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RESEARCH ARTICLES

AUTHOR GUIDELINES

Global Medical and Health Communication is a journal that publishes medical and health scientific articles published every 4 (four) months. Articles are original research that needs to be disseminated and written in English.

The submitted manuscript must be an article that has never been published, and the author must ensure that all co-authors have agreed by signing a statement on the seal. For original research, we accept the study which is last then 7 (seven) years when the manuscript is submitted. The manuscript is an original article free from plagiarism. When the article is published in another journal then in the next journal, the article will be disallowed.

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Table title is the typed center, font size 11 pt, bold, initial letter of each word written with a capital letter, except conjunctions. The titles are numbered and written on top of the table. Example: Table 3 *Neisseria gonorrhoeae* Resistance to 8 Types of Antimicrobials in 20 Specimens. Table, no vertical dividing line, and there are only three horizontal borderlines. Created tables in sequence two spaces from the text. Table descriptions and abbreviations are placed in the table description, not on the table title.

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Figures (graphs, diagrams, and photos) and tables besides being written in place, are also made separately on other text pages with sufficient sharpness and darkness. A maximum number of tables and or images are 6 (six) pieces. Figures are sent in black and white or colored format when required, uploaded to the Supplementary File(s) are in high-resolution jpeg, jpg, or png formats.

Write correspondence as to the footnote on the first page containing the full name of the author with degrees/academic degrees, institution, address, mobile phone, and e-mail.

Content and Format Articles

The article contains results of original research in the field of basic medical or applied, and health. The article format consists of Title, Introduction, Methods, Results, Discussion, Conclusion(s), Conflict of Interest, Acknowledgments, and References.

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Introduction

The introduction begins with the general background of the study in a brief maximum of one paragraph. Then, load the State of the Art (a brief review of literature or previous studies, 1–2 paragraphs) to justify/strengthen the statement of novelty or significance or scientific contribution or originality of this article and try to have references to articles from journals of the last 10 years that strengthen the justification for originality or contributions.

Before writing the purpose of the study, there must be a clear and explicit Gap Analysis or statement of gaps (originality) or a statement of the contribution of novelty (novelty statement), or the unique difference of this research compared to previous studies, also in

terms of the importance of whether or not the research was conducted.

Methods
Methods contain the material under study, and the way described briefly by the order of operation as well as the location and time of the study. Explain statistical methods in detail. Consideration of ethical issues is included. If the protocol has been approved then the ethical clearance/approval letter number and the health research ethics committee must be written.

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Discussion of the article reveals, explains, and discusses the results of the study with an analysis by the research design, interpretation, and explanation of its synthesis. Also, the results obtained are compared with the results of previous research of others. Suggestions are also written here.

Conclusion(s)
The conclusion is submitted by the results obtained by the researcher and written briefly and clearly in two or three sentences in one paragraph.

Conflict of Interest
All authors must make a formal statement at the time of submission indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product.

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Zhang B, Kunde D, Tristram S. *Haemophilus haemolyticus* is infrequently misidentified as *Haemophilus influenzae* in diagnostic specimens in Australia. Diagn Microbiol Infect Dis. 2014;80(4): 272–3.

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RESEARCH ARTICLE

The Effect of Turmeric and Mangosteen Peel on Rat PPARα Gene Expression Induced by High-Fat Diet

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Abstract

High levels of fat in the blood are a risk factor for nonalcoholic steatohepatitis liver disease. Indonesian medicinal plants that can decrease blood fat levels are turmeric and mangosteen peel. One of the mechanisms of blood fat-lowering drugs is to increase the expression of the PPARα gene. The purpose of this study was to assess the effect of turmeric and mangosteen peel on the expression of the PPARα gene in the rat liver induced by a high-fat diet. This research was conducted at Maranatha Biomedical Research Laboratory in February–October 2021, using male Wistar rats that were divided into 5 groups (n=5): negative control groups (no treatment), positive control groups (high-fat diet), turmeric, mangosteen, and fenofibrate groups, that was given high-fat diet continued by ethanol extract of turmeric, ethanol extract of mangosteen peel, and fenofibrate. At the end of the study, the animals were terminated, and the liver was extracted for RNA extraction and semi-quantitative PCR. The results showed that there was an increase in PPARα gene expression in the turmeric group and fenofibrate group, which were significantly different from the positive control group that received a high-fat diet ($p<0.05$) and between the fenofibrate group compared to negative controls that received standard chow diet ($p<0.05$). In conclusion, turmeric and fenofibrate are suggested to increase the expression of the PPARα gene in the liver induced by a high-fat diet.

Keywords: Mangosteen peel, PPARα, turmeric

Introduction

High levels of fat in the blood are a risk factor for cardiovascular diseases such as coronary heart disease, stroke, and nonalcoholic steatohepatitis liver disease.[1] Therefore, high-fat content must be overcome. Drugs that can reduce fat levels include fibrate-group drugs, such as fenofibrate.[2] Indonesians often use medicinal plants to lower blood fat levels. Examples of medicinal plants that can decrease blood fat levels are turmeric and mangosteen peel.[3–5] One of the mechanisms of blood fat-lowering drugs is by increasing the expression of the PPARα gene.[6]

Peroxisome proliferation activating receptors-alpha (PPARα) is a part of the superfamily of nuclear hormone receptors. PPARα is expressed in many body cells, such as cardiomyocytes, brown adipocytes, renal tubular cells, and hepatocytes in the liver. The liver is essential in energy homeostasis, especially in regulating lipid metabolism.[7] Its role in lipid metabolism is influenced by PPARα, which can induce oxidation of liver fatty acids, which reduces excess lipid accumulation in the liver and eventually prevents fatty liver.

Previous studies have shown that PPARα upregulated medium-chain and long-chain acyl coenzyme-A (CoA) dehydrogenase, carnitine palmitoyltransferase 1A (CPT1A), and fatty-acid binding protein 1 (FABP1), proved its crucial role in fatty acid clearance and catabolism in the liver.[7] Furthermore, PPARα is also involved in sphingolipid synthesis through modulating serine palmitoyltransferase (SPT) enzyme in mouse liver.[8]

Modulators of PPARα could be found in herbal ingredients and synthetic compounds such as the fibrate class of drugs to treat hyperlipidemia.[9] Natural compounds such as terpenes, carotenoids, phenylpropanoids, and polyphenols have been investigated for their role in modulating PPARα.[9] As primary polyphenols isolated from *Curcuma longa*, curcumin in turmeric has a potential

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role as a PPARα modulator.[10] Phenolic acids and flavonoids in mangosteen peel ethanol extract also have a potential role in modulating PPARα.[11] The investigation of the role of turmeric and mangosteen peel in modulating PPARα expression in the liver still needs to be completed. Therefore, the purpose of this study was to assess the effect of turmeric and mangosteen peel on the expression of the PPARα gene in the rat liver induced by a high-fat diet.

Methods

Eight-week-old male Wistar rats weighing 200± 20 g were divided into five groups (n=5): negative control groups, positive control groups, turmeric, mangosteen peel, and fenofibrate groups. The negative control group was given no treatment, and the positive control was given a high-fat diet. The turmeric group was assigned a high-fat diet continued by ethanol extract of turmeric 270 mg/kgBW/day orally. The mangosteen peel group was given a high-fat diet, continued by ethanol extract of mangosteen peel 270 mg/kgBW/day orally. In contrast, the fenofibrate group was assigned a high-fat diet, continued by fenofibrate 15 mg/kgBW/day orally. All Wistar rats were housed at room temperature with 12 hours of light and dark cycles daily in Maranatha Biomedical Research Laboratory from February to October 2021. All procedures were based on the use and care of laboratory guidelines. After 2 weeks of the adaptation period, the animals were given seven weeks of a high-fat diet, followed by seven weeks of turmeric, mangosteen peel, and fenofibrate treatment. At the end of the study, the animals were terminated, and the liver was extracted for RNA extraction and semi-quantitative PCR. Approval of all protocols was based on the Research Ethics Committee of the Faculty of Medicine, Universitas Kristen Maranatha No: 131/KEP/IX/2022. The high-fat diet used in this study was obtained from PT Prospet consists of 34.9 gm% fat, 26.2 gm% protein, and 26.3 gm% carbohydrate.[12]

Extract ethanol of turmeric and mangosteen was obtained from PT Sidomuncul. Every turmeric capsule was composed of 500 mg *Curcuma domesticate rhizoma*, equivalent to 100 mg curcuminoid, and this dose was equal to 40 grams of fresh turmeric. While every mangosteen peel capsule was composed of 400 mg *Garcinia pericarpium*, and this dose was equivalent to 10 grams of fresh mangosteen peel. Fenofibrate dose 15 mg/kgBW/day obtained from fenofibrate capsules 100 mg. All treatments were given for 7 weeks.

Frozen liver tissues from the rats were extracted to obtain a good quality of RNA, using Trisure reagent (Bioline, United Kingdom), following its manufacturer's instruction. The quality (purity and concentration) of the RNA was measured using spectrophotometry at 268/280 nm absorbance (Multiscan Go). Then, the procedure was followed by semi-quantitative PCR, where we used The One Step RT PCR Kit (Bioline, United Kingdom). GAPDH was used to normalize the data in this study as a housekeeping gene. The process was then followed by electrophoresis, and in order to visualize the electrophoresis gels, we used the BluePad Detection System. This process was followed by quantifying each PCR band using Image J software.

The list of primer sequences used in the study was provided in Table. The design of the study was randomized design for grouping the animals, and the assessment was done at the end of the experiment. Statistical analysis was done using SPS 26.0, and normality and homogeneity tests were done before comparing the differences between groups using one-way ANOVA followed by post hoc LSD.

