CAT/CLAMS scores between HIV and control groups

CAT/CLAMS scores	HIV group (median)	Control group (median)	p-value
First month			
CAT	86.6	91.0	0.01
CLAMS	86.35	92.45	0.01
Sixth month			
CAT	86.35	92.35	0.01
CLAMS	85.65	91.65	0.01

After the sixth month's examination, mental retardation was found in 1 patient (1.5%), the delayed speech was found in 2 patients (2.29%), while 25 patients were suspect (36.8%), and 40 patients (58.8%) were mostly in normal developmental milestone. Clinical manifestation in the HIV group was found in the gastrointestinal tract, such as diarrhea and vomiting, upper respiratory tract infection, skin hyperpigmentation and wasting syndrome, and others mainly without complaint. We selected HIV subjects in clinically stable conditions and controlled by antiretroviral treatment, and able to undergo the examination.

In Table 3, we showed the first CAT examination of the HIV group. We found one patient with mental retardation, one patient with delayed speech, 25 patients were suspects and 40 patients within normal limits. CLAMS examination resulted in 1 patient suffering from mental retardation, three patients with delayed speech, and 49 were in suspect criteria. After six months of CAT examination, we found the same patients still in mental retardation, one in delayed speech, and 59 in suspect criteria. There was an increasing number of subjects in suspect criteria. As a result of the CLAMS examination, one patient was still in mental retardation, and two patients were in delayed speech. There was an increase in normal subjects from 40 to 42 and a decrease in suspect subjects from 25 to 24. The milestone development in the HIV group tended to be abnormal or impaired, but in the control group, almost all subjects were within the normal limit (Table 4).

DISCUSSION

Using CAT/CLAMS assessment, this study breaks down neurocognitive and psychosocial functions among HIV-infected children using CAT/CLAMS assessment. Based on the characteristics of the subjects, the HIV group was predominantly male, but the control group was predominantly female. The same result was stated by Lindsey et al. (2007) that HIV-infected children were mostly males. Kube et al. (2000) found that male children tend to have cognitive problems. In contrast to a study by Whitehead et al. (2014), the HIV-infected children were primarily females. On the contrary, Nakasuja et al. (2012) stated that HIV-positive females suffered more severe cognitive impairments in comorbid psychosis.

We found that HIV children aged 12-24 months almost suffered delayed speech and were in suspect criteria. The first 24 months of life is technically denoted as the infancy period. It was the time when a child's brain underwent rapid development. During this phase, a child attains several motors, cognitive, and behavioral milestones.

Based on their socioeconomic status, HIV children were found to have poorer socioeconomic status, similar to the one found in the previous study by Bunyasi and Coetzee (2017). We found the educational level of their parents was the same in both groups. The result is concordance with a study by Smith et al. (2006) that no significant correlation was found between cognitive score and maternal educational level. Another study by Bunyasi and Coetzee (2017), Bello et al. (2013), and Ngoma et al. (2014) stated that the HIV child had low-educated parents, especially maternal educational level.

The difference in CAT/CLAMS scores between HIV and control group

We found a significant difference in CAT and CLAMS scores of the HIV group compared to the control group in the initial examination ($p<0.01$) and also in the sixth-month examination ($p<0.01$). This result was in contrast to that of Bruck et al. (2001), where there was no significant difference in CAT/CLAMS scores between positive and negative HIV groups.

This might be caused by the early treatment of ARV that could maintain CD4 levels and prevent brain damage due to encephalopathy HIV. Meanwhile, poor ARV adherence was correlated with poorer global neurocognitive functioning and a deficit in working memory.

Our finding was supported by Tahan et al. (2006), that observed significant differences in CAT/CLAMS scores between HIV with control groups, although the median score was still in the normal range. A previous study conducted by Nakasuja et al. (2012) found differences in cognitive function in individuals with HIV positive and HIV negative with psychosis. They found that the HIV group had higher cognitive function than the control group ($p <0.001$).

Bruck et al. (2001) observed significant differences in the mean of CLAMS scores between the HIV and control groups, and the HIV group had lower CLAMS scores than the control group. Both groups were followed for seven years. We also found significantly lower CLAMS scores in the HIV group than in the control group, both during the first and six-month examinations ($p<0.01$). As declared previously by Redmond et al. (2016), HIV exposure was the risk for persistent language impairment, such as delayed speech. Walker et al. (2013) stated that neurological impairment in HIV resulted from HIV encephalopathy. The decrease in CAT/CLAMS scores must be the result of neurophysiological damage that worsened with age. The difference in cognitive and psychosocial development between HIV and the control group must also be the result of brain abnormalities. Children perinatally exposed to HIV were at high risk for language impairment (Rice et al. 2012). Clinically and immunologically, stable HIV-infected children had more frequent behavioral problems and lowered developmental and cognitive scores than normal children.

Strength and limitation

The study had a large sample size of 136 children, increasing the statistical power of the results. The study focuses on an important issue affecting the quality of life of HIV-infected children.The study used a widely recognized and standardized assessment tool, the Capute scale, to evaluate cognitive, motor, and language development in both the HIV-infected and control groups. The study was conducted in a specific setting and population, limiting the generalizability of the findings to other contexts and populations.The study did not investigate the causes of the observed differences in Capute scores between HIV-infected and normal children, such as the effect of HIV on brain development.

CONCLUSION

The HIV group had lower cognitive, motoric, and language performance than a normal child by Capute scores assessment from the first- and sixth-month examination. Early detection and intervention of neurodevelopmental problems must be programmed to prevent progressive loss of cognitive, motoric, and language ability. Routine control of clinical manifestation and antiretroviral treatment in the HIV-infected group should also be continued to minimize the risk of neurological damage that could affect the neuro-developmental milestone.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

INS, KDKW, and DR were conseptual design and collected and analysis data. PIBA write and revised the

manuscript. All author was manuscript arrangement to the final content.

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Original Research

HYPERGLYCEMIA PREVALENCE AMONG ARTISANS AND WORKERS IN SELECTED FACTORIES IN LAGOS, SOUTHWEST, NIGERIA

Tajudeen O. Yahaya[1], Mutiu O. Sifau[2], Esther O. Oladele[3], Danlami M. Bashar[4], Aminu L. Abubakar[5], Naziru Salisu[1], Bello M. Usman[1], Jamilu D. Koko[1]

[1]Department of Biological Sciences, Federal University, Birnin Kebbi, Nigeria
[2]Department of Cell Biology and Genetics, University of Lagos, Nigeria
[3]Biology Unit, Distance Learning Institute, University of Lagos, Nigeria
[4]Department of Microbiology, Federal University Birnin Kebbi, Nigeria
[5]Department of Biochemistry, Usmanu Danfodio University, Sokoto, Nigeria

ABSTRACT

The increased global prevalence of hyperglycemia is linked partly to increasing industrial emission exposure, necessitating risk evaluations of various categories of workers worldwide. This study measured the blood glucose levels of selected non-obese artisans and workers from three companies (Imperio International, Mouka Foam, and Continental Iron) in Lagos, Nigeria. The participants' demographic data were collected using structured questionnaires, after which their blood glucose levels were measured using a glucometer. The results were compared with the World Health Organization (WHO) standards (88–126 mg/dL). On average, Imperio International participants were 32 years old, Mouka Foam and Continental Iron were 28 years old, and the artisans were 32 years old. Most of the participants were male secondary school graduates who worked an average of nine hours per day, six days a week. Artisans had the highest hyperglycemic population (46.15%), followed by Imperio International and Continental Iron (33% each), and Mouka Foam (29.41%). Smokers accounted for 10.53% of the hyperglycemic population, followed by alcoholics (36.84%), those who drank and smoked (42.11%), and those who did not drink or smoke (10.53%). Age class ≥41 accounted for 36.84% of the hyperglycemic population, class 31-40 (34.21%), and class 21-30 (28.95%). Participants with secondary school education constituted 63.16% of the hyperglycemic population, primary education (18.42%), individuals having no education (13.16%), and tertiary education (5.26%). The findings indicate that workplace pollutants predispose workers to hyperglycemia and that smoking and alcohol increase the risks. The findings necessitate exposure reduction and healthy lifestyles in the workplace.

***Keywords**: Alcohol use; healthy lifestyles; hyperglycemia; industrial emission; pollutants*

Correspondence: Tajudeen O. Yahaya, Department of Biological Sciences, Federal University Birnin Kebbi, Kebbi State, Nigeria. Email: yahaya.tajudeen@fubk.edu.ng/ yahayatajudeen@gmail.com

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Highlights:

1. Workplace pollutants predispose people to hyperglycemia through beta cell dysfunction and insulin resistance.
2. The risk is increased by unhealthy lifestyles such as smoking and drinking.
3. Aging, due to mitochondrial function decline, also promotes hyperglycemia.

INTRODUCTION

The rising global prevalence of high blood glucose is associated with increasing industrial pollution exposure, necessitating risk evaluations of various categories of workers worldwide. Glucose is the primary energy source for the body's cells, which is transported from the liver or intestines or absorbed through a hormone known as insulin (Gailliot & Baumeister 2007, Yahaya et al. 2021). The glucose concentration in the bloodstream, termed the blood glucose level, is regulated through insulin actions and other mechanisms (Ogbonna et al. 2018, Yahaya et al. 2019). Glucose levels are usually lowest before the first meal in the morning, termed the fasting level, and rise after meals for an hour or two by a few millimolar (Ogbonna et al. 2018). Normal fasting blood glucose levels are maintained within a narrow physiological range of 63–99 mg/dL (Güemes et al. 2015). However, certain medical conditions can disrupt blood glucose homeostasis, causing either low or high blood glucose (Ceriello et al. 2013). High blood glucose, also known as hyperglycemia, is defined as blood glucose levels greater than 126 mg/dL while fasting and greater than 180 mg/dL two hours after eating (Villegas-Valverde et al. 2018). Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production (Mouri & Badireddy 2020). Prolonged hyperglycemia may cause diabetes mellitus (DM) and multi-organ damage involving the kidney, eyes, nerves, heart, and blood vessels (Piero et al. 2014, Yahaya & Salisu 2020).

Hyperglycemia and DM have exploded over the last two decades due to increased obesity, physical inactivity, and an aging population (Mouri & Badireddy 2020). About 463 million people worldwide were diagnosed with DM in 2020, of which around 2,743,800 cases were recorded among adults in Nigeria (International Diabetes Federation 2020). The deaths resulting from hyperglycemia and DM are also high. For instance, in 2020, DM was the direct cause of 4.2 million adult deaths worldwide (International Diabetes Federation 2019). In Nigeria, at least 63,957.7 people between the ages of 20 and 79 died from DM in 2019 (Federation, 2019b).