Table Primers Used for Semi-Quantitative-PCR Analysis

Gene Symbol	Primer Sequence (5' to 3') Upper Strand: Sense Lower Strand: Antisense	Product Size (bp)
PPARα	ACGATGCTGTCCTCCTTGATG	407
	GCGTCTGACTCGGTCTTCTTG	
GAPDH	GTTACCAGGGCTGCCTTCTC	177
	GATGGTGATGGGTTTCCCGT	

Results

In this study, we found a significant result of the ANOVA test (p=0.029) when comparing the relative ratio of PPARα gene expression between groups after induction of a high-fat diet. A post hoc LSD test was used to compare the differences between groups. The result showed significant increases of PPARα gene expression in turmeric (a, p=0.034) and fenofibrate (b, p=0.004) groups compared to positive control groups and between fenofibrate group and negative control group (c, p=0.015). The PCR band expression of PPARα is shown in Figure 1, while the graphical result of the relative ratio is shown in Figure 2.

Discussion

The results showed that there was an increase in PPARα gene expression in the turmeric group and fenofibrate group which were significantly different from the positive control group that received high-fat feed (p<0.05), there was also an increase in PPARα gene expression in the fenofibrate group compared to negative controls that received standard feed (p<0.01). It means that turmeric and fenofibrate increased the expression of the PPARα gene, thus the mechanism of decreasing blood fat levels in this study through increased expression of the PPARα gene. PPAR is a group of receptors involved in metabolic diseases such as hyperlipidemia, diabetes, and obesity.[13] PPAR is a receptor found in vertebrate creatures containing Zn. The PPAR family consists of three members: PPARα, PPARδ (PPARβ), and PPARγ. PPARα can be activated by natural and synthetic agents, such as PUFAs, eicosanoids, and hypolipidemic drugs (fibrates). Activating PPARα by various ligands can modify critical biological processes,

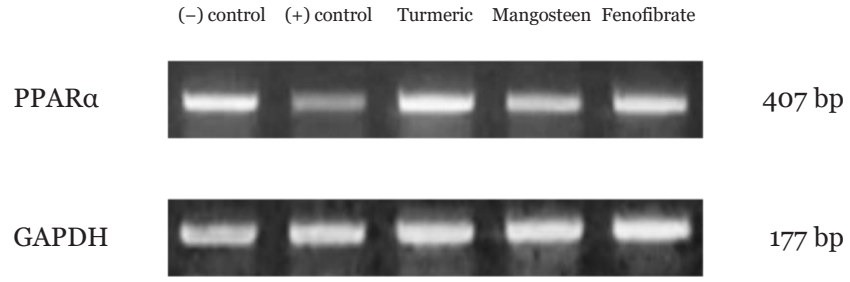

Figure 1 PCR Band of PPARα Gene Expression

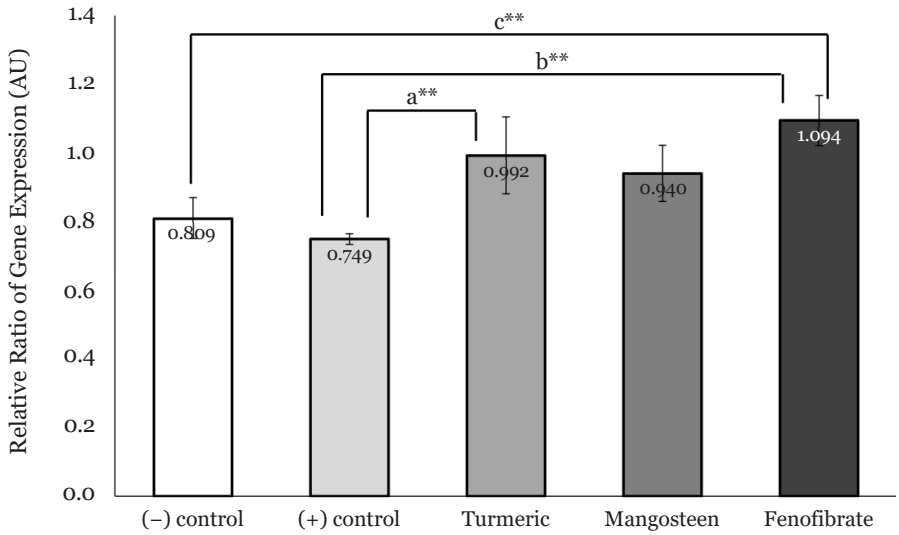

Figure 2 Relative Ratio of PPARα Gene Expression
Note: *significant (p<0.05), **very significant (p<0.01)

especially those related to the body's energy production mechanisms and inflammatory responses.[14] PPARα inside the liver organs are activated by fasting. PPARα is a molecular target for hypolipidemic drug fibrate, which is used in treating dyslipidemia.[15,16] Control of metabolic syndrome and dyslipidemia that can cause atherosclerosis is carried out by the peroxisome proliferator-activator receptors family (PPARs). PPARα is expressed in high concentrations in liver cells, intestinal cells, monocytes/ macrophages, smooth muscle cells, endothelial cells, lymphocytes, microglia, and astroglia. PPARα activation affects lipoprotein metabolism and reduces dyslipidemia associated with metabolic syndrome and hypertension.[17] PPARα activation also causes inhibition of expression of nuclear factor κB (NF-κB) or inflammatory protein activator 1.[18,19] Fibrate a PPARα agonist and have been used to treat dyslipidemia, studies have also proven PPARα agonists have anti-inflammatory that suppresses pro-inflammatory cytokines interleukin-1 beta, TNFα, ICAM-1 and anti-thrombotic effects.[20–22] PPARα receptors are commonly found in liver cells and play a role in fat metabolism, including the degradation of fatty acids.[23] PPARα is a transcription factor that regulates the transcription of mitochondrial and peroxisomal genes β-oxidation and inflammatory reactions. Research shows that PPARα expression is significantly reduced in nonalcoholic steatohepatitis liver disease patients (NASH).[24] Agents that increase the expression of the PPARα gene are expected to prevent nonalcoholic steatohepatitis liver disease patients.[25,26]

Conclusion

The conclusion of this research is turmeric and fenofibrate are suggested to increase the expression of the PPARα gene in Wistar rat liver induced by a high-fat diet.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

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RESEARCH ARTICLE

Personal Perceptions of Filariasis of Patients at Kodi Bolaghar Subdistrict, Southwest Sumba Regency, East Nusa Tenggara, Indonesia

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Abstract

Perception is a mental process that occurs in humans that will show how we see, hear, feel, give, and feel around us. Patients' positive and negative self-perceptions are internal factors that significantly affect the healing process. Chronic filariasis patients experience a decline in physical condition, which becomes a mental burden for the patients and their families. Patients may experience negative stigma from their family and surrounding community. Some communities still believe in myths, supernatural powers, and magic, and patients suffer illness due to their evil deeds or that they have violated cultural norms that were passed down from generation to generation. How patients perceive themselves, their environment, and their families are rarely studied, though this information is essential to elucidate their needs. Kodi Balaghar subdistrict in the Southwest Sumba regency, East Nusa Tenggara, still has many filariasis cases. This study aimed to know the self-perception of filariasis patients in the Kodi Balaghar subdistrict, Southwest Sumba regency. We have selected ten patients to collect answers regarding self-perception from March to May 2021. The results of our study showed that respondents perceive themselves more negatively to both themselves and their families. We conclude that emotional and spiritual support from family, community, religious leaders, and medical personnel are critical to building self-confidence, life expectancy, enthusiasm, and fighting power to survive and undergo treatment for the disease.

Keywords: Family support, filariasis, self-perception

Introduction

Health problems in Indonesia are complex conditions that are a combination of several issues, including environmental problems, both natural and man-made, socio-cultural, behavioral, genetics, and population.[1] Each person has a different perception of how to assess a complex problem. Perception will arise from each other as perception is an automatic process as a response to mental processes that occur in humans; it happens very quickly and sometimes unconsciously, where we can recognize the stimulus we receive from the senses. Perceptions that arise will affect our actions. Perception is also called a view, image, or assumption because there is a person's response to a thing or object in perception. Public perception of a disease occurrence that is contrary to health science is still there, can be passed down from one generation to the next, and can even expand.[2–4]

Lymphatic filariasis is an infectious disease that still causes health problems in the community.[5,6] Untreated filariasis patients, although the condition is not lethal, are very detrimental because the sufferer will experience pain, physical disability, poverty, and even psychosocial problems in the community where the patient lives.[7,8] Disability due to filariasis experienced by the patients also causes dependence on others, so economically, it will be very detrimental to the sufferer's family and cause poverty.[8,9]

The World Health Organization (WHO) in 2000 declared "The global goal of elimination of lymphatic filariasis as a public health problem by the year 2020". The Indonesian government responded to this global agreement by launching the elimination of filariasis in 2002 in Musi Banyuasin regency and establishing the elimination of filariasis as one of the priority programs for eradicating infectious diseases in Indonesia.[10–12]

Filariasis occurs chronically, and this condition causes lymphedema or fluid build-up that causes swelling of the legs and arms. Accumulation of fluid and infections that occur due to weak immunity will eventually lead to damage and thickness of the skin layer. Accumulation of fluid can also occur in the abdominal cavity, testes in men, and breasts in women; this condition is

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known as elephantiasis.[13]

Chronic manifestations, caused by reduced lymphatic function, occur months to years from the acute episode. Clinical symptoms vary from mild to severe, followed by a regular course of obstructive disease. The main clinical signs were hydrocele, lymphedema, elephantiasis, and chyluria, which increase with age. Genital manifestations, in many areas, the chronic feature that occurs is hydrocele. In addition, chronic epididymitis, funiculitis, and edema due to thickening of the scrotal skin may be found, whereas, in women, vulvar lymphedema may be found. Lymphedema and elephantiasis of the extremities: episodes of lymphedema of the extremities will lead to elephantiasis in the area of the affected lymphatic ducts throughout years.[14,15]

Chronic conditions will have a psychological impact on filariasis patients; loss of self-confidence, psychiatric disorders, and long-term stress due to not being able to accept one's situation will become a problem in itself. People who are already disabled will usually feel inferior, ostracized, and embarrassed to meet other people, especially with the erroneous assumption from some people that this disease is disgusting. It is even believed that the disease is related to supernatural powers, magic, supernatural, curses/hereditary. The emergence of positive and negative self-perceptions will be one of the points/keys to give suggestions to sufferers to stay excited about life.[16,17]

The province of East Nusa Tenggara (*Nusa Tenggara Timur*, NTT) is the second largest contributor to filariasis cases after Papua 15,18. This case is spread in almost all cities/districts in NTT, including four districts on Sumba island. The number of reported cases was 311 from 3 regency, namely Central Sumba, Southwest Sumba, and West Sumba.[19,20] In 2011, 90 chronic cases were reported in Southwest Sumba regency, while the microfilariae (Mf) rate was >1%. The Mf rate was determined based on a finger blood smear sampling survey (*survei darah jari*, SDJ) conducted in Buru Kaghu and Mata Kapore villages in 2009.[5] Patanduk et al.[21] reported that the Kodi Balaghar subdistrict had a Mf rate of 4.2% based on the results of SDJ collection in 2012 with a total sample of 500 people.