Furthermore, the global financial burdens of DM are high. The estimated global direct health expenditure on DM in 2019 is USD 760 billion and is projected to increase to USD 825 billion by 2030 and USD 845 billion by 2045 (Williams et al. 2020). In Nigeria, the national direct costs of DM are estimated at $1.071 billion to $1.639 billion per year (Mapa-Tassou et al. 2019). Indeed, the prevalence of hyperglycemia and DM has reached epidemic proportions, and studies are necessary to identify the cause of the increasing prevalence and stem it. To this end, pollutant exposure has been identified as a cofactor in the rising incidence of these diseases, most noticeably after industrialization began in some parts of Europe and North America around the mid-29th century (Gale 2002, Yahaya et al. 2017). Thus, it has become imperative to conduct a risk evaluation of various workers worldwide. To our knowledge, such a study has not been conducted in most workplaces in Nigeria. This study, therefore, measured the blood glucose levels of some artisans and factory workers in Ogba, Lagos, Nigeria. The findings of this study will provide primary data for controlling blood glucose among factory workers in Nigeria.

MATERIALS AND METHODS

Description of the study site

This study was carried out in Ogba, Lagos State, Nigeria (Figure 1). The state is located between latitudes 6° 30′ N and 6° 40′ N and longitudes 3° 00′ E and 4° 00′ E (Balogun et al. 2017). It is bordered on the south by the Atlantic Ocean, on the west by the Benin Republic, and the north and east by Ogun State. The state has tropical vegetation, with a short dry season from December to February and a long rainy season from March to November. The state's dense population is projected to exceed 20 million people by 2025 (Oketola & Osibanjo 2009). Lagos is Nigeria's economic capital, with over 70% of the country's industries based there. Ogba is one of the state's most industrialized areas, and its location in Ikeja, the state capital, has earned it the moniker "heart of Lagos." The state's rapid population growth and urbanization have increased environmental pollution.

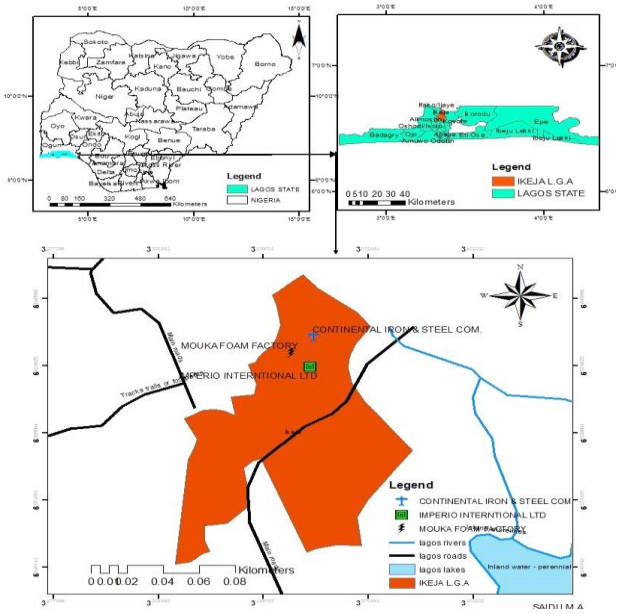

Figure 1. Locations of the study areas (drawn using ArcGIS 10.3 software)

Study population and data collection

Ninety-six (96) non-obese factory workers and artisans were enrolled in the study, comprising 12 participants from Imperio International, 17 from Mouka Foam, and 15 from Continental Iron and Steel. Fifty-two (52) artisans, mainly welders, mechanics, and carpenters, also participated in the study. After giving informed consent, each participant was given a questionnaire to indicate demographic data such as sex, age, drinking and smoking status, work hours, level of education, and work department. After that, the raw materials used in each company were recorded, after which blood samples were taken from the participants, and their blood glucose levels were measured.

Determination of blood glucose levels

The fasting blood glucose of the participants was measured using a Fantastik-Accu Glucose Meter (IVD version 180705-1) as described by Yahaya (2017b). The participants were made to fast for 8 hours, after which a drop of blood was taken from them and applied to a test strip. The strip was inserted into the glucose meter, and the reading was displayed on the instrument in mg/dL.

Ethics Statement

The Ethics and Research Committee of the National Open University of Nigeria, Lagos, approved the study. The participants also consented to the study.

Criteria for selection of participants

Participants must have agreed to participate in the study, have worked in the industry for at least two years, have no history of DM prior to working in the factory, and have not worked anywhere else. Excluded participants were those with a body mass index above 30 and individuals with a family history of DM.

Data analysis

Descriptive statistics were used to present values as numbers and percentages and mean ± standard errors (SE). The student's t-test was used to test the significance level among variables, in which $p \leq 0.05$ was considered statistically significant.

RESULTS

Some toxic materials used in the selected factories and artisans' workshops

Table 1 presents some materials used for production in the selected factories and artisans' workshops. Coal tars, ethanol, bisphenol A, phthalate, and brominated flame retardants were some of the toxic materials used by Imperio International. In contrast, Mouka Foam used polyurethane foam, antimony, toluene, and polybrominated diphenyl ethers (PBDEs). Continental Iron and Steel uses iron ore, limestone, nickel, and coal, while artisans used steel, cast iron, gasoline, engine oil, lubricants, anti-knock agents, and lead-acid batteries.

Demographic information on age, sex, education, and lifestyles of the workers of the selected factories and artisans

The participants from Imperio International comprised four females and eight males (a total of 12), with ages ranging between 22 and 44 (Table 2). Most of them worked in the production/ packaging unit and had at least a secondary school education, except for one participant who had none. Five of the participants were alcoholics; 3 of them smoked and drank, and 4 of them did neither drink nor smoke. The lowest blood glucose level among the participants was 88 mg/dL, while the highest was 162 mg/dL. Four participants had blood glucose levels above normal (>126 mg/dL).

Table 1. Some of the toxic materials used for production by Imperio International, Mouka Foam, Continental Iron and Steel, and Artisans in Ogba, Lagos, Nigeria

Company	Solid materials	Liquid materials	Gaseous by-products
Imperio International	Coal tars	Ethanol, Bisphenol A, phthalate, brominated flame retardant	Benzene, Acetylene
Mouka Foam	Polyurethane Foam, Antimony	Toluene, Polybrominated diphenyl ethers (PBDEs)	Volatile organic compounds
Continental Iron and Steel	Iron ore, Limestone, Nickel, Coal	Water	Carbon monoxide, Nitrogen
Artisans	Steel, Cast Iron, Sawdust	Gasoline, Engine oil Lubricants, Antiknock agents, lead-acid batteries	Argon, Helium

The total participants from Mouka Foam comprised 17 people, of which 15 were males, and 2 were females (Table 3). Their ages ranged from 21 to 34, and they all worked in the production/packaging unit with at least a secondary school certificate. Three participants were alcoholics, 2 were smokers, 7 were alcoholics and smokers, and 5 did neither drink nor smoke. The lowest blood glucose among the participants was 92 mg/dL, while the highest was 182 mg/dL. Five participants had blood glucose levels above normal values (>126 mg/dL).

The total number of Continental Iron and Steel participants was 15, and they were all males (Table 4). The participants were within the 21–34 age range, and all worked in the production unit with at least a primary education except for one person. Five participants were alcoholics; 1 was a smoker, four smoked and drank, and five did not drink nor smoke. The lowest blood glucose level among the participants was 81 mg/dL, and the highest was 142 mg/dL. Five participants had blood glucose levels above normal (>126 mg/dL).

Table 5 revealed that the selected artisans comprised 52 males, mainly mechanics, carpenters, and welders, between the ages of 16 and 60. Twenty-one participants were alcoholics, 7 were smokers, 12 were alcoholics and smokers, and 12 did neither drink nor smoke. The lowest blood glucose in the group was 85 mg/dL, while the highest was 189 dL. Twenty-four participants had blood glucose levels above normal (>126 mg/dL). The majority had primary and secondary education, except five, who had none.

Table 2. Demographic data on sex, age, education level, and lifestyles of the participants from the Imperio International, Ikeja Industrial Estate, Ogba, Lagos, Nigeria

S/N	Gender	Age	Work hours	Department	Education level	Drinking status	Smoking status	Blood glucose levels (mg/dL)
1	F	38	9	Supervisor	Tertiary	No	No	110
2	F	44	9	Supervisor	Tertiary	No	No	162*
3	F	26	9	Packaging	Secondary	Yes	No	88
4	F	27	12	Security	Secondary	Yes	No	101
5	M	30	9	Production	Primary	Yes	Yes	129*
6	M	28	9	Production	Secondary	Yes	No	121
7	M	31	9	Production	None	Yes	Yes	135*
8	M	50	7	Engineering	Tertiary	Yes	No	116
9	M	22	9	Production	Secondary	No	No	95
10	M	26	9	Packaging	Secondary	Yes	Yes	118
11	M	34	12	Security	Secondary	Yes	No	103
12	M	33	9	Sales rep	Secondary	No	No	127*

*= values above WHO limit (>126 mg/dL)

Table 3. Demographic data on sex, age, education level, and lifestyles of the participants from the Mouka Foam Limited, Ikeja Industrial Estate, Ogba, Lagos, Nigeria

S/N	Gender	Age	Work hours	Department	Education level	Drinking status	Smoking status	Blood glucose level (mg/dL)
1	F	22	9	Packaging	Secondary	No	No	95
2	F	27	9	Packaging	Tertiary	Yes	Yes	110
3	M	21	9	Packaging	Secondary	Yes	No	106
4	M	28	9	Packaging	Tertiary	Yes	Yes	112
5	M	27	9	Packaging	Secondary	Yes	Yes	102
6	M	31	9	Packaging	Secondary	Yes	No	152*
7	M	26	9	Production	Secondary	No	No	108
8	M	32	9	Production	Secondary	No	Yes	128*
9	M	34	9	Production	Secondary	Yes	No	118
10	M	25	9	Production	Technical	Yes	Yes	97
11	M	30	9	Production	Technical	No	No	126
12	M	31	9	Production	Secondary	Yes	Yes	182*
13	M	29	9	Production	Tertiary	Yes	Yes	145*
14	M	23	9	Production	Secondary	No	No	92
15	M	34	9	Production	Secondary	No	No	116
16	M	32	9	Production	Secondary	No	Yes	151*
17	M	28	9	Production	Secondary	Yes	Yes	10

*= values above WHO limit (>126 mg/dL)

Table 4. Demographic data on sex, age, education level, and lifestyles of the participants from the Continental Iron and Steel, Ikeja Industrial Estate, Ogba, Lagos, Nigeria

S/N	Gender	Age	Work hours	Department	Education level	Drinking status	Smoking status	Blood glucose level (mg/dL)
1	M	22	9	Production	Secondary	Yes	Yes	128*
2	M	27	9	Production	Primary	No	No	100
3	M	21	9	Production	Secondary	Yes	No	135*
4	M	28	9	Production	None	Yes	No	92
5	M	27	9	Production	Technical	No	No	101
6	M	31	9	Production	Secondary	No	No	81
7	M	26	9	Production	Secondary	Yes	Yes	142*
8	M	32	9	Production	Secondary	Yes	Yes	138*
9	M	34	9	Production	Secondary	Yes	No	111
10	M	25	9	Production	Secondary	No	Yes	122
11	M	30	9	Production	Secondary	No	No	96
12	M	31	9	Production	Secondary	No	No	87
13	M	29	9	Production	Primary	Yes	No	104
14	M	23	9	Production	Technical	Yes	Yes	129*
15	M	34	9	Production	Secondary	Yes	No	106

*= values above WHO limit (>126 mg/dL)

Table 5. Demographic data on sex, age, education level, and lifestyles of the selected artisans in Ogba, Lagos, Nigeria

S/N	Age	Occupation	Education level	Drinking status	Smoking status	Blood glucose level (mg/dL)
1	55	Carpenter	None	Yes	No	182*
2	48	Carpenter	Primary	Yes	No	135*
3	40	Carpenter	Secondary	Yes	Yes	162*
4	42	Carpenter	None	No	No	120
5	25	Carpenter	Secondary	Yes	No	91
6	28	Carpenter	Secondary	Yes	Yes	122
7	21	Carpenter	Secondary	Yes	No	108
8	18	Carpenter	Primary	Yes	No	102
9	25	Carpenter	Secondary	No	No	110
10	60	Carpenter	Primary	Yes	No	172*
11	58	Carpenter	Secondary	Yes	No	145*
12	25	Carpenter	Secondary	Yes	Yes	128*
13	26	Carpenter	Primary	No	Yes	121
14	19	Carpenter	Secondary	No	No	85
15	16	Carpenter	Primary	No	No	88
16	18	Carpenter	Secondary	Yes	No	97
17	24	Carpenter	Secondary	No	Yes	120
18	23	Carpenter	Secondary	No	Yes	102
19	57	Carpenter	Primary	Yes	Yes	142*
20	33	Mechanic	None	Yes	Yes	158*
21	30	Mechanic	Primary	Yes	No	126
22	22	Mechanic	Secondary	Yes	No	122
23	32	Mechanic	Secondary	No	No	125
24	28	Mechanic	Secondary	Yes	Yes	135*
25	18	Mechanic	Secondary	No	No	105
26	25	Mechanic	Primary	No	No	98
27	27	Mechanic	Primary	Yes	No	88
28	16	Mechanic	Primary	No	No	92
29	20	Mechanic	Secondary	Yes	Yes	110
30	21	Mechanic	Secondary	Yes	Yes	117
31	15	Mechanic	Primary	No	No	98
32	32	Mechanic	Secondary	Yes	Yes	126
33	45	Mechanic	Secondary	Yes	No	140*
34	39	Mechanic	Secondary	Yes	No	158*
35	41	Mechanic	Secondary	Yes	Yes	172*
36	40	Mechanic	Secondary	Yes	Yes	180*
37	27	Mechanic	Primary	No	No	128*
38	26	Mechanic	Secondary	Yes	No	126

39	52	Mechanic	None	No	No	162*
40	54	Mechanic	Secondary	Yes	No	178*
41	55	Mechanic	Secondary	Yes	No	189*
42	45	Welder	Secondary	Yes	No	180*
43	42	Welder	Primary	Yes	Yes	179*
44	30	Welder	Secondary	Yes	No	170*
45	35	Welder	Secondary	No	Yes	161*
46	18	Welder	Secondary	No	Yes	123
47	16	Welder	Primary	No	No	100
48	21	Welder	Secondary	Yes	No	102
49	20	Welder	Secondary	No	Yes	125
50	51	Welder	None	Yes	No	183*
51	33	Welder	Secondary	Yes	No	147*
52	37	Welder	Primary	No	Yes	172*

*= values above WHO limit (>126 mg/dL)

Comparison of blood glucose levels and age of participants from the selected factories and artisans

Continental Iron and Steel participants had the lowest mean age (28±9.1), while Imperio International had the highest (32±2.3). Continental Iron and Steel participants had the lowest blood sugar levels (81 mg/dL), while artisans had the highest (189 mg/dL). Mouka Foam had the lowest percentage of participants (29.41%) having blood glucose levels above normal levels, while artisans had the highest (46.15%) (Table 6).

Influence of smoking and alcohol consumption on blood glucose levels

In Imperio International, none of the participants who smoked or drank were hyperglycemic. However, participants who combined smoking and drinking accounted for 50% of the hyperglycemic population, while participants who neither drank nor smoked also accounted for 50%. In Mouka Foam, smokers accounted for 40% of the hyperglycemic population, alcoholics accounted for 20%, and participants whom neither drank nor smoked accounted for 40%. In Continental Iron and Steel, alcoholics accounted for 20% of the hyperglycemic population, while participants who smoked and drank accounted for 80%. Among the artisans, smokers accounted for 8.33%, alcoholics (50%), participants who smoked and drank (33.33%), and participants who neither smoked nor drank (8.33%). Overall, smokers accounted for 10.53% of the hyperglycemic population, alcoholics (36.84%), participants who drank and smoked (42.11%), and participants whom neither drank nor smoked (10.53%) (Table 7).

Influence of age on the blood glucose levels of the participants

In Imperio and Mouka, age class 31–40 accounted for the highest proportion of the hyperglycemic population, while class 21–30 was the highest in Continental Iron, and class 41 and above was the highest among artisans. Overall, those aged 41 and above had the highest proportion of the hyperglycemic population, followed by those aged 31–40 and those aged 21–30 (Table 8).

Influence of education qualification on blood glucose levels of the participants

Across all the companies, secondary school certificate holders accounted for the highest proportion of the hyperglycemic population, except in Imperio International. Overall, secondary school certificate holders accounted for the highest proportion of hyperglycemia, while tertiary education had the least (Table 9).

Table 6. Comparison of blood glucose levels and age of participants from Imperio International, Mouka Foam, Continental Iron and Steel, and Artisans in Ogba, Lagos, Nigeria

Company	Mean age	Mean work hour	Lowest blood sugar level (Mg/Dl)	Highest blood sugar level (Mg/Dl)	Mean blood sugar level (Mg/Dl)	Percentage hyperglycemic (>126 Mg/Dl)	WHO blood glucose limits (Mg/Dl)
Imperio International	32 ± 2.3	9.3 ± 0.4	88	162	117 ± 5.8	33.33	72-126
Mouka Foam	28 ± 1.1	9 ± 0.0	92	182	120 ± 6.1	29.41	72-126
Continental Iron and Steel	28 ± 1.1	9 ± 0.0	81	142	111 ± 5.0	33.33	72-126
Artisans	32 ± 1.9	-	85	189	133 ± 4.3	46.15	72-126

Table 7. Influence of smoking and alcohol consumption on blood glucose levels of participants from Imperio International, Mouka Foam, Continental Iron and Steel, and Artisans in Ogba, Lagos, Nigeria

Company	Number of hyperglycemic individuals	Individuals who smoked (%)	Individuals who drank (%)	Individuals who smoked and drank (%)	Individuals who neither drank nor smoked (%)
Imperio International	4	0	0	50	50
Mouka Foam	5	40	20	40	0
Continental Iron and Steel	5	0	20	80	0
Artisans	24	8.33	50	33.33	8.33
Overall Percentage Hyperglycemic	38	10.53	36.84	42.11	10.53

Table 8: Influence of Age on the Blood Glucose Levels of Participants from Imperio International, Mouka Foam, Continental Iron and Steel, and Artisans in Ogba Lagos, Nigeria

Company	Number of hyperglycemic individuals	Age class 21 – 30 (%)	Age class 31 – 40 (%)	Age class >41 (%)	p-values
Imperio International	4	25	50	25	0.09786
Mouka Foam	5	20	80	nil	0.01822*
Continental Iron and Steel	5	60	40	nil	0.04857*
Artisans	24	25	20.83	54.17	0.06628
Overall Percentage Hyperglycemic	38	28.95	34.21	36.84	-

* $p < 0.05$ = significantly different; $P > 0.05$ = not significantly different; nil = no participant

Table 9. Influence of education qualification on the blood glucose levels of participants from Imperio International, Mouka Foam, Continental Iron and Steel, and Artisans in Ogba, Lagos, Nigeria

Company	Number of hyperglycemic individuals	Individuals with no education (%)	Individuals with primary education (%)	Individuals with secondary education (%)	Individuals with tertiary education (%)
Imperio International	4	25	25	25	25
Mouka Foam	5	0	0	80	20
Continental Iron and Steel	5	0	0	100	0
Artisans	24	16.67	25	58.33	0
Overall Percentage Hyperglycemic	38	13.16	18.42	63.16	5.26

DISCUSSION

This study measured the blood glucose levels of randomly selected non-obese workers of Imperio International, Mouka Foam, Continental Iron and Steel, and artisans in Ogba, Lagos, Nigeria. The study investigated the strength of the link between industrial pollution exposure and the prevalence of hyperglycemia. The prevalence of hyperglycemia among the participants from Imperior International was 33.33%, Mouka Foam Industries (29.41%), Continental Iron and Steel Company (33.33%), and artisans (46.15%) (Tables 2, Table 6). These proportions are too high and contradict a review by Adeloye et al. (2017), which reported a 5.8% prevalence of hyperglycemia among Nigerians. It also contradicts a systematic review by Uloko et al. (2018), who put the overall prevalence of DM in Nigeria at 5.77%. However, the findings were consistent with those of Nwafor and Owhoji (2001), who reported a 23.4% prevalence of DM among the higher socioeconomic classes in Port Harcourt, Nigeria. Meo et al. (2018) also reported a 63.30% and 23.74% incidence of prediabetes and typed 2 diabetes mellitus (T2DM) among workers in the plastic industry. In a steel company in China, the overall prevalence of DM and prediabetes was 7.5% and 16.8%, respectively (Yang et al. 2015).

Some toxic raw materials used by the selected companies in the present study could be partly responsible for the high prevalence of hyperglycemia among the participants (Table 1). Imperior International uses known endocrine disruptors such as bisphenol A (BPA) and phthalate to produce plastics. Over time, BPA can trigger the release of almost double the insulin needed, desensitizing the body to the hormone and culminating in weight gain and DM (Lynne 2012). A prospective cohort study also reported that urinary BPA and butyl phthalate were associated with T2DM (Jeon et al. 2015). Dioxins are formed during the combustion of plastics, which has been linked with insulin resistance (Chang et al. 2016).