This study aimed to know the self-perception of filariasis patients in the Kodi Balaghar subdistrict, Southwest Sumba regency. The healing process of chronic sufferers is not enough to rely on medical treatment; emotional support is a critical need for sufferers. The research results are hoped to provide input to families, the general public, medical personnel, and community leaders in providing a support system for filariasis sufferers.

Methods

This type of research is descriptive quantitative with a cross-sectional approach using questionnaires and interviews to collect answers from respondents. Its nature is to explore in-depth information from informants about self-perception of filariasis. As many as ten respondents from filariasis patients from the Kodi Bolaghar subdistrict, Southwest Sumba regency, East Nusa Tenggara, were willing to participate in the study by signing an informed concern. This research was carried out from March to May 2021 and registered with the Ministry of Health's Kupang Poltekkes Ethics Committee with registration number LB.02.03/I/0075/2020.

The determination of overall perception is stated in the score; perception is good if the score is >67.8, and perception is quite good if the score is <67.80. Respondents' answers to each question (43 numbers) were scored. From the data processing results, six respondents were in the sufficient category, and four were in the good category, with a median value of 65 and a mean of 67.8.

Results

Respondents were interviewed to find the most appropriate answer; it was feared that if they filled it out on their own, it would result in a biased/inappropriate answer. The characteristics of the respondents are shown in Table.

Collecting answers from the questionnaires given, we classify them into four minor themes: positive perceptions of oneself with the environment and with family, as well as negative perceptions of oneself with the environment and with family.

Positive perception of self and environment as described in Figure 1. Of the ten respondents who answered the questionnaire, ten considered themselves honest people, would try to change if they realized what they were doing was wrong, and quickly adapt to other people. Nine of the respondents rated themselves as gregarious and easy to lose their minds; eight rated themselves

Table Respondent Characteristics

Characteristics	n=10
Age (years)	
40–50	2
51–60	4
61–70	–
71–80	4
Gender	
Female	9
Male	1
Marital status	
Married	10
Not married	–
Education	
Not in school	10
Elementary	–
Middle school	–
High school	–
Occupation	
Farmer	10
Civil servant	–
Self-employed/employee	–
Income (rupiah)	
<1,000,000	10
1,000,000–2,500,000	–
>2,500,000	–

as easy to adapt to circumstances and can accept mistakes without feeling hurt or angry; seven of the respondents think they can maintain body cleanliness and are religious in life; and only five who think they have a healthy body.

Positive perception of oneself and family as described in Figure 2. Respondents reside and live with their families during illness, so it is natural to have positive and negative perceptions about their respective families. The results showed that ten respondents were satisfied with their relationship with their family and felt that the family cared about them. In addition, nine think that they are someone who means a lot to their family and consider themselves to be a happy family member.

Negative perception regarding self and the environment is described in Figure 2. Patients with filariasis tend to have unfavorable perceptions about themselves, severe physical conditions, and difficulty in accommodation and activities, which will lead to negative self-assessments. Ten respondents rated it negatively, saying they felt their physical appearance was not as expected, hoped not to give up as quickly as it is now, and should be more polite to others. Nine respondents want to improve some parts of their body. Eight feel they are not the person they want to be, feel sick, are too lazy to exercise, sometimes use dishonest ways to get ahead and find it difficult to be friendly to others; seven find it challenging to make friends; and five feel not a good person.

Togetherness with family also creates negative perceptions; nine respondents feel they should be able to trust their family more and try to be more honest with them, and eight feel that their family does not trust them in certain areas (Figure 4).

Discussion

According to Mulyana,[22] perception is an internal process that allows us to select, organize, and interpret stimuli from our environment. These processes affect us so that perception determines us to choose messages and ignore other messages.[23] According to Walgito,[24] perception

Figure 1 Positive Perception regarding Self and Environment

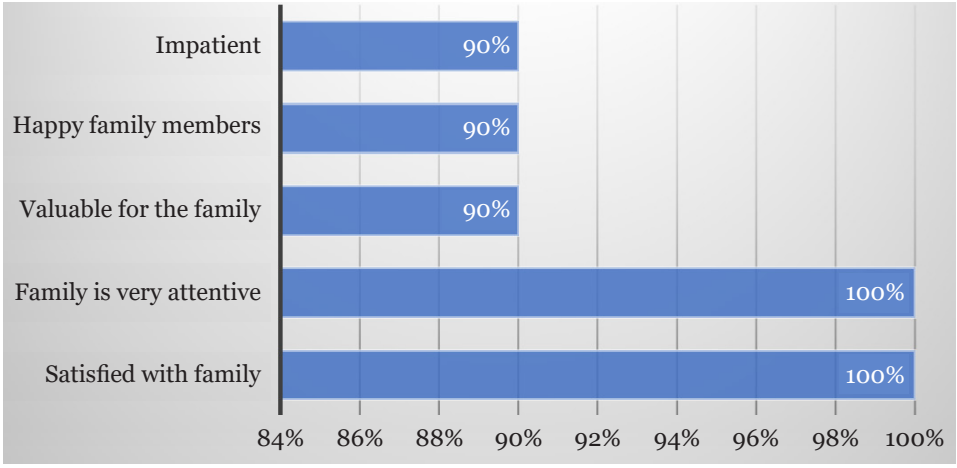

Figure 2 Self-Perception with Family

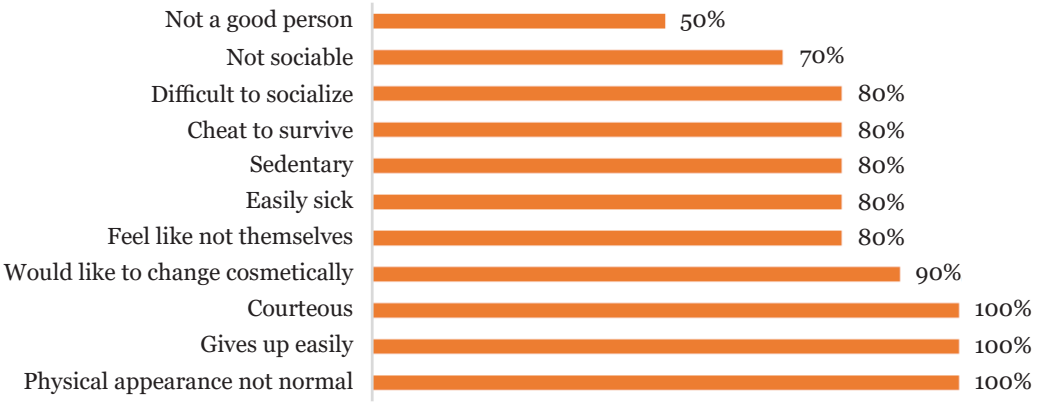

Figure 3 Negative Perception regarding Self and Environment

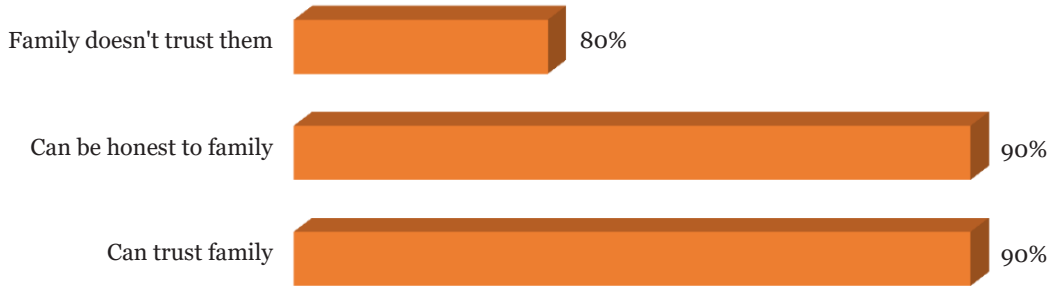

Figure 4 Negative Perception regarding Families

occurs because of a stimulus from within the individual, preceded by sensing. Sensing here is a process received from the stimulus by the individual through the receiver; the nerves transmit the stimulus to the brain as the center of the nervous system. The process is the perception process. Perception is related to how to gain knowledge about objects or events at a particular time so that the perception of a person or group is different because they have other points of view.[2,25]

Perception includes interpreting objects, signs,

and people from the experience of a person or group. So self-perception is a view or assessment of oneself obtained from learning or experience that influences the individual to interact or behave with his surroundings. The theory of self-perception is a derivative of the theory of self-concept. Based on the research conducted, Daryl Benn stated that self-perception means that a person makes his conclusions according to his way of thinking and experience by observing the behavior of others.[1,26] With perception, an individual can be aware of and understand the state of the environment around him and the state of the individual concerned. Thus, the perception of the stimulus can come from outside the individual but can also come from within the individual concerned. Because perception is an integrated activity, all that is in the individual, such as experience, thinking ability, and other aspects that exist in the individual, will play a role in the perception.[23,27]

If what is perceived by oneself as the object of perception is called self-perception, then self-perception is a view or assessment of oneself that is obtained from the results of learning and experience that motivates the individual to interact or behave with the surroundings in the hope that it can be beneficial for the community.