Mouka Foam Industry employs polybrominated diphenyl ethers (PBDEs). This fire retardant accumulates in adipose tissues and predisposes people to obesity, insulin resistance, and diabetes (Le Magueresse-Battistoni et al. 2017, Siddiqi et al. 2003). Antimony, another material used in foam industries, is also reported to increase DM risk (Feng et al. 2015). Continental Iron and Steel Company uses nickel, coal, limestone, and iron ore, which could predispose to high blood glucose. Nickel can disrupt glucose uptake and change networks of activities that maintain glucose balance (Serdar et al. 2009). Iron is required for normal functioning of the system, but iron overload may induce oxidative stress, causing β-cell failure and insulin resistance, resulting in high blood glucose (Simrox & McClain 2013, Sung et al. 2019). Long-term exposure to nitrogen dioxide, one of steel production's by-products, causes oxidative stress (Strak et al. 2017). Carbon monoxide from iron and steel burning can cause inflammatory and immunological reactions in the pancreas, predisposing humans to DM (Huang et al. 2017). The artisans' constant exposure to manganese from anti-knock agents and welding can disrupt metabolic activities, resulting in insulin resistance and T2DM (Li & Yang 2018). Through spray painting, soldering, welding, and lead-acid batteries, artisans may be exposed to lead, disrupting metabolic functions, including insulin metabolism (Leff et al. 2018).

Furthermore, Table 2, 3, 4, 5 showed that all the participants worked at least 9 hours daily and six days weekly, which could have contributed to the observed high prevalence of hyperglycemia. Although this study did not examine the relationship between exposure duration and blood glucose levels because all the participants worked nearly the exact durations, similar studies have established the link. In a study that investigated the occurrence of prediabetes and T2DM among non-smoking plastic industry workers, the prevalence was associated with the duration of work exposure (Meo et al. 2018). Chang et al. (2016) also found that men with the highest dioxin levels due to prolonged exposure had insulin resistance five-fold higher than those with the lowest levels.

Another factor contributing to the high blood glucose among the participants is their lifestyle. Tables 4a and b showed that hyperglycemia was more prevalent among smokers and alcoholics than among participants who combined the two, compared with non-smokers and non-alcoholics. Oladoyinho et al. (2019) reported an increased risk of DM among artisans who indulged in alcohol consumption. Yang et al. (2017) also stated that industrial pollutant exposure and heavy smoking are independent risk factors for DM, and the two may interact to raise the disease's risk.

Moreover, the distribution of hyperglycemia in this study varies with age, class, and education qualifications (Tables 8 and 9). Hyperglycemia was more prevalent in those aged 41 and above, possibly due to an age-related decline in metabolic function. According to Huizen (2019), being over 45 is a risk factor for T2DM. In a study by Al Mansour (2020), DM was more prevalent among the older respondents than the younger age group. Aging reduces mitochondrial function, resulting in decreased insulin sensitivity and hyperglycemia Suastika et al. (2012). Regarding educational qualifications, hyperglycemia was least common among those with tertiary education and most common among those with secondary education. This is consistent with Aldossari et al. (2018), who observed that, aside from old age and

smoking, a lack of education increases the risk of hyperglycemia.

Strength and limitation

The study results could have been better and more convincing with a more significant number of participants. However, the companies were not too comfortable with the research because of the fear of the unknown, so access to some staff was denied. Some of the staff were unwilling to participate for the same reasons mentioned above.

CONCLUSION

The results showed that hyperglycemia was more prevalent among the participants than in the general population of Nigeria. Hence, long-term exposure to pollutants from the studied factories and artisans' workshops increases the risk of hyperglycemia. The risk was higher among smokers, alcoholics, older people, and individuals with less education. At the same time, we recommended further studies to confirm our claims. There was an urgent need for health-boosting lifestyles and pollutant exposure-reducing strategies in the studied workplaces and elsewhere in Nigeria.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

All authors conceived the idea of the study. EGO and DMS ware analysis data. ALA, NS and BMU ware study design. TOY revised the manuscript . TOY, MOS, JDK and JDK have final content and agreetment.

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Original Research

PATIENT SATISFACTION, PERCEPTION-EXPECTATION GAP, AND CUSTOMER SATISFACTION INDEX IN ANNUAL SURVEY 2021 AT DR. SOETOMO GENERAL ACADEMIC HOSPITAL, INDONESIA

Cita Rosita Sigit Prakoeswa[1,2], Nur Hidayah[1], Arlina Dewi[1], Indah Purnamasari[2], Agus Aan Adriansyah[3,5], Amak M. Yaqoub[4,6]

[1]Master of Hospital Administration, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia
[2]Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3]Department of Public Health, Faculty of Health, Universitas Nahdlatul Ulama Surabaya, Surabaya, Indonesia
[4]Faculty of Economics and Business, University of Groningen, Netherlands
[5]Doctoral Study Program of Public Health, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[6]Department of Management, Faculty of Economics and Business, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Service quality is essential in health institutions that can affect patient satisfaction and loyalty. The growth in the number of patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, triggered the diversification of services that require periodic quality control. This study aimed to investigate the performance of 31 departments/units in the hospital, the level of customer satisfaction with services provided, and factors that could influence satisfaction. A survey about service performance, perception, and expectation of services was carried out in 31 departments/units using questionnaires from August to October 2021. Convenient respondents consisted of 2121 patients and their families aged >15. Questionnaire items assessed performance, perceptions, and expectations of health services using the SERVQUAL method. Statistical Package for the Social Sciences (SPSS) software was used to perform an analysis of the results of the measurement and the difference in responses between demographic groups of respondents ($p<0.05$ was significant). The mean performance score was 92.86, and the gap between their perception and expectation averaged -0.23. Customers' expectations of the provider's competence were met, and its performance was perceived to be the best. Meanwhile, handling complaints was perceived as having the lowest performance, while customers' satisfaction over it had not been met. The results showed that the hospital could still not fully meet some of the customer expectations, with immediate improvements needed in handling complaints.

Keywords: *Health services; health system; healthcare quality; hospital management*

Correspondence: Cita Rosita Sigit Prakoeswa, Master of Hospital Administration. Universitas Muhammadiyah Yogyakarta/ Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya. Indonesia. Email: cita.rosita.psc21@gmail.umy.ac.id

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Highlights:

1. Customers expectations at Dr. Soetomo General Academic Hospital has a higher quality of service.
2. The handling of complaints has a low performance on the quality of services at Dr. Soetomo General Academic Hospital.
3. Improving service quality requires improvements in efficient complaint handling.

INTRODUCTION

The COVID-19 pandemic has further emphasized the importance of comprehensive health care management. At a time when most people's attention is focused on the quality of health services and health service organizations (i.e., hospitals), are increasingly required to provide excellent service quality (Lim et al. 2018). Creating service quality is a continuous effort of a service organization, including hospitals. This is triggered by the continuous change in public expectations, which is also accompanied by an increasingly competitive environment (Rivers & Glover 2008). Therefore, hospitals need to carry out a continuous cycle of planning, implementation, evaluation, and action to achieve complete service quality. Hospitals that fail to understand the importance of customer satisfaction can slowly experience setbacks (Aghamolaei et al. 2014).

In measuring service quality, two feasible approaches can be applied: direct and an indirect approach. The direct approach is a concept related to the customer's perception of the actual performance of the services. This direct approach supports the fact that satisfaction is the psychological state of customers after receiving service, which they express during an assessment. Meanwhile, indirect approach assumes that the service quality perceived by customers is influenced by their perception before receiving service and what they perceive from service performance (Endeshaw 2021). Several indicators can be used to measure customer satisfaction with the services provided by the hospital, including traditional rating score and service quality method (SERVQUAL) (Endeshaw 2021).

Dr. Soetomo General Academic Hospital is located in Surabaya, Indonesia. It serves as the main referral and academic hospital in East Java, a province with a population of 39.74 million. In 2021, 556,226 patients visited the hospital at least once, and 10,701 patients visited the hospital >11 times in that year. With the large number of patients and development of health services to become patient-centered, efforts to identify aspects of service that still need to be improved are very much needed. This study aimed to investigate the performance of 31 departments/units in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, as well as the level of customer satisfaction towards health and administrative services provided by the hospital.

MATERIALS AND METHODS

A survey about service performance, perception of services, and expectation of services was carried out in 31 departments/units at Dr. Soetomo General Academic Hospital using questionnaires from August to October 2021. The subjects were patients and their families aged >15 who were using health and administration services at the hospital in 2021. Ethical approval for this study was obtained from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital: Ref. No. 0818/LOE/301.4.2/III/2022). All respondents consented to participate in this study and agreed that their answers to the questionnaire would be analyzed and anonymously published.

Measurement of the perception and expectation was done using a questionnaire with variables referring to Indonesia's Ministry of Administrative and Bureaucratic Reform regulations number 14 of 2017 concerning Guidelines for Compiling a Community Satisfaction Survey for Public Service Providers. The nine variables are service terms and conditions, service procedures, completion time, cost, product compatibility, provider's competence, provider's behavior, handling of complaints, and facilities and infrastructure. The questionnaire consisted of two parts.

In the first part, sociodemographic data of the respondents were collected. In the second part, respondents give their rating on how much satisfaction they expect with the services to be provided and how satisfied they are with the services already provided by the hospital on 26 sub-indicators using a Likert scale (0=don't know, 1=very dissatisfied, 2=dissatisfied, 3=satisfied, and 4=very satisfied). The 26 sub-indicators were developed from the 9 measurement indicators that have been described previously. It should be noted that the number of sub-indicators tested in each department/unit may vary according to the type of service available. The survey questionnaire is presented in Table 1. Prior to dissemination, the instrument's validity and reliability were tested to collect valid data.

The data were coded, entered into a computer, and analyzed using Statistical Package for Social Sciences (SPSS) version 18 (USA). After excluding incomplete responses, we obtained 2121 respondents. Descriptive analysis with frequencies and percentages was generated to describe respondents' demographic profiles. In general, the analysis technique was carried out based on Indonesia's Ministry of Administrative and Bureaucratic Reform regulations number 14 of 2017 concerning Guidelines for Compiling a Community Satisfaction Survey for Public Service Providers.

Table 1. Survey questionnaire items

No.	Indicators	Sub-indicators
1	Service terms and conditions	Clarity of service terms and conditions Ease of fulfilling terms and conditions
2	Service procedures	Clarity of registration flow Clarity of service flow
3	Completion time	Timeliness of service according to schedule Rapid medical services by nurses/midwives Rapid medical services by general practitioners Rapid medical services by residents Rapid medical services by specialists Rapid services by receptionists
4	Cost	Cost affordability Compatibility between costs with facilities and services Clarity of cost details
5	Product compatibility	Compatibility between the services offered and those provided
6	Provider's competence	Competence of doctors Competence of nurses/midwives Competence of administrative officers
7	Provider's behavior	Courtesy and friendliness of doctors Courtesy and friendliness of midwives/nurses Courtesy and friendliness of administrative officers
8	Handling of complaints	Ease of expressing complaints Promptness in resolving complaints
9	Facilities and infrastructure	Room cleanliness and tidiness Convenience of waiting room Restroom's cleanliness Hospital environment safety

The performance of each department/unit is assessed from the respondent's perception on the services provided. Performance scores were calculated using each service element's "weighted average". Every element in the service has the same weight.

$$\text{Weighted average} = \frac{\text{Indicator}}{\text{Total number of indicators}} = \frac{1}{9} = 0.11$$

$$\text{Performance} = \frac{\text{Sum of perception score per indicators}}{\text{Total number of indicators rated}} \text{ x Weighted average}$$

Performance scores were converted by multiplying by 25. Score conversion of 25.00-64.99 was categorized as very poor performance, the score of 65.00-76.60 was classified as poor performance, the score 76.61-88.30 was classified as good performance, and the score of 88.31-100.00 is classified as excellent performance. SERVQUAL method was used to analyze the difference between the expected service (expectations) and the service perceived by the customer (perception) by subtracting expectation scores from perception scores to obtain P-E gap. P-E gap with a value of 0 indicates that there is no difference between customer expectation and customer perception, P-E gap <0 means that customer expectations exceed the perception of the services provided, and P-E> 0 means that the service provider's performance exceeds customer expectations.

Customer Satisfaction Index (CSI) was measured by comparing perceptions with expectations, then multiplied by 100%. Welch's analysis of variance (ANOVA) test was conducted to explore the difference of responses amongst the sociodemographic groups, and Games-Howell post hoc analysis was performed to determine exactly which groups are significantly different. However, 6 respondents were found not to have complete sociodemographic data, hence excluded from this analysis; $p<0.05$ is considered statistically significant.

RESULTS

Findings from the preliminary study signified the validity of the questionnaire items with r>0.05 and Cronbach's alpha >0.6 when tested in respondents from all 31 departments (Table 2). The sociodemographic data of the respondents are shown in table 3. The distribution of gender is 38.8% male and 61.2% female. The age distribution of respondents in descending order from the most abundant to the least is 25-44 years (53.4%), 45-65 years old (34%), 15-24 years old (9.3%), and above 65 years old (3.3%). Amongst the 2121 respondents that completed the survey, 5 people (0.2%) are uneducated, while the majority of respondents completed secondary education (62.9%). The results of performance, expectation, and P-E gap analysis in 31 departments/units is shown in table 3. The service quality as measured by performance from 31 units at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, showed a mean score of 92.86. The mean value of customers' expectation to the services averaged 93,09, and the gap between their perception and expectation averaged -0.23.

Table 2. Validation and reliability instrument result of IKM survey on 2021 in 31 installations

No	Department/ unit	n	R table	Corrected total item correlation	Cronbach's alpha
1.	Regenerative Biomaterial and Tissue Bank Unit	10	0.632	0.743	0.957
2.	Minimally Invasive Urology Unit	10	0.632	0.738	0.955
3.	Cardiovascular Diagnostics and Interventional Unit	15	0.154	0.670	0.937
4.	Obstetrics and Gynecology Ward	30	0.361	0.625	0.939
5.	Pediatric Ward	30	0.361	0.673	0.944
6.	Radiodiagnostics Unit	30	0.361	0.611	0.938
7.	Radiotherapy Unit	30	0.361	0.525	0.906
8.	Anatomic Pathology Unit	30	0.361	0.581	0.931
9.	Surgical Ward	30	0.361	0.585	0.928
10.	Hemodialysis Unit	15	0.514	0.657	0.931
11.	Nutritions Unit	15	0.514	0.646	0.918
12.	Intermediate Care and Infectious Disease Unit	15	0.514	0.692	0.952
13.	Graha Amerta	20	0.444	0.688	0.962
14.	Clinical Microbiology Unit	15	0.514	0.670	0.937
15.	Medical Ward	30	0.361	0.594	0.927
16.	Intensive Care and Reanimation Unit	15	0.514	0.670	0.937
17	Dental and Mouth Unit	15	0.514	0.663	0.934
18.	Health Financing Unit	20	0.444	0.675	0.928
19	Blood Transfusion Unit	15	0.514	0.633	0.928
20.	Outpatients Clinic	20	0.444	0.618	0.930
21.	Clinical Pathology Unit	20	0.444	0.550	0.893
22.	Medical Check Up Unit	20	0.444	0.646	0.941
23.	Medical Rehabilitation Unit	20	0.444	0.665	0.950
24.	Psychiatric Ward	10	0.632	0.743	0.960
25.	Pharmacy Unit	15	0.514	0.674	0.934
26.	Integrated Cardiac Service Center	20	0.444	0.641	0.941
27.	Mortuary Services	20	0.444	0.663	0.937
28.	Central Surgery Unit	20	0.444	0.550	0.881
29.	Forensic and Medicolegal Unit	15	0.514	0.639	0.928
30.	Palliative and Pain-free Unit	20	0.444	0.615	0.928
31.	Emergency Department	20	0.444	0.575	0.908

Table 3. Sociodemographic characteristics of the respondents

Variable	n (%)
Total (n)	2121 (100)
Gender	
Male	822 (38.8)
Female	1.299 (61.2)
Age	
15-24	197 (9.3)
25-44	1.132 (53.4)
45-65	722 (34.0)
>65	70 (3.3)
Education	
Uneducated	5 (0.2)
Primary	173 (8.2)
Secondary	1335 (62.9)
Diploma/bachelor	568 (26.8)
Master/doctoral	40 (1.9)

Meanwhile, the results of an independent analysis of 9 satisfaction indicators from 31 units at Dr. Soetomo General Academic Hospital, showed the correlation between performance and CSI (Figure 1). The mean performance and CSI score was 92.20 and 93.74, respectively. Handling of complaints was the lowest rated among the 9 indicators. The SERVQUAL analysis which showed perception-expectation gap (P-E gap) was presented in Figure 2, which indicated negative P-E gap value in all departments/units, with the greatest gap in the radiotherapy unit and the least gap in the medical rehabilitation unit.

The results of perception, expectation, P-E gap, and CSI measurement for each demographic group of respondents are shown in Table 5. Welch's ANOVA test revealed significant differences in the mean of perception, expectation, P-E Gap, and CSI across the education levels, as well as in respondents' perceptions of health services across age groups. However, no significant difference in the mean of perception, expectation, P-E Gap, and CSI was found between genders. Games-Howell post hoc analysis revealed that people with diploma or bachelor degree had a significantly lower perception and CSI score, as well as wider P-E gap (more negative score), compared to people with uneducated or primary, secondary, and magister or doctoral education ($p<0.05$).

Table 4. Measurements of performance and P-E gap in all 31 departments/units

Department/unit	n	Performance	P-E gap
Medical Rehabilitation Unit	66	99.08	-0.04
Nutrition Unit	66	98.90	-0.04
Hemodialysis Unit	66	98.82	-0.05
Blood Transfusion Unit	66	98.78	-0.05

Department/unit	n	Performance	P-E gap
Psychiatric Ward	24	97.95	-0.08
Central Surgery Unit	66	97.65	-0.09
Palliative and Pain-Free Unit	66	97.63	-0.09
Intensive Care and Reanimation Unit	66	97.52	-0.1
Radio Diagnostics Unit	88	96.58	-0.14
Pharmacy Unit	81	96.49	-0.14
Minimally Invasive Urology Unit	45	96.30	-0.15
Cardiovascular Diagnostics and Interventional Unit	32	94.93	-0.2
Mortuary Services	66	94.73	-0.21
Obstetrics and Gynecology Ward	76	93.90	-0.24
Dental and Mouth Unit	66	92.99	-0.28
Clinical Microbiology Unit	66	92.93	-0.28
Health Financing Unit	66	92.75	-0.29
Graha Amerta	66	92.60	-0.27
Integrated Cardiac Service Center	102	91.78	-0.31
Intermediate Care and Infectious Disease Unit	66	91.42	-0.34
Surgical Ward	117	90.97	-0.24
Medical Check Up Unit	66	89.76	-0.27
Pediatric Ward	101	88.47	-0.33
Outpatients Clinic	102	87.97	-0.38
Medical Ward	126	87.60	-0.3
Regenerative Biomaterial and Tissue Bank Unit	16	87.56	-0.28
Radiotherapy Unit	88	87.47	-0.5
Emergency Department	66	87.36	-0.42
Anatomic Pathology Unit	45	86.70	-0.17
Forensic and Medicolegal Unit	22	86.49	-0.47
Clinical Pathology Unit	66	84.60	-0.31
Total	2.121	92.86	-0.23

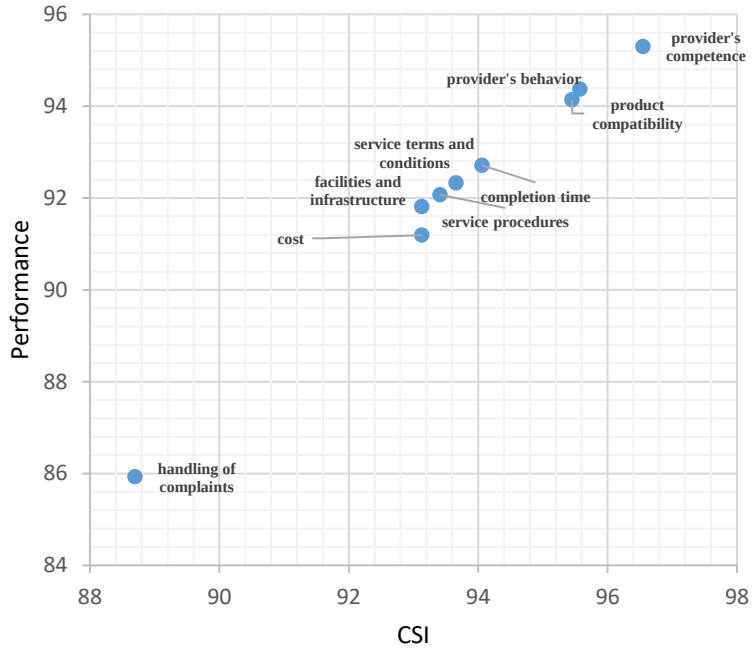

Figure 1. Performance scores and CSI scores of the 9 indicators in 31 departments/units