How a person with filariasis makes the perception of himself becomes very important. Filariasis disease is chronic, and if it does not get treatment, it can cause permanent disability in the form of enlargement of the legs, arms, and genitals for both women and men. Chronic manifestations, caused by reduced lymphatic function, occur months to years from the acute episode. Symptoms of chronic filariasis include persistent enlargement (elephantiasis) of the legs, arms, breasts, and testicles (elephantiasis scroti) caused by adult worms in the lymphatic system.

Physical conditions like this will undoubtedly cause mental disorders in sufferers, loss of self-confidence, and difficulty doing anything independently. In general, many people with disabilities will feel inferior, abandoned by family and society, and not confident to meet other people. The belief that develops in the community is also a matter of psychological pressure for sufferers. Filariasis is considered a disgusting disease and is even believed to be related to supernatural powers, magic, supernatural, curses/hereditary. Complex problems cause psychological pressure both from oneself and from outside. Patients will have their perception of their illness and how their families and society accept them. The emergence of positive and negative self-perceptions will be one of the points/keys to give suggestions to sufferers to stay excited about life.[28]

Our results show that filariasis sufferers have positive self-perceptions about themselves, their environment, and family. Positive self-perceptions that are built are self-acceptance as honest people, willing to change themselves if they make mistakes, like making friends, being able to accept their own mistakes, maintaining personal hygiene, and being religious. It was found that only five respondents took themselves as healthy people, and five respondents had self-perceptions as sick and unhealthy. On the other hand, respondents admitted that they were satisfied with their family relationships, their family cared about them very much, they were significant family members, and they were pleased. One interesting thing is that 50% of respondents admit it is easy to lose their minds. Perception of losing your mind quickly shows depressed mental conditions, stress, and even tends to be depressed. This can be caused by the inability to accept oneself with the condition of filariasis.[29]

A positive self-perception will have a long-term impact on healing, enthusiasm, and suggestions for patients to seek treatment and struggle to recover. Exceptional social support from the family is critical; when the patient is in a supportive family situation, it will indirectly impact healing.

We found more negative self-perceptions from respondents in this study due to the disfiguration of their physical appearance and found it difficult to socialize or blend in with society. Negative self-perception requires psychological therapy to build back self-confidence and the willpower to live. Patients should not be allowed to create perceptions that harm the healing process. On the other hand, respondents also negatively perceive their family, as some still do not trust their own family, are not honest with them and feel that their family does not trust them.

Munadhir[3] concluded that the negative public perception of filariasis patients was a critical factor in making them suffer and miserable, as well as psychological burdens such as feelings of shame, irritation, confusion, hurt, fear, and losing their source of income. The public's perception

of filariasis patients based on the socio-cultural values of the community still considers the disease to be a curse or a violation of the norms of society. Silalahi[2] concluded that knowledge, education, and access to health services influence people's perceptions of filariasis. They suggest health promotion efforts to change the public's negative perception of filariasis by increasing public knowledge and understanding so that they can adequately prevent filariasis. Lismayanti et al.,[23] in their study of life experiences of filariasis patients, reported that people infected with filariasis in Tasikmalaya city related to five themes, namely emotions, perceptions, clinical, economic, and social symptoms as well as experiences in accessing health services. The results of their research can be used as a reference for improving community nursing services, both physically, psychologically, socially, and economically. Prevention of filariasis is also essential to reduce the risk of transmission. Besides that, the rehabilitative process is also vital to minimize disability and assist the adaptation of sufferers in their lives biologically, psychologically, socially, and spiritually.

Based on the results of this study, we recommend that assistance from close family is very much needed, and community leaders and religious leaders are also expected to play a role. In particular, spiritual assistance/spiritual life to build life hope and the ability to accept one's situation. Medical treatment is considered insufficient to continue to provide enthusiasm and fighting power to patients with filariasis.

Conclusions

Filariasis patients can build positive and negative perceptions of themselves, their environment, and their families. We found that negative self-perceptions dominated the respondents' answers, so support from families and communities was crucial during the treatment and healing.

Conflict of Interest

All authors state whether there was a conflict of interest in this article or not.

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RESEARCH ARTICLE

Histopathological Review of Granuloma in Diagnosis of Tuberculosis Lymphadenitis (TBL)

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Abstract

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis and is the second leading cause of death from an infectious disease. Indonesia has the highest TB cases in West Java, East Java, and Central Java. Tuberculosis lymphadenitis (TBL) represents about 30–40% of cases of extrapulmonary tuberculosis. The study aimed to study the clinical and histopathological characteristics of TBL patients. The research design in this study used an exploratory, descriptive method. Data was taken from Al Islam Hospital Bandung as medical records from January 2019 to December 2020. The result showed that TBL primarily affects patients aged 6–11 years (28%), male gender (57%), patients not working (25%), and those residing in the East Bandung area (34%). Histopathological appearance showed granulomas of caseous necrosis, epithelioid cells, and Langhan's cells, indicated by types 1, 2, and 3. The most common type was type 1 (47%), which was more widely distributed in the right neck (46%) with size 1–3 cm. In conclusion, the frequency of TBL is higher in boys aged 6–11 years, residents of the East Bandung area, and patients who did not work. Well-formed granuloma of enlarged lymph nodes in the right neck with size 1–3 cm is most commonly found in TBL.

Keywords: Histopathological review, lymphadenitis, tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. According to the World Health Organization, in 2021, an estimated 10 million people developed TB, resulting in 1.6 million deaths, making it the second leading cause of death from an infectious disease after COVID-19. Southeast Asia accounted for almost half of TB cases, reaching 4.82 million (45.4%). Eight countries are responsible for 66% of global cases, and Indonesia ranks second after India (9.2%).[1]

There are 450,000 new tuberculosis cases in Indonesia, with a death rate of 175,000 yearly. According to the Global Tuberculosis Report 2022, there were 969,000 TB cases reported in Indonesia, and 144,000 died because of TB. The highest TB cases were found in the most populous regions, including West Java, East Java, and Central Java.[2,3]

The two types of TB are pulmonary and extrapulmonary. Extrapulmonary TB constitutes about 15–20% of all TB patients. Tuberculosis lymphadenitis (TBL) is the most common form of extrapulmonary TB and represents about 30–40% of cases. In developing countries, the incidence of TB is high. TBL is often located in the cervical lymph nodes; many benign and malignant conditions mimic the disease.[4]

Diagnosis of TBL still faces many challenges because each diagnosis method has limitations. Clinically, TBL may be challenging to distinguish from other causes of lymphadenitis due to its nonspecific clinical presentation and overlap with granulomatous lymphadenopathy.[5] Diagnosis TBL should be combined between clinical findings, histopathological staining, and culture as the gold standard. Histopathology remains one of the most important methods for diagnosing TBL, and in a high TB area, histopathology is the reliable diagnostic method. In the histopathological picture of TBL, granulomas, caseous necrosis, epithelioid cells, and Langhan's cells will usually be found.[6,7]

Lymphadenitis TB is still a public health problem. Although TBL is one of the most common forms of extrapulmonary TB, few studies on approaching diagnosis of the clinical and histopathology of TBL in Bandung have been

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done. Therefore, this study aimed to study the clinical and histopathological characteristics of TBL patients at Al Islam Hospital Bandung.

Methods

This type of research is exploratory, descriptive research. The data obtained is secondary from the medical records of TBL patients treated at Al Islam Hospital Bandung from January 2019 to December 2020. The sampling method used the total sampling method with 76 cases that fit the inclusion criteria. The inclusion criteria are the patients who have yet to be treated based on medical records. The exclusion criteria is a patient diagnosed with other diseases. The ethical clearance of the study is No. 021/KEPPIN-RSAI/10/2021.

Results

Demographic characteristics of TBL patients at Al Islam Hospital Bandung can be seen in Table 1. TBL is more common in patients with an age range of 6–11 years, with as many as 21 people (28%). Based on gender, men were more often affected by TBL, with 43 patients (57%).

In this study, histopathology diagnosed 76 patients with enlarged lymph nodes as having TBL. These patients were further divided into three groups according to the granuloma histopathological pattern. TBL patients in Table 2 show the grouping of granulomas based on three types: type 1 shows a well-formed granuloma consisting of necrosis caseous, epitheloid cells, and Langhan's cells. Type 2 indicates the presence of one of the structures of necrosis caseous, epitheloid cells, and Langhan's cells. Type 3 shows no granuloma features. Histopathological features in patients mainly were in type 1, namely 36 patients (47%), and the least in type 2, namely 19 patients (25%).

Clinical manifestation of TBL patients in Table 3 shows symptoms of enlarged lymph nodes in TBL patients, more often distributed in the right neck in as many as 35 patients, and distribution is rare in preauricular, submental, inguinal, subclavicular, and chin, only one patient. The most enlarged lymph nodes were 1–3 cm in size in 25 patients. The number of enlarged lymph nodes was, at most, two enlarged lymph nodes in 15 patients.

Systemic features like fever more often accompanied patients with TBL in five patients, cough in four patients, and manifestation that rarely occurred was weight loss in one patient.