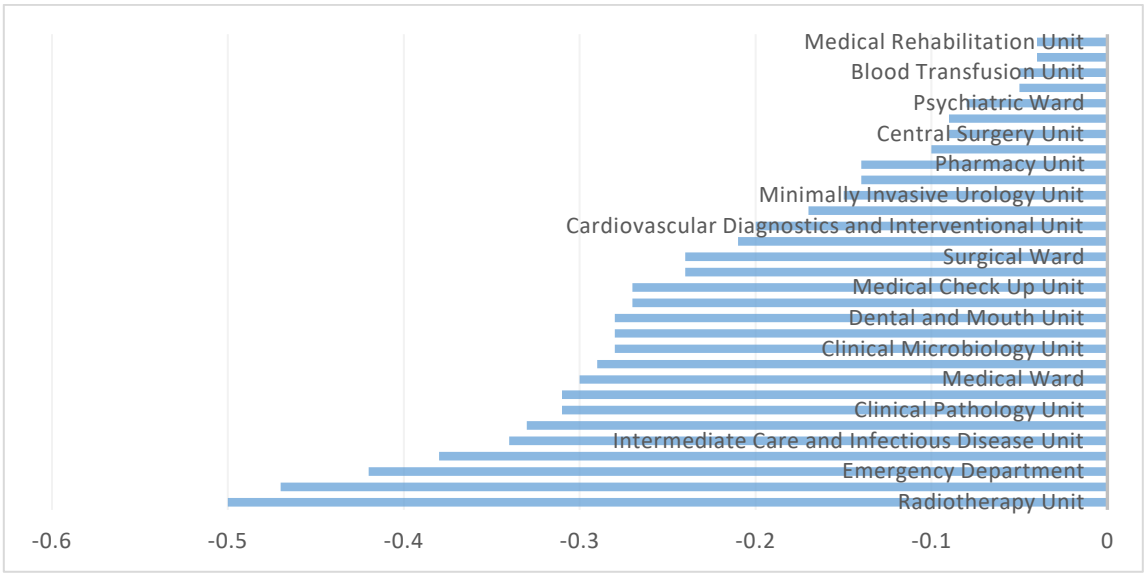

Figure 2. P-E gap analysis in all 31 departments/units

Table 5. Comparison between perception, expectation, P-E Gap, and CSI across respondents' demographic groups

Variable	P	p-value	E	p-value	P-E Gap	p-value	CSI	p-value
Total = 2115								
Gender								
Male	3.70	0.10	3.94	0.98	-0.24	0.90	0.94	0.09
Female	3.73		3.94		-0.21		0.95	
Age								
15-24	3.70	0.01	3.94	0.60	-0.22	0.07	0.95	0.08
25-44	3.70		3.94		-0.24		0.94	
45-65	3.75		3.95		-0.20		0.95	
>65	3.79		3.97		-0.18		0.95	
Education								
Uneducated/primary	3.77	<0.001	3.96	0.03	-0.19	0.001	0.95	0.001
Secondary	3.75		3.95		-0.20		0.95	
Diploma/Bachelor	3.64		3.92		-0.20		0.95	
Master/Doctoral	3.68		3.93		-0.17		0.96	

Hospital performance can be measured by standardized surveys of patients and relatives, which can then provide information to service providers about the aspects of services valued by the public. In Indonesia, the government requires every institution to conduct annual routine performance and customer satisfaction. Our study found that from the total 31 departments/units studied, 23 departments/units were rated as having excellent performance, while 8 units had good performance. No departments/units were rated as having poor performance.

Performance of hospital is an important dimension in delivering quality services to the customers, and as an effort to fulfill customer's satisfaction. A study by Fatima et al. (2018) found that better healthcare services quality produces satisfaction and loyalty among patients. Aspects of healthcare services (i.e., physical environment, customer's friendly environment, responsiveness, communication, privacy and safety) have a positive relationship with patient loyalty mediated through patient satisfaction. Similar results were obtained by Alghamdi (2014) that patient satisfaction was significantly impacted by the health service quality. Therefore, healthcare providers need to pay special attention to satisfaction and patient loyalty because the concept of the relationship between these aspects had an influence on the image and profitability of the institution (Ramli 2019). This can happen because of the impact on increasing patient base and market share, which also increase profits through increased sales of services (Karatepe et al. 2005, Chang et al. 2013, Neupane & Devkota 2017). However, satisfied patients could still switch to other providers, so it showed the complexity of the relationship between patient satisfaction and loyalty (Astuti & Nagase 2014).

Perception and expectation measures are part of the SERVQUAL analysis that was first proposed by Parasuraman et al. in 1988 (Lee et al. 2000). SERVQUAL model consisted of a multiple-item scale measurement tool to assess services quality as measured by customer's perception on quality. Service quality can be defined as the gap between the level of service perceived and expected by customers (P-E gap). Since then, SERVQUAL had been adopted and widely used as a reliable and valid means of quality assessment in hospital environments (Mangold & Babakus 1991). In the healthcare environment, patient satisfaction is defined as the conclusion that patients and their families perceive after comparing between the services they received during the visit/stay and their previous expectations (Fang et al. 2019). Service quality is assessed based on customer satisfaction with the fulfillment of their expectations of the service provider. If the service received or perceived is in accordance with customer expectations, then the service quality will be perceived as good. On the other hand, if the service received or perceived is yet to meet customer expectations, the quality of the service will be perceived as bad. Thus, whether or not the quality of service depends on the ability of the service provider to consistently meet the expectations of its customers (Vinagre & Neves 2008).

A negative score on one or more SERVQUAL dimensions could give the signal for an in-depth investigation of that dimension to discover the factors interfering with the fulfillment of patient satisfaction with the services provided (Mangold & Babakus 1991). Ultimately, the results of patient satisfaction measurements carried out systematically and continuously could be expected to improve the quality and ultimately increase the profitability of hospitals.

In this study, the result of P-E gap measurement showed a negative value, indicating that the patient's expectations for services had not been met fully. Similar studies in hospitals in Riyadh and Pakistan reported the same results, where all aspects still had a negative P-E gap (Aghamolaei et al. 2014, Al-Momani 2016, Fatima et al. 2018, Sharifi et al. 2021). Patient satisfaction is influenced by expectations, and patient perceptions that have not been fully explained because the marketing-oriented conceptual model is not always appropriate for various health care conditions. Patients can have a complex set of important and relevant beliefs that cannot always be expressed in terms of satisfaction. Satisfaction survey results should be interpreted in terms of a number of assumptions about what patients actually mean by "satisfied" (Williams 1994). Jenkinson et al. (2002) reported that the main determinants of patient satisfaction were physical comfort, emotional support, and respect for patient preferences. Patient satisfaction refers to the patient's perception of the quality of health services, including the provision of quality health services that are timely, well-organized, and patient-centered (Astuti & Nagase 2014).

Several factors can contribute to the satisfaction perceived by the patients. A cross-sectional study in a tertiary public hospital in Nepal found that age, gender, ethnicity, education, occupation, and religion were among the sociodemographic factors associated with patient satisfaction (Adhikari et al. 2021), while the research conducted by Elizar et al. (2020) proved that payment methods can be a factor that affects satisfaction and loyalty at the pediatric polyclinic of a private hospital in East Jakarta, Indonesia. A survey about satisfaction on medical services conducted in Wuhan, China, found that the service attitude of the medical staff affects patient satisfaction the greatest, followed by technology in medical services, and the convenience of the hospital (Fang et al. 2019). Amongst the 9 measurement indicators, only handling of complaint aspects is still rated "not good", with low rating on performance and CSI. Complaint handling includes service recovery, service quality, switching cost, service failure, service guarantee, and perceived value. Similar findings were also reported in Sragen Regency hospitals (Fatonah & Palupi 2020).

Based on the post hoc analysis, our study found that respondents who completed secondary education gave lower perception and expectation ratings than respondents who did not attend school/completed primary school education ($p<0.05$), and respondents who completed diploma/bachelor education gave the lowest ratings compared to the two previous groups ($p<0.001$). Respondents in the 25-44 years old age group had significantly lower perception scores compared to respondents from the 45-65 years old group ($p=0.02$). Previous studies related to the influence of sociodemographic factors on patient satisfaction with health services revealed various findings. Patients demographic characteristics had no significant effect on satisfaction (Fang et al. 2019), while other studies reported that age, health status, and race consistently had a statistically significant effect on satisfaction scores (Young et al. 2000). Hospital size also consistently had a significant effect on patient satisfaction. A study by Kelarijani et al. (2014) found that the level of patient satisfaction on health services has been associated with accommodation. Patients domiciled from rural areas are more satisfied than those from the cities due to cultural differences in the patient's perspective. In our study, diploma or bachelor graduated respondents have a lower satisfaction as indicated by low CSI (perception : expectation). Patient satisfaction is also related to their educational level. Patients with higher levels of education were less satisfied, since they had higher expectations on the

services, influenced by higher education, higher incomes and social status.

Strength and limitation

There were several limitations to our study. This study used a retrospective method and some of the data obtained from respondents was incomplete. We did not take into consideration about the length of stay, marriage status, and outcome of treatment in the analysis, which in previous similar studies could affect customer satisfaction. Factors causing customers' satisfaction of certain indicators in some departments/units to be low could not be determined due to the limitations of the questionnaire model which only utilized a Likert scale as an assessment. In the future, a higher number of respondents is expected to be achieved by engagement of website or application-based surveys with more interactive interface and convenience for the younger respondents.

CONCLUSION

The questionnaire that can be used to measure performance, as well as SERVQUAL analysis for hospital customers, was valid and reliable to be used in future service quality assessments. The health and administrative services in Dr. Soetomo General Academic Hospital were generally perceived as good by the customers. However, immediate action needs to be taken for further review and improvement of service quality related to the complaints handling indicators. P-E gap analysis in all departments showed that the service received by customers was still not up to their expectations. The fulfillment of customer satisfaction was not influenced by gender and age but is influenced by education level. Customers with diploma/bachelor's education tend to be less satisfied with the services. In the future, a broader analysis was needed regarding the influence of other sociodemographic factors, length of stay, the outcome of health services, and funding source of the patients on their satisfaction in order to know the gap in the hospital system. Furthermore, factors causing customer satisfaction/dissatisfaction with each service indicator must be investigated. Thus the health services can be improved.

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Conflict of interest

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Funding disclosure

None.

Author contribution

CRSP, IP, AD, and AAA contributed conceptual the study's idea. AMY, NH, and CRSP ware analysis data and revised the manuscript. CRSP have final check the manuscript content.

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Case Report

EXCISION OF RECURRENT HEMANGIOMA IN HAND WITH RECONSTRUCTION USING ABDOMINAL FLAP

Ivan J Mangara Tua[1], Andi M Ardan[2], Hari D Pagehgiri[3], Amy R Sukamto[4], Made AP Dwipayana[4]

[1]Division of Thoracic, Cardiac, and Vascular Surgery, Universitas Mulawarman/Abdul Wahab Sjahranie Hospital, Samarinda, Indonesia
[2]Division of Plastic, Reconstructive and Aesthetic Surgery, Universitas Mulawarman/Abdul Wahab Sjahranie Hospital, Samarinda, Indonesia
[3]Resident of Thoracic, Cardiac, and Vascular Surgery, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[4]Internship Doctor of Thoracic, Cardiac, and Vascular Surgery, Abdul Wahab Sjahranie Hospital, Samarinda, Indonesia

ABSTRACT

Hemangiomas are known for their typical involution with age. However, around 40% of cases require intervention. Hemangioma in hand is challenging because the hand function and the aesthetic appearance need to be preserved. Hereby we reported a 21-year-old woman with a recurrent hemangioma on the left hand in Abdul Wahab Sjahranie Hospital, Samarinda, Indonesia. The patient's previous surgery was ineffective since the mass reappeared in the same area. We performed surgical excision and reconstruction with an abdominal flap. One-month and one-year postoperative follow-up indicated good flap viability and preserved hand functions without the need for amputation. This report also emphasizes the importance of collaboration from multiple surgical and medical fields to allow favorable outcomes in this case.

Keywords: *Hemangioma; vascular tumor; benign vascular tumor; abdominal flap; hand surgery; good health and well-being*

Correspondence: Ivan J Mangara Tua. Division of Thoracic, Cardiac, and Vascular Surgery, Universitas Mulawarman/ Abdul Wahab Sjahranie Hospital Samarinda, East Borneo, Indonesia. Email: aesculap99@gmail.com

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Highlights:

1. Hemangioma of the hand is a challenging case due to the need to maximize eradication of the mass while minimizing damage to the healthy tissue to preserve the physiologic function of the hand.
2. The reconstruction of the defect also needs to be taken into account to maintain the cosmetical appearance.
3. Collaborative multidisciplinary work is essential to achieve these demands and maintain the patientôs quality of life.

INTRODUCTION

Hemangioma is a relatively common benign proliferative lesion of vascular tissue origin. It is known for its typical occurrence during infancy and involution with age, usually negating the need for invasive treatment. Nevertheless, cases of recurrence that might require further intervention are also present (Richter & Friedman 2012). Hemangioma develops most commonly in subcutaneous adipose tissue but a rare emergence in muscles might occur. This lesion is most frequently found on the thigh (Wierzbicki et al. 2013), while the upper extremity is an uncommon site, only accounting for 15% of cases (Jacobs et al. 2010). Hemangioma of the hand is particularly challenging. In this study, we emphasized the importance of collaborative work to provide comprehensive management. The mass has to be completely excised

while maintaining as much physiologic function of the hand as possible to allow daily activities. Apart from the physiologic function, we also noted the need to maintain the cosmetic appearance of the hand, particularly in a young woman, to maintain the patient's quality of life. We hereby presented a case report describing the excision of recurrent hand hemangioma that was reconstructed with an abdominal flap. Informed consent had been obtained from the patient for publication of the case report and accompanying images.

CASE REPORT

A 21-year-old woman was admitted to our hospital because of a mass on her left hand. The mass has been there since birth and was operated upon at the age of four, but reemerged on the same site. It was located on the medial palmar side of the left hand with compressible and soft consistency (Figure 1). There was no thrill or bruit on physical examination.

Figure 1. Hemangioma on the medial left palmar region

MSCT angiography revealed a subcutaneous soft tissue mass and calcification on the medial side of the left hand with indistinct borders suggestive of hemangioma (Figure 2).

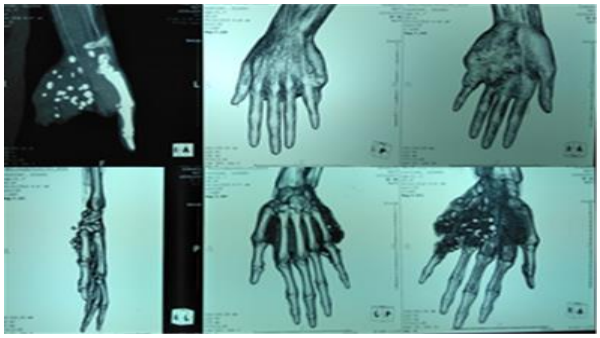

Figure 2. MSCT angiography revealed a subcutaneous soft tissue mass with calcification and indistinct borders

Surgical excision was performed. An 8 x 6 cm mass infiltrating the muscles and fascia was excised, resulting in a large defect on the medial palmar side. This was simultaneously reconstructed with an abdominal flap (Figure 3).

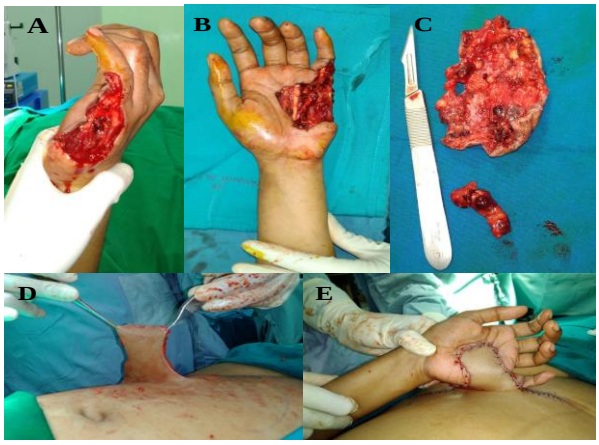

Figure 3. (A-C) An 8 x 6 cm mass infiltrating the muscles and fascia was excised, resulting in a large defect on the medial palmar side of the hand. (D-E) The resultant defect was reconstructed with an abdominal flap

Aside from being the patient's choice, we settled for a random pattern abdominal flap since it has more versatility and a relatively short surgery time. The cosmetic appearance was another point of consideration. The resultant scar was positioned on the inguinal area that is easier for the patient to conceal with clothing, while a free flap would have left a quite visible scar on the thigh. Histopathologic evaluation of the excised mass confirmed a capillary hemangioma (Figure 4).

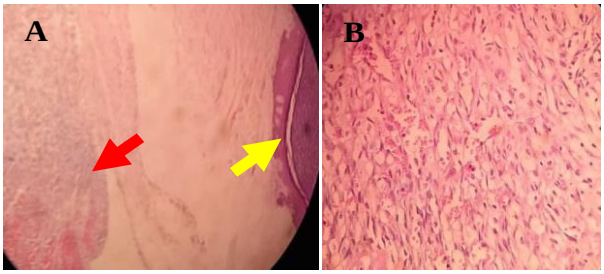

Figure 4. (A) Microscopic examination showing (red arrow) an area with hemangioma adjacent to (yellow arrow) the skin epidermis. (B) Small blood vessels lined with endothelial cells containing red blood cells (hematoxylin and eosin staining; 100x and 400x magnification)

The flap was divided after 21 postoperative days to provide sufficient time for neovascularization. The flap was re-evaluated after one month and one year following the surgery (Figure 5). The postoperative investigation included skin color, temperature, capillary refill time, and signs of hematoma, all of which were normal, indicating the flap's viability. All

clinical outcomes remained as mentioned and there were no signs of tumor recurrence after one year of follow-up. The hand functionality was also preserved.

There was a slight contracture on the fifth finger which was further followed up by a plastic surgeon.

Figure 5. Evaluation on (A) one-month and (B-C) one-year follow-up exhibited good clinical outcomes with preserved hand functions. There were no clinical signs of recurrence within a one-year follow-up

DISCUSSION

Hemangiomas are the abnormal proliferation of blood vessels that may develop in any vascularized tissue. They may be asymptomatic or may cause symptoms such as pain and swelling (Katz & Damron 2021). Hemangioma is experienced by 7% to 10% of infants (Jacobs et al. 2010), making it a relatively common tumor in infancy. It might be present at birth or arise during early childhood, the latter being much more prevalent. A small number of cases that are linked to trauma might also be found (Wierzbicki et al. 2013). It is classified as a benign vascular tumor with typical developmental phases, including proliferation in which the lesion undergoes rapid growth, followed by dormancy, and involution (Richter & Friedman 2012, Shah et al. 2014). Involution generally occurs within the first few years of life. This is in contrast to another entity of vascular anomalies, vascular malformations (i.e., arteriovenous malformations, capillary malformations), which do not undergo the involution phase. A hemangioma can be histologically classified into capillary and cavernous forms based on its vascular network. Capillary hemangioma consists of small capillaries each lined by a single layer of endothelial cells (Kumari et al. 2015), whereas cavernous hemangioma is composed of large, dilated vessels with thin walls (Kamala et al. 2014).

Hemangioma makes up 7% of all benign soft tissue tumors (Wierzbicki et al. 2013). It mostly affects the upper extremity (15%) and largely occurs in subcutaneous adipose tissue. Intramuscular emergencies are rare, accounting for less than 1% of hemangioma, most of which are located in the thigh (36%) and the calf (17%) (Wierzbicki et al. 2013). Most intramuscular hemangiomas are self-limited and invasive interventions bear varied outcomes; therefore, surgical intervention is unnecessary unless indications are compelling. Thrombocytopenia, intractable pain, rapid tumor growth, local skin necrosis risk, cosmetic or functional impairment, and malignancy suspicion may necessitate surgical intervention (Mitsionis et al. 2010, Tang et al. 2002). An average symptom duration at an initial presentation is 13 months, chronic extremity pain should increase suspicion of an intramuscular hemangioma (Kiran et al. 2012, Wild et al. 2000).

A new mass and chronic pain are the most common presenting symptoms (Kryzak & DeGroot 2008). In cases of bleeding, ulceration, excessive pain, the risk for cosmetic disfigurement, and other functional impairment corresponding to the affected area, surgery may be considered. Around 18% to 61% of cases might recur, incomplete excision being the greatest risk factor. Wierzbicki et al. (2013) and Lu et al. (2017) reported a persistent recurrence of intramuscular hemangioma despite repeated surgeries, resulting in multiple physiologic insults and sufferings on the patient's side. Considering the patient's overall well-being, the right upper limb was amputated without the patient's consent. Our case reflected the need for surgery due to functional impairment and cosmetical indications in a young woman.

Conservative management is the first line of treatment for nearly all isolated intramuscular hemangiomas (Henderson et al. 2010). The reconstruction of skin defects of the hand and forearm aims at restoring their function with a good aesthetic appearance (Ali et al. 2007). Soft tissue reconstruction for large defects of the hand remains a challenge due to the need to restore its physiologic function and maintain a good appearance. Several options of reconstruction techniques are available depending on the general condition of the patient and the local condition of the wound and donor site. Some commonly used techniques are random pattern flap, axial pattern flap, and free flap (Chen et al. 2021, Monreal et al. 2017).

Axial pattern reverse radial forearm flap can be used for hand defect reconstruction (Hawary 2020). It is safe, simple, only involves a one-stage procedure, and provides sufficient tissue coverage with robust vascularization for a good flap outcome. A major drawback is that it sacrifices a major artery, consequently jeopardizing the donor site and hand viability (Ali et al. 2007). In our case, this method was not chosen since there was suspicion of ulnar artery incompetence due to the hemangioma. This would further harm the hand viability. A free flap is another reconstruction technique that can be used. However, this procedure takes considerably longer and requires a more complex technique as well as complicated

postoperative care (Ali et al. 2007, Monreal et al. 2017).