Table 1 Demographic Characteristics of TB Lymphadenitis Patients

Characteristics	n=76 (%)
Age (years)	
0–5	9 (12)
6–11	21 (28)
12–16	10 (13)
17–25	15 (20)
26–35	9 (12)
36–45	8 (11)
46–55	2 (3)
56–65	2 (3)
Gender	
Male	43 (57)
Female	33 (43)
Residence	
East Bandung	26 (34)
South Bandung	17 (22)
Central Bandung	2 (3)
Bandung regency	21 (28)
Out of Bandung	10 (13)
Occupation	
Laborer	4 (5)
Housewife	7 (9)
Private sector employee	11 (14)
Student	18 (24)
Self-employed	2 (3)
Not working or not yet working	19 (25)
Etc.	15 (20)

Discussion

Tuberculosis has been a major health problem worldwide since the discovery of *Mycobacterium tuberculosis* in 1882. Each year, there are more than eight million new cases of tuberculosis and 1.3 million deaths—extrapulmonary forms of tuberculosis as its relative frequency increases. Among extrapulmonary organs, TBL is the

Table 1 Histopathological Pattern of TB Lymphadenitis Patients

Histopathological Pattern	n=76 (%)
Type 1	36 (47)
Type 2	19 (25)
Type 3	21 (28)

Table 3 Clinical Manifestation of TB Lymphadenitis Patients

Clinical Manifestation	n=76	%
Lymph node enlargement		
Distribution	(54)	
Right cervical	35	46
Left cervical	8	11
Submandibular	5	7
Preauricular	2	3
Submental	1	1
Inguinal	1	1
Subclavicular	1	1
Axilla	2	7
Mentum	1	1
Size (cm)	(30)	
<1	2	
1–3	25	
>3	3	
Number of enlarged lymph nodes	(18)	
1	2	
2	15	
3	1	
Fever	(76)	
Yes	5	
No	71	
Cough	(76)	
Yes	4	
No	72	
Weight loss	(76)	
Yes	1	
No	75	

most common. Their diagnosis is often difficult based on clinical, radiological, bacteriological, and histological findings.[8] All the study subjects (n=76) were previously diagnosed with TBL, depending on the presence of variable histological TB evidence. Demographic features of TBL in various ages, genders, residences, and occupations were evaluated. It was found that TBL is more prevalent in children in the age group range of 6–11 years. This finding is similar to the previous study by Yang and Du;[9] TBL represents about 30% of cases with an average of children. TBL was found to be more common in children, 78%, compared to adults, around 65%. Tuberculosis is a common illness for vulnerable populations in resource-limited settings, with the latest figures showing an annual incidence of 10 million, including 1 million children. Gender distribution in this study found men were more often affected. It was quite consistent with the study conducted by Ali et al.;[10] the frequency of TBL is higher in the male gender. Most patients came from the East Bandung area, and patients did not work or had not worked. The demographic profiles of this study were consistent with studies of Southeast Asian regions, where most of the subjects were from rural areas.[11–13]

The right cervical lymph node was the most common predilection in our study (46%), a consistent survey of Kamal et al.,[14] but much higher in north India (67.8%). Gautam et al.[15] study found that cervical lymph nodes are the most common site of tuberculous lymphadenopathy in 60%–90% of cases. The involvement of the cervical region nodes is dominant due to enriched lymphatics in this area and close communication with the pulmonary system. The most common enlarged lymph nodes were 1–3 cm with multiple lymph nodes, mostly around two lymph nodes. Jha et al.[16] found multiple lymph nodes in 57% of the cases. Clinical manifestations like fever more often accompanied patients with TBL in five patients, cough in four patients, and weight loss in one patient. While evaluating these kinds of patients, an adequate physical examination and diagnostic studies should be done. In instances like this study, where systemic signs and symptoms seldom appear, identification of TBL can become challenging.[17]

We assess the histopathology by grouping the granulomas' histological features depending on the histomorphology features of TBL. The histological tissues that showed the presence of a well-formed granuloma consisting of necrosis caseous, epithelioid cells, and Langhan's cells were considered as type 1 in 47% of cases, followed by type 2 in 25%, and type 3 with no granuloma, which was 28% case. The Huda et al.[7] study found that well-formed granuloma is detected in 68% of cases, which is higher than in this study. Granuloma formation and necrosis caseous are two specific pathology criteria for identifying TBL. Necrosis caseous is more specific and sensitive.[18] In the present study, 68 lymph nodes were of caseating granuloma type, and 32 were noncaseating granuloma type.[3] This is in correlation with Lake and Oski,[19] who reported 76% caseating granuloma and 24% noncaseating granuloma, and Fatmi and Jamal,[20] who reported 62% caseating granulomas and 38% noncaseating granuloma. In endemic countries, the majority of granulomatous lesions without necrosis are considered to be TBL.[21,22]

Conclusions

The frequency of TBL is higher in males and children aged 6–11 years, residents of the East Bandung area, and patients who did not work. Type 1 histopathologic features of well-formed granuloma, necrosis caseous, epithelioid cells, and Langhan's cells are most commonly found in TBL. Clinical symptoms of enlarged lymph nodes in the right neck with size 1–3 cm.

Conflict of Interest

None declared.

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RESEARCH ARTICLE

Difference between Nutrition Status in First and Recurrent Ischemic Stroke Patients: a Retrospective Cross-Sectional Study

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Abstract

Malnutrition in stroke patients can be caused by neurological deficits such as decreased consciousness, dysphagia, cranial nerve paresis, and hemiparesis/hemiplegia. The condition of malnutrition seriously impacts healing and can exacerbate the underlying disease, in this case, stroke, so malnutrition in stroke patients extends the length of stay and increases morbidity and mortality. This study compares nutritional status between first and recurrent ischemic stroke patients based on body mass index (BMI) and subjective global assessment (SGA). This study is a comparative analysis of the medical records of ischemic stroke patients in Dr. Hasan Sadikin General Hospital Bandung from January 2018 until December 2020. The chi-square and Fisher's exact tests were used for statistical analysis. The significance criteria are the p-value if $p \leq 0.05$ means statistically significant. A total of 236 subjects in both groups of first and recurrent ischemic stroke patients consisting of 130 men and 106 women with an average age of 56.64 and 61.75 years, and the majority had risk factors for hypertension. The first ischemic stroke group has a good nutrition status compared with the recurrent stroke group ($p<0.05$). Thirteen patients (11.02%) of first ischemic stroke and 11 patients of recurrent ischemic stroke (9.32%) were underweight, 67 patients (56.78%) of first ischemic stroke and 74 patients of recurrent ischemic stroke (62.71%) had average weight, 31 patients (26.27%) first ischemic stroke and 33 patients (27.97%) recurrent ischemic stroke were overweight, five patients (4.24%) first ischemic stroke and seven patients (5.93%) recurrent ischemic stroke were obese ($p<0.05$). In conclusion, there was a significant difference in the nutritional status of first and repeated ischemic stroke patients. The nutritional status of recurrent ischemic stroke patients is worse than that of first ischemic stroke patients.

Keywords: BMI, first ischemic stroke, nutritional status, recurrent ischemic stroke, SGA

Introduction

Stroke is a life-threatening disease and causes a significant burden of death in developing and developed countries. At present, stroke is one of the major global health problems, causing 75.2% of deaths and 81.0% of disability in developing countries. Up to 87% of the global burden of stroke is ischemic stroke.[1] The prevalence of stroke in Indonesia, according to the Basic Health Research (*Riskesdas*), in 2018 was 10.9 cases per mile, while in West Java province, it was 52,511 cases or around 11.4%.[2] One of the data on hospitals in Indonesia explained that more than 500 people per year are treated for stroke.[3]

Stroke has various clinical symptoms, depending on the location of the brain damage caused. One of these manifestations is a neurogenic deficit that can lead to low nutritional intake in stroke patients. In addition, the presence of chronic diseases such as diabetes mellitus and hypertension and difficulty swallowing are also associated with an increased risk of malnutrition in stroke patients.[4,5] If this occurs continuously, stroke patients may experience malnutrition, which will affect clinical outcomes, quality of life, bodily functions, and patient autonomy.[6]

In addition to the resulting clinical manifestations, stroke can also cause various complications, one of which is recurrent stroke.[5,7] Malnutrition in recurrent stroke is exacerbated by disruption of nutritional intake caused by clinical manifestations after the first attack.

In a previous study conducted on stroke patients, it was found that the majority of stroke patients were malnourished in the moderately malnourished category based on the subjective global assessment (SGA) rating.[8] The nutritional status of recurrent ischemic stroke patients is worse than that of first ischemic stroke patients. Compared with the first stroke, the resulting nerve damage is more serious, more difficult to treat, and has a higher mortality.[5,7] This causes the resulting nutritional status to be worse. If this is known, management in terms of nutrition, such as providing adequate and appropriate nutrition,

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can produce positive results for the health and well-being of the patient.[9]

Based on this description, it is necessary to conduct research on the comparison of the nutritional status of first and repeat ischemic stroke patients, with a relatively high prevalence of stroke (11.4%) and exceeding the national prevalence (10.9%).[2] In this study, nutritional status based on SGA and body mass index (BMI) will be the parameters studied so that it can meet the criteria for detection of malnutrition based on the Global Leadership Initiative on Malnutrition (GLIM), namely one phenotypic criterion and one physiological criterion.[10]

In addition, this study also assessed the characteristics of the subjects consisting of gender, age, time of measurement, and various risk factors for ischemic stroke, such as history of active smoking, history of hypertension, history of dyslipidemia, and history of type 2 diabetes mellitus obtained from record data patient medical.

Methods

Data analysis for categorical data was tested with the chi-square test to see if the data was normally distributed with the alternative Fisher's exact test. For numerical data, the p-value was tested with the unpaired t-test if the data was normally distributed with the alternative Mann-Whitney test if the data was not normally distributed. The significance criterion used is the p-value if $p \leq 0.05$ means significant or statistically significant. The Research Ethics Committee of Universitas Padjadjaran approved this study for exemption, with approval number 527/UN6.KEP/EC/2021.

Results

There were 236 subjects, each of which 118 subjects were first and repeat ischemic stroke patients. The majority of research subjects in both groups were male. The average age of first ischemic stroke patients was 56.64 years, with a standard deviation of 14.60. In contrast, the average age of recurrent ischemic stroke patients was slightly higher, 61.75 years, with a standard deviation of 11.36. Measurement of nutritional status was carried out on average on the first day the patient was admitted to the hospital. The majority of patients with both first and repeat ischemic stroke did not smoke, had a history of hypertension, and had no history of dyslipidemia and type 2 diabetes mellitus (Table 1).

Based on the SGA rating, most first and repeat ischemic stroke patients experienced mild-moderate malnutrition (SGA B). There was a significant difference ($p<0.05$) from the characteristics of patients based on SGA, namely changes in functional capacity and physical examination results, where the characteristics of patients with recurrent ischemic stroke were worse than those of the first ischemic stroke (Table 2). The results of statistical tests on the SGA rating also show the same thing (Table 3).

When viewed from each component of the SGA, the majority of ischemic stroke patients experienced a decrease in nutritional intake. More ischemic stroke patients experienced a decrease in nutritional intake, although there was no significant difference. In addition, most ischemic stroke patients did not experience weight changes, but not a few also experienced weight loss (28.81% of first ischemic stroke and 25.42% of recurrent ischemic stroke). The majority of ischemic stroke patients experience digestive system symptoms, which include nausea, vomiting, diarrhea, decreased appetite or anorexia, dysphagia, constipation, dental problems, pain when eating, and feeling full quickly, with a higher proportion in patients with recurrent ischemic stroke (59.32%). Almost all ischemic stroke patients, both first and repeat, have decreased functional capacity. The results of the physical examination, which included loss of subcutaneous fat muscle mass, as well as the presence of edema and ascites, showed that the majority of ischemic stroke patients did not experience any changes but showed that re-ischemic stroke patients experienced more physical changes (16.10% in the mild-moderate category and 9.32% in the category of mild-moderate stroke) compared with first ischemic stroke patients (9.32% mild-moderate and severe category, Table 2).

Based on BMI, the majority of ischemic stroke patients were in the normal category (62.71% in recurrent ischemic stroke and 56.78% in first ischemic stroke). In addition, 27.97% of first ischemic stroke patients and 22.03% of recurrent ischemic stroke patients were overweight, 4.24% of first ischemic stroke patients, and 5.93% of recurrent ischemic stroke patients were obese. Not a few patients also fall into the category of underweight, namely 11.02% of patients with

Table 1 Research Subjects Characteristics

Characteristics	Ischemic Stroke		p
	First Event n=118 (%)	Recurrent n=118 (%)	
Gender			
Male	60 (50.84)	70 (59.32)	0.028*
Female	58 (49.15)	48 (40.68)	
Age (mean±SD)	56.64±14.60	61.75±11.36	
Time assessment (mean±SD)	1.14±1.53	1.19±1.35	0.106
Smoking			
Yes	28 (23.73)	31 (27.27)	<0.001*
No	81 (68.84)	81 (68.84)	
N/A	10 (8.47)	6 (5.08)	
Hypertension			
Yes	94 (79.66)	107 (90.68)	0.360
No	24 (20.34)	11 (9.32)	
Hyperlipidemia			
Yes	42 (35.59)	48 (40.68)	0.172*
No	76 (64.41)	70 (59.32)	
Type 2 diabetes mellitus			
Yes	32 (27.12)	28 (23.73)	0.083
No	86 (72.88)	90 (76.27)	

Note: *Fisher's exact test

Table 2 Subject Characteristics based on SGA

SGA	Ischemic Stroke		p
	First Event n=118 (%)	Recurrent n=118 (%)	
Nutrition intake			
Good	34 (28.81)	30 (25.42)	0.090
Fair	84 (71.19)	88 (74.58)	
Body weight changes			
Decrease	34 (28.81)	42 (35.59)	0.081*
Increase	2 (1.69)	3 (2.54)	
No change	82 (69.50)	73 (61.86)	
Gastrointestinal problem			
Yes	60 (50.84)	70 (59.32)	0.278
No	58 (49.15)	48 (40.68)	
Functional capacity changes			
Decrease	116 (98.30)	116 (98.30)	0.035
Increase	0 (0)	1 (0.85)	
No change	2 (1.70)	1 (0.85)	
Physical examination changes			
No change	96 (81.36)	88 (74.58)	0.009
Mild to moderate change	11 (9.32)	19 (16.10)	
Severe change	11 (9.32)	11 (9.32)	

Note: *Fisher's exact test

Table 3 Nutrition Status based on SGA

SGA	Ischemic Stroke		p
	First Event n=118 (%)	Recurrent n=118 (%)	
Well-nourished (SGA A)	31 (26.27)	28 (23.73)	<0.001*
Mild/moderately malnourished (SGA B)	76 (64.41)	79 (66.95)	
Severely malnourished (SGA C)	11 (9.32)	11 (9.32)	

Note: *Fisher's exact test

first ischemic stroke and 9.32% of patients with recurrent ischemic stroke.

The average body mass index in patients with the first ischemic stroke was 23.06 with a standard deviation of 3.87, while in the second ischemic stroke, it was 23.56 with a standard deviation of 4.32. The two groups significantly differed in BMI ($p<0.05$, Table 4).

Discussion

Based on the results of the study above, it is known that the general characteristics of the research subjects are primarily male, with the average age of the first ischemic stroke patient at 56.64 years and the recurrent ischemic stroke patient at 61.75 years. These results follow the Framingham Study, which showed that based on the frequency of stroke events, men have a higher stroke frequency than women, and as a person ages, the risk of stroke increases.[11] The mean age at a re-ischemic stroke is higher than at first ischemic stroke, according to the study of Zhou et al.,[5] which states that older age is a higher risk for recurrence, in addition to smoking, suffering from diabetes, and others. Most research subjects have a history of hypertension as a risk factor. High blood pressure causes increased oxidative stress, inflammatory processes, endothelial dysfunction, plaque formation in blood vessels, and the progression of the atherosclerosis process that leads to ischemic stroke.[6]

This study showed that most patients from both groups (first and recurrent ischemic stroke) had mild-moderate malnutrition based on the SGA rating. Several theories and research results explain the pathogenesis of malnutrition due to stroke. First, in one study, it was found that most stroke patients did not meet their caloric needs, i.e., the average caloric intake during their hospital stay was 60% of their estimated average requirement and increased to only 81% at six months afterward.[8] Other studies have also shown the ratio of carbohydrate to protein intake to be associated with National Institutes of Health Stroke Scale (NIHSS) scores. From this study, it was found that protein intake was inversely proportional to the NIHSS score, which indicated an increase in protein intake would lead to an improvement in the condition of post-stroke patients.[6] Stroke patients also experience weight loss due to loss of appetite caused by depression,

Table 4 Nutrition Status based on BMI

BMI	Ischemic Stroke		p
	First Event n=118 (%)	Recurrent n=118 (%)	
Nutrition intake	13 (11.02)	11 (9.32)	<0.001*
Body weight changes	67 (56.78)	74 (62.71)	
Gastrointestinal problem	33 (27.97)	26 (22.03)	
Physical examination changes	5 (4.24)	7 (5.93)	
Mean±SD	23,06±3.87	23,56±4.32	
Median	23.11	23.99	
Range (min–max)	16.56–35.80	12.49–39.56	

Note: *Fisher's exact test

cognitive deficits, paralysis. Upper extremity, visual and cognitive changes such as hemianopsia and apraxia.[8] Second, associated with dysphagia. Recurrent stroke events often cause dysphagia. Based on a retrospective study of 261 post-stroke patients by Kim et al.,[12] patients with mild and severe dysphagia were malnourished based on levels of albumin, albumin, protein, and lymphocytes. Dysphagia often causes weight loss due to decreased food intake. In addition, dysphagia also often causes discomfort during swallowing, which causes the patient to lose appetite and ultimately leads to malnutrition in hospitalized patients.[8] Chronic or acute deficiency and inflammatory conditions, which can lead to nutritional-related complications, can also reduce muscle mass, resulting in impaired swallowing function recovery after stroke.[13,14]

In addition, malnutrition in stroke patients is usually caused by the inability of the body of stroke patients to tolerate enteral nutrition due to decreased intestinal motility, weak gastrointestinal muscle tone, and impaired excretion of gastrointestinal hormones and enzymes, as well as damage to the intestinal mucous membrane. As a result, nutrient absorption is decreased, and malnutrition occurs. This condition causes inadequate digestion of food and tends to reduce the patient's digestive function.[8,15] Reduced muscle mass in patients with oropharyngeal dysphagia can also lead to worsening of the ability to swallow and can impair swallowing effectiveness.[10] Malnutrition is also associated with location of residence, diabetes mellitus, anorexia, reduced food intake, and reduced preference for sweet and fatty foods.[16]

Most stroke patients in both groups belonged to the normal BMI category. This is in line with the research results of Kartika et al.,[8] who explained that stroke patients majority have a normal BMI. Although obesity is usually associated with hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia, which causes atherosclerosis, which ultimately results in ischemic stroke, the patient's dyslipidemia factors influence the pathogenesis of stroke more than the patient's BMI.

The overall results of comparing the nutritional status of the first and recurrent ischemic stroke patients showed a significant difference ($p<0.05$), with the nutritional status of the recurrent ischemic stroke patients being worse than the first ischemic stroke. It can happen because, in recurrent ischemic stroke, there are clinical manifestations that appear, such as gastropathy, enteropathy, and impaired swallowing function, compared to malnutrition in the first attack, which is mainly caused by the patient's underlying disease and lack of nutritional intake after the attack. Recurrent stroke is a leading cause of death, re-hospitalization, and long-term disability. Compared with the first stroke, the resulting nerve damage is more serious, more difficult to treat, and has a higher mortality.[5,7] This causes the nutritional status also to be worsened.

The limitations of this study are the type of research that is retrospective and measurements of SGA and BMI are generally only carried out at the time of initial admission to the hospital, so it is difficult to distinguish a decrease in nutritional status caused by a pre-existing disease (underlying disease) or caused by an underlying disease. Clinical manifestations of the patient's current stroke. Future research needs to identify further risk factors that can affect nutritional status in stroke patients outside of stroke types based on the time of occurrence (first and recurrent), especially underlying disease and dietary habits, and it is necessary to carry out a comprehensive nutritional status assessment for stroke patients, especially in recurrent stroke. Appropriate dietary interventions can be implemented to prevent the deterioration of the nutritional status of stroke patients, reduce the risk of secondary complications, shorten the length of stay, and reduce morbidity and mortality.[17,18]

Conclusions

There was a significant difference in the nutritional status of the first and recurrent ischemic stroke patients in terms of patient characteristics based on the results of the SGA examination (decreased functional capacity and physical examination results), SGA rating, and BMI. The nutritional status of recurrent ischemic stroke patients is worse than that of the first ischemic stroke patients.

Conflict of Interest

There is no competing interest.

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RESEARCH ARTICLE

Relationship between Knowledge, Attitudes, and Practices of Universitas Mataram Students regarding the Use of Masks on the Occurrence of Maskne

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Abstract

Coronavirus disease 2019 (COVID-19) is transmitted from human to human and primarily via the respiratory route; hence, wearing a mask is the first step in preventing the spread of COVID-19. Behind the benefits of these masks are adverse consequences on the skin, such as lesions and acne. This study aims to ascertain the relationship between students' knowledge, attitudes, and practices regarding the use of masks on the occurrence of maskne. This research is a cross-sectional analytic observational study. The research subjects were 100 students from the Universitas Mataram's 2018 class, from November 2020 to January 2022, using a stratified random sampling technique—data collection from primary data via a Google Form. Data analysis was carried out by testing the lambda hypothesis. In this study, 38% (n=38) of the respondents reported maskne, while 62% (n=62) reported not maskne. Among the respondents who reported not maskne, the majority mentioned having good knowledge, positive attitudes, and good practice. The lambda hypothesis analysis indicates significant correlations between students' knowledge (p=0.004), attitudes (p=0.001), and practices (p=0.006) regarding mask usage and the occurrence of maskne. A relationship exists between students' knowledge, attitudes, and practices regarding mask usage and maskne occurrences.

Keywords: Attitudes, knowledge, maskne, practices, student

Introduction

Coronavirus disease 2019 (COVID-19), detected in December 2019, has developed into a pandemic affecting several countries worldwide.[1] COVID-19 is transmitted from person to person, primarily via the respiratory route. Hence, wearing masks for sick and healthy individuals is the primary and most significant step in preventing the spread of COVID-19.[2,3] Behind the benefits of masks in reducing the spread of COVID-19 are side effects experienced by the skin, such as skin lesions and acne.[4] Previous research has revealed that the usage of masks can induce acne on the nose, cheeks, chin, and lesions behind the ears.[5–7] Acne that emerges owing to the usage of this mask is called maskne.[8,9] Han et al.'s[10] findings showed that five of the 12 masked patients encountered acne for the first time after at least one month of frequent usage of masks, while the other seven patients reported worsening acne. Another study found that of the 833 students studied, 333 suffered acne due to incorrect use of masks.[11]

Proper masks can limit the occurrence of masknes.[12] In earlier research evaluating the knowledge, attitudes, and practices of students in Vietnam regarding the usage of masks, it was observed that students had good knowledge, positive attitudes, and good practices using masks.[13] Another study at the STIKes Raflesia Depok revealed that the respondents had high knowledge, positive attitudes, and good action in preventing COVID-19, specifically wearing masks.[14] Students who are predominantly adolescent in age are prone to develop masks during adolescence because of the influence of growth hormones and androgens, which increase during puberty and induce an increase in sebum production, which contributes to the creation of acne.[15]

This study aims to ascertain the relationship between students' knowledge, attitudes, and practices regarding the use of masks on the occurrence of maskne.

Methods

It is an analytical observational study with a cross-sectional design conducted at the Universitas Mataram from November 2020 to

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January 2022. Students were chosen for the study sample due to their adolescent age range, which is susceptible to the onset of acne. Considering the extensive population, the 2018 batch was selected as a representation because it was the most accessible.

The minimum sample in this study was calculated using the correlational formula, resulting in a minimum sample of 92. Subsequently, the research sample consisted of 100 students from the 2018 cohort. The sampling technique employed was the stratified sampling technique in each faculty, composed of 10 students from each faculty (faculty of medicine, faculty of law, faculty of engineering, faculty of business, faculty of animal husbandry, faculty of agriculture, faculty of food technology, faculty of mathematics and natural sciences, faculty of education and teacher training, and programs under the rectorate). The research instrument utilized was a self-constructed questionnaire in a Google Form. It consisted of eight questions concerning knowledge about mask usage, nine questions about attitudes toward mask usage, and ten questions about behaviors related to mask usage.

Additionally, there were questions regarding acne experienced, and respondents were requested to attach facial photographs capturing the front, right side, and left side to assess the acne condition they were experiencing. The questionnaire was validated using the Pearson product-moment correlation, resulting in an r value<0.05 (indicating questionnaire validity). The questionnaire's reliability was tested using Cronbach's alpha, yielding a result of 0.61 (indicating questionnaire reliability).

Because the sample size exceeded 50, the researcher conducted a normality test on the data using the exact method, which yielded a normality result of p=0.139 (p>0.05). The researcher used the hypothesis lambda to analyze the relationship between knowledge, attitudes, and mask usage behavior (ordinal data) with the occurrence of maskne (nominal data). The results indicate that if the p value<0.05, it is considered to be associated, and if the r value falls within the range of 0.00–0.19, it is a very weak correlation; 0.2–0.39 is a weak correlation; 0.4–0.59 moderate correlation; 0.61–0.8 is strong; and 0.81–1.00 is a very strong correlation.

Ethical issues may arise, including the willingness to participate in the research and the confidentiality of respondent data. The researcher has provided informed consent before respondents answered the questionnaire, and the researcher ensures the confidentiality of respondent data. Ethical clearance approved by the Health Research Ethics Committee of the Faculty of Medicine of Universitas Mataram under the number 152/UN18.F7/ETIK/2021.

Results

Table 1 shows respondents' characteristics based on gender and acne history. There were more female respondents than male. Out of 100 respondents, the majority were female respondents, and most had a history of acne.

Out of 100 respondents, most demonstrated good knowledge about using masks, as seen in Table 2. The data analysis also revealed that most respondents had positive attitudes toward using masks and showed that the most significant proportion of respondents had good practices.

Table 3 shows the best aspect of knowledge is the frequency of mask use since most respondents correctly responded, and the worst aspect is maskne prevention because most respondents incorrectly answered. Table 3 also revealed that the best aspect of respondents' practices is the frequency with which they use masks (duration of using a mask), while the worst aspect is the length of time they use masks (duration to rest the face). The best aspect of attitudes is facial hygiene, as most respondents strongly agreed, and the worst aspect is how to use masks, as the majority strongly disagreed, as seen in Table 4.

According to Table 5, we found that most students did not have maskne, with most of them being female and having never experienced acne before. Meanwhile, most students with masks were female and had experienced acne before. A bivariate analysis between gender and a history of acne with maskne occurrence using the chi-

Table 1 Characteristics of Respondents

Characteristics	n=100 (%)
Gender	
Male	25 (25)
Female	75 (75)
History of acne	
Had acne before	59 (59)
Never had acne before	41 (41)

Table 2 Description of Respondents' Knowledge, Attitudes, and Practices

Aspects	Good n (%)	Enough n (%)	Bad n (%)	Total n (%)
Knowledge	38 (38)	36 (36)	26 (26)	100 (100)
Attitudes	35 (35)	31 (31)	34 (34)	100 (100)
Practices	49 (49)	30 (30)	21 (21)	100 (100)

Table 3 Description of Respondents' Knowledge and Practices regarding Using Masks

Aspects	True (n)	False (n)
Knowledge		
Aggravating or precipitating factors	31	69
The duration of using the mask	78	22
Frequency of using masks	98	2
How to care for a mask	25	75
How to use a mask	83	17
Maskne prevention	23	77
Maskne treatment		
Must be treated	31	69
Heal yourself	41	59
Practices		
Mask type		
Cloth mask	50	50
Medical mask	81	19
Duration of using the mask		
Time to rest the face	17	83
Usage duration	24	76
Frequency of using masks		
Time of using mask	96	4
Mask replacement	63	37
How to care for a mask	64	36
How to use a mask	76	24
Prevention	20	80
Treatment	51	49

Table 4 Description of Respondents' Attitudes regarding Using Masks

Aspects of Attitudes	"Strongly Agree"	Agree	Neutral	Disagree	"Strongly Disagree"
How to use a mask	6	19	25	30	20
Duration of using the mask	5	32	31	24	8
Frequency of use	12	30	30	21	7
Facial hygiene	43	27	17	10	3
Decorative cosmetic use	25	19	28	21	7
Side effects	18	26	38	14	4
How to care for a mask	22	35	28	10	5
Use of moisturizer	9	26	37	17	11
Treatment	29	26	22	10	13

Table 5 Distribution of Occurrence Maskne by Gender and Acne History

Characteristics	No Maskne (n=62)	Maskne (n=38)	Total (n=100)	p*
Gender				
Male	18	7	25	0.234
Female	44	31	75	
History of acne				
Had acne before	29	30	59	0.001
Never had acne before	33	8	41	

Note: *chi-square test

square test found a relationship between a history of acne and maskne, but no relationship between gender and maskne occurrence.

In Table 6, among the respondents who did not have maskne, the majority had good knowledge, positive attitudes, and with good practices. Meanwhile, among the respondents who had maskne, the majority had poor knowledge, negative attitudes, and harmful practices. Table 6 also revealed a weak correlation between knowledge and the occurrence of maskne, a relationship between attitude and maskne with a moderate correlation strength, and a relationship between behavior and the occurrence of maskne with a moderate correlation strength.

Discussion

In this study, we found that the majority of students did not have masks, with most of them being female. However, statistical testing in this study revealed no relationship between gender and the occurrence of masks. According to prior research by Mahmood and Shipman,[16] gender does not affect the occurrence of maskne. Most students who did not have maskne in this study had never experienced acne before. In contrast, most students who had maskne had a prior history of acne. Students who got maskne had been wearing masks regularly for more than six weeks. Statistical testing in this study revealed a relationship between acne history and the occurrence of maskne. It is consistent with the findings of previous studies by Rosner,[7] which indicated that a history of acne was associated with maskne. American Academy of Dermatology Association explained that acne is a risk issue for mask use in theory because the skin is readily irritated by the friction of the mask, which increases the warmth and humidity of the skin

Table 6 Description of Relationship of Respondent's Knowledge, Attitudes, and Practices regarding Using Masks Between Occurrence of Maskne

Aspects	Occurrence of Maskne		Total (n=100)	Lambda Hypothesis	
	No Maskne (n=62)	Maskne (n=38)		p	r
Knowledge					
Good	34	4	38	0.004	0.368
Enough	22	14	36		
Bad	6	20	26		
Attitudes					
Positive	31	4	35	0.001	0.474
Enough	23	8	31		
Negative	8	26	34		
Practices					
Good	46	3	49	0.006	0.500
Enough	14	16	30		
Bad	2	19	21		

covered by the mask, exacerbating acne.[12]

According to the findings of this study, the majority of respondents demonstrated good knowledge. The best aspect of knowledge was related to the frequency of mask use, as most respondents provided the correct answer. Conversely, the worst aspect is maskne prevention, with most respondents answering incorrectly. The results of this study differ from those of previous studies. Limbong et al.'s[13] study found that 99.5% of students at Universitas Padjadjaran had adequate knowledge about the use of masks, and Duong et al.'s[17] study reported that 89.7% of students in Vietnam had sufficient knowledge about the use of masks. Additionally, a study at Melaka Manipal Medical College found that most students, about 55.2%, had adequate knowledge about using masks.[18]

Based on this study, most students did not have masks, and most had good knowledge regarding the use of masks. However, it was determined that most students who had masks needed more knowledge.

According to the study's findings, most respondents had positive attitudes. The best aspect of attitudes was related to facial hygiene, as most respondents strongly agreed. In contrast, the worst aspect was related to how to use masks, as most respondents strongly disagreed. The results of this study differ from those of previous studies in that Limbong et al.'s[13] research found that most of the students had a positive attitude toward the use of masks, about 87.9% of students and Duong et al.s'[17]s research found that most of students in Vietnam had positive attitude toward the use of masks about 72.8% students, and also Wachemo University's research found that most of students had positive attitude toward the use of masks about 81% students.[19]

Based on this study, most students did not have masks, and most had positive attitudes regarding the use of masks. However, for students who had maskne, it was determined that most of them had negative attitudes. After conducting statistical tests, it was determined that there was a moderate correlation between students' attitudes toward mask use and the occurrence of maskne. It explains why the more negative the attitude toward mask use is, the more likely maskne will arise, and vice versa.

According to the study's findings, most respondents had good practice. The best aspect of respondent practices is the frequency with which they use masks (time of using a mask), while the worst aspect is the length of time they use masks (time to rest the face). The results of this study differ from those of previous studies, including Duong et al.'s[17] research, which found that 76.5% of students in Vietnam had positive attitudes toward mask use, Larebo and Abame's[19] research at Wachemo University, which found that 89.5% of students had positive attitudes toward mask use, and also Universitas Padjadjaran's research, which found that 67% of students had positive attitudes toward mask use.[13]

Based on this study, most students did not have masks, and most had good practices regarding the use of masks. However, for students who had maskne, it was determined that most of them had bad practices. After conducting statistical tests, it was determined that there was a moderate correlation between student practices regarding the use of masks and the occurrence of masks. It explains that the worse the attitude regarding the use of masks, the greater the possibility of the occurrence of maskne and vice versa.

Conclusion

There is a significant relationship between students' knowledge, attitudes, and practices regarding the use of masks and the occurrence of masks.

Conflict of Interest

The authors declare that there are no competing interests.

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RESEARCH ARTICLE

Impact of the COVID-19 Pandemic on Laboratory Services

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Abstract

The positive impact of the coronavirus disease 2019 (COVID-19) pandemic is that hospital laboratory services are excellent when other services are declining. Aside from molecular biology laboratory (polymerase chain reaction, PCR) services for COVID-19 diagnostics, public demand has dramatically increased. It is a retrospective descriptive study that uses data on the total number and types of results of laboratory examination orders that have been verified from the laboratory information system of a hospital from 2018 to 2022. Data analysis is presented in the frequency of the number and type of results of laboratory examination orders and differences in requests for laboratory services before and during the pandemic since the government established it on March 8, 2020. The total number of laboratory requests between January 2018 and December 2022 was 1,943,539 services. The highest increase in laboratory examination services was in molecular biology (98.4%). As the need for community services increases for the PCR severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) examination, which is used in addition to diagnosing confirmed COVID-19 patients, it is also necessary for the community to conduct tracing if a family member has a COVID infection or travel requirements and follow-up for hospital employee exit tests who contracted COVID-19. In conclusion, the COVID-19 pandemic has positively impacted laboratory performance. There have been changes and an increase in the number and types of laboratory examination services and personal performance and management in laboratories.

Keywords: Biology molecular test, COVID-19 pandemic, laboratory services, PCR SARS-CoV-2

Introduction

A pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a highly contagious pathogen with rapid disease development and impacts all hospital services. Drastic changes in services, especially laboratory services are challenged to meet the need for fast and accurate diagnostics, triage, managing and guide therapy, disease-related monitoring strategies, and limiting the spread of the disease in a community. Many challenges occur in the laboratory regarding management, requirements for personnel trained and courageous in carrying out new and sophisticated tests, procurement of reagents and scarcity of supplies, and the risk of staff shortages due to coronavirus disease 2019 (COVID-19) infection.[1]

Laboratory services, as a result of the pandemic, are trying to carry out tests that were previously not the main examination and referred to, such as the COVID-19 polymerase chain reaction (PCR) molecular biology examination and IL-6 cytokines, which are the superior tests to be carried out, because they have to follow world developments to diagnosis, therapy guidance and monitoring of COVID-19 patients.[2–4]

The positive impact of the COVID-19 PCR molecular biology examination service unexpectedly became the prima donna of services in hospitals when other services declined due to the pandemic. Aside from molecular biology laboratory (PCR) services for COVID-19 diagnostics, public demand has dramatically increased. Different types of tests have also increased because monitoring of patients infected with COVID-19 requires a variety of other tests, so it has increased, as well as the IL-6, cytokine examination, hemostasis, blood sugar, and others. Clinical pathology analysis is challenged to perform routine examination interpretation services (such as hematology, clinical chemistry, immunoserology, and microbiology) and analyze the results of molecular biology examinations in assisting patient diagnostics.

Based on the research of Durant et al.[5] between February 2 and April 11, 2020, in a tertiary hospital in urban USA with 1,541 beds. It has obtained data with increasing local COVID-19 incidents that significantly impacted laboratory

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operations. There has been an apparent increase in laboratory tests for diagnostic purposes, monitoring disease patterns that direct the management of COVID-19, and several types of supporting laboratory tests, which have increased in overall volume. The COVID-19 pandemic also impacted laboratory management, staffing, and recommendations for managing resources and supply availability.[5]

Based on the observations of Dunbar et al.[6] in 2022, during the COVID-19 pandemic, clinical laboratory examinations played a crucial role in making a diagnosis. It is greatly influenced by various factors, including differentiating SARS-CoV-2 from other respiratory infection-causing pathogens; this is important for prompt clinical intervention and infection control. In addition to the incredible patient spike during the COVID-19 pandemic, few diagnostic tests were available initially. Only a few laboratories could develop, validate, and run the RT-PCR as the gold standard test for detecting SARS-CoV-2. Laboratories are challenged to continuously change and adapt to each pandemic and the mitigation strategies implemented to overcome them.

Based on the background above, Al Islam Hospital Bandung is one of the COVID-19 referral hospitals in the East Bandung area. Hence, this study aims to provide analysis relating to comparisons and changes in the number and types of patient services and the efforts made at the Al Islam Hospital Bandung laboratory before (2018–2019) and during (2020–2022) COVID-19 pandemic.

Methods

This retrospective descriptive research uses data on the number and types of results of laboratory examination orders that have been verified from the Al Islam Hospital Bandung laboratory information system from 2018 to 2022.

Data analysis is presented in terms of frequency, number, and type of results of laboratory examination orders that have been verified. The total volume was calculated two years before and after determining the pandemic period. This total calculates the absolute and relative differences in the volume of inspection orders between the pre-pandemic and the COVID-19 pandemic surge periods. The details of the types of laboratory examination orders analyzed in this study were grouped based on the service department at the hospital laboratory, namely examinations consisting of hematology, clinical chemistry, immunoserology, routine clinics, microbiology, molecular biology, anatomical pathology, and blood bank. The number and type of laboratory examination order services analyzed is the total number regardless of the origin of the patient's status (from within the hospital, outpatient, and emergency department or requests from outside the hospital). The Health Research Ethics Committee of Al Islam Hospital Bandung approved the study with letter 038/KEPK-RSAI/6/2023.

Results

The total number of types of laboratory requests between January 2018 and December 2022 was 1,943,539 services, with types of requests for clinical pathology laboratory examinations and anatomical pathology having decreased in 2020. Still, there was an increase in 2021–2022 for clinical pathology laboratory examinations. In contrast to the demand for types of anatomical pathology laboratory examinations, it has declined from 2020 to 2022 compared to 2018 to 2019 (Table 1).

The impact of the COVID-19 pandemic since the government established it on March 20, 2020, can be seen in the trend of the number of details for each examination in the laboratory. Since 2018, the types of services can be classified into seven major groups: hematology examination, clinical chemistry, immunoserology, microbiology, molecular biology, routine clinics (and others), anatomical pathology, and blood bank services. During the pre-pandemic period (2018–2019), hematology and clinical chemistry examinations dominated the sequence of laboratory examination services. The last examination is an examination of anatomical pathology. This situation persists during a pandemic (2020–2022).

Hematological examinations increased drastically during the pandemic to post-pandemic (Figure 1) linearly. Clinical chemistry examinations, which had a downward trend during the pre-pandemic, experienced a slight increase during the pandemic but decreased again in 2021 (Figure 2). Previously, immunoserological examination was a type that did not dominate during the pre-pandemic, but this type of examination has an increasing trend during a

Table 1 Types of Laboratory Patient Examination and Visit Services at Al Islam Hospital Bandung for the 2018–2022 Period

	Period					Total
	2018	2019	2020	2021	2022	
Types of laboratory services						
Clinical pathology laboratory	70,435	393,910	347,541	401,596	394,295	1,907,777
Anatomical pathology laboratory	1,597	1,336	1,110	1,122	1,105	6,270
Blood bank	4,650	4,425	5,592	7,642	7,183	29,492
						1,943,539
Patient visit services						
Clinical pathology