Abdominal flap for the reconstruction of soft tissue defects on the dorsum of the hand distant flap had a long-time role. A random pattern abdominal flap is frequently used to cover traumatic defects involving the hand. However, the bulkiness of the flap and the two-stage procedure are the main disadvantage of the abdominal flap. In particular, the bulkiness of the flap is bothersome to the patient and is frequently subjected to debulking surgery. In this work, abdominal thin skin flaps were raised and reconstructed (thirty soft tissue defects on the dorsum of the hand and forearm) with a maximum of 9 x 16 cm flap dimension. All flaps had survived. Furthermore, the flaps were thin that did not require revision (Ali et al. 2007). Lin et al. (2005) used the pedicled skin flaps of the subdermal vascular plexus for the reconstruction of hand defects. They achieved complete survival in all the flaps used to reconstruct 22 hand defects.

The abdominal flap has long been used as a modality to cover soft tissue defects, such as the upper extremities and following mastectomy. In the case of upper extremity defects such as that in our study, this approach generates a bulky flap and requires a two-stage procedure flap (Ali et al. 2007), which opposes the general goal of an efficient surgery. Nevertheless, our team settled for a random pattern abdominal flap since it has more versatility, relatively shorter surgery time, as well as being the patient's method of choice. The choice of the flap is mainly based on the anatomical location and size of the defect.

The positioning of the flap can be modified to fit the size of the defect and the patient's comfort. The hand may be supinated or pronated accordingly. In our case, the hand was supinated to accommodate the location of the defect. Follow-up was done in one month and one year postoperatively. The patient had slight contracture on the fifth finger but the overall hand functions (basic functions such as grasping objects and more advanced functions such as writing, cutting) were preserved to carry out daily activities. The viability of the flap was good with normal skin color, temperature, and capillary refill time. No signs of hematoma and tumor recurrence were observed.

Strength and limitation

The case report highlights a challenging case of a recurre hemangioma in a difficult location, emphasizing the need for appropriate intervention.The use of surgical excision and reconstruction with an abdominal flap is a unique approach that may be useful for other similar cases.The report provides evidence of successful treatment with good follow-up results, indicating the effectiveness of the intervention. The report is limited to a single case, and therefore the generalizability of the findings may be limited.

CONCLUSION

Surgical intervention is still the treatment of choice for recurrent hemangioma. Excision of hemangioma on the upper extremity poses a challenge due to the need to maximize tumor eradication while minimizing damage to normal functions. Comprehensive management involving multiple surgical and medical fields was substantial to maintain physiological functions and cosmetic appearance. The resultant defect of excision could be reconstructed using an abdominal flap with a satisfactory clinical outcome.

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Conflict of interest

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Author contribution

All authors contributed to design's study. IJMT write and revised the manuscript. AMA, HDP, and ARS were final grammar check. MAPD was final content.

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Case Report

A RARE CASE OF NEUROENDOCRINE TUMOR FOLLOWING RADICAL NEPHRECTOMY

Muhammad Rozaqy Ishaq, Nafis Audrey Febriansyah, Soetojo
Department of Urology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Neuroendocrine Tumors (NETs) are a diverse range of neoplasms with various biological and histologic features and therapeutic responses. The prevalence of primary renal carcinoids is scarce worldwide. At the moment, complete surgical resection is the primary treatment against primary neuroendocrine tumors of the kidney. Nephrectomy followed by the lymph node dissection is a standard procedure for localized primary renal NETs. Since renal carcinoid tumor is extremely rare, we decided to present a unique case of a 25-years-old male with neuroendocrine renal carcinoid tumor following radical nephrectomy. The results indicated a solid, solitary tumor verified on the frozen section because a postoperative CT–scan showed a recurring mass in the renal fossa following radical nephrectomy. The case emphasized the need to investigate primary renal NET in the workup and histological examination of renal tumors and also contributed to our understanding of this infrequent clinical entity.

Keywords: *Neuroendocrine tumors; NETs; carcinoid tumor; radical nephrectomy; tumor*

Correspondence: Soetojo, Department of Urology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. E-mail: s.tojowirjopranoto@yahoo.com

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Highlights:

1. Rare occurrence of a large, well-differentiated primary renal neuroendocrine tumor in a young man.
2. Identifying primary renal NET from the workup and histological examination of renal tumors needs to be done to understand more of this infrequent type of tumor.

INTRODUCTION

Neuroendocrine Tumors (NETs) are a diverse range of neoplasms that vary in biological and histologic features and therapeutic responses. NETs are divided into well-differentiated and poorly-differentiated neoplasms (Klimstra et al. 2010). The gastrointestinal system, pancreas, and lungs are the most common sites for well-differentiated NET carcinoid tumors. Carcinoids of the genitourinary tract, especially those arising primarily from the kidney, are extremely rare (Bégin et al. 1998). Less than 1% of reported carcinoid tumors were discovered in the genitourinary system (Murali et al. 2006). However, reported renal carcinoid tumors are only within 19% of all patients with carcinoids in the genitourinary system (Martignoni & Eble 2003). Primary renal carcinoid tumors do not advance progressively. Instead, they grow slowly and become non-functional in most cases. They were detected incidentally and showed no sex predilection. Patients are usually around 23 to 78 years old, with an incidence age lower than renal cell carcinoma (Jain et al. 2010).

Complete surgical resection is the primary treatment against primary neuroendocrine tumors of the kidney. Nephrectomy followed by dissection of the lymph node is a standard procedure for localized primary renal NETs (Korkmaz et al. 2013). Since renal carcinoid tumor is extremely rare, we decided to present a unique case of a 25-years-old male with neuroendocrine renal carcinoid tumor following radical nephrectomy.

CASE REPORT

A 25-year-old male was admitted to the outpatient clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with a chief complaint of a lump on the left flank area for a year, and the lump is getting more prominent over the last five months. The patient also complained that the pain was arising from the lump for the last five months. The patient also reported intermittent hematuria. The patient denied fever,

nausea, and vomiting. The patient was also denied for stone expulsion history, and there was no history of smoking. There was no history of diabetes mellitus and hypertension in the family. This patient underwent a radical nephrectomy in Dr. Soetomo General Academic Hospital in 2019. Physical examination showed a tender left flank mass, with no costovertebral angle tenderness.

The mass was solid, round, and mobile with a distinct border. No prostate enlargement was found on digital rectal examination, so it was otherwise normal. Urinalysis and complete blood count showed normal results. Thorax radiographic X-Ray showed normal results, as shown in Figure 1. An abdominal CT scan with contrast showed a complex cyst (16 HU) in the left renal fossa with 14.7 x 9.5 x 6.8 cm in size with contrast enhancement (53 HU). The mass pushed the spleen into the superior area and attached to the psoas major muscle with an indistinct border (Figure 2). The patient was assessed with residual left renal tumor post-radical nephrectomy. We periodically evaluated the clinical features (the sign of haematuria, mass, and metastasis), radiological assessment, and periodic surveillance were done annually.

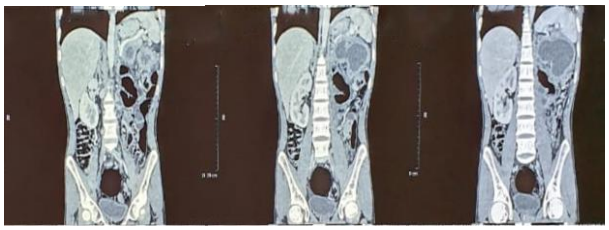

Figure 1. Plain thorax X-ray showing a normal result

Figure 2. Abdominal CT-Scan with contrast examination indicating a mass in the left renal fossa

DISCUSSION

The prevalence of primary renal carcinoids is scarce worldwide. Approximately 65 cases have been reported (Litwinowicz et al. 2011). The previous study by Romero et al. (2006) showed that the median age of the patients was 49 years old (ranging from 12 to 68), with 35.7% of patients being under the age of 40. Overall, there was no sex preference, but primary carcinoid tumors in the horseshoe kidneys were more prevalent in males, with a 1.5:1 male-to-female ratio (Romero et al. 2006). The right kidney had more involvement than the left (60.9% vs. 39.1% of all cases). The renal parenchyma was the apparent source of carcinoids in 76.2% of patients with non-horseshoe kidneys. In two cases, the predominant site was the renal pelvis (4.3%) (Kuba et al. 2017, Rudrick et al. 1995). The isthmus or paraisthmus area was predominantly implicated in cases with horseshoe kidneys.

Primary renal carcinoid is often associated with another renal pathology. Horseshoe kidneys were present in 10 patients (17.8%), renal teratomas were present in 8 patients (14.3%), and polycystic kidney disease was found in 1 patient (1.8%) (Kim & Suh 2004 Kurzer et al. 2005). However, the association between primary renal carcinoid tumor and other congenital renal defects is still unclear (Lodding et al. 1997, Okoń 2008). The relative risk (RR) was assessed by Krishnan et al. (1997) to be 62 and by Motta to be 120 (Kawajiri et al. 2004, Lane et al. 2007). The histogenesis is unknown since neuroendocrine cells are not detected in normal adult renal parenchyma, whilst these cells arise in the kidney throughout embryogenesis (Lane et al. 2007, Shurtleff et al. 2005). Abdominal or flank discomfort, hematuria, fever, and weight loss are the most prevalent clinical symptoms identical to those of other renal tumors.

A palpable mass may be seen in 28% of cases. As what was found in this patient, left flank mass and hematuria were apparent. Renal carcinoids seem in-distinguishable from other renal tumors on imaging examinations (CT, MRI, USG). Renal cell carcinoma is thus a common diagnosis prior to surgery. Carcinoid tumors are generally solitary, yellowish to tan to grey tumors on the surface. The sizes recorded range from 2 to 17 cm (average 6.4 cm). The lesion is normally solid. However, it might rarely include a cystic component, as found with this patient. Partial or radical nephrectomy with lymph node dissection is the sole therapeutic option. Chemotherapy is only administered when liver metastases are present (Kawajiri et al. 2004, Romero et al. 2006). Due to the tumor's rarity, there is limited information on prognosis or prognostic factors (Rodríguez-Covarrubias et al. 2007).

Strength and limitation

The study reports a rare case of primary neuroendocrine renal carcinoid tumor, which can contribute to the

understanding and knowledge of this infrequent clinical entity.The case emphasizes the importance of investigating primary renal NET in the workup and histological examination of renal tumors, which can help in the diagnosis and management of these tumors.

CONCLUSION

We presented a rare occurrence of a large, well-differentiated primary renal neuroendocrine tumor in a young man. The operational results indicated a solid, solitary tumor verified on the frozen section. A postoperative CT–scan showed a recurring mass in the renal fossa following radical nephrectomy. The case emphasizes the need to investigate primary renal NET in the workup and histological examination of renal tumors and contributes to our understanding of this infrequent clinical entity.

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Conflict of interest

None.

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None.

Author contribution

MRI and NAS contributed to design's study. MRI write the manuscript and grammar check. S was final content and agreetment.

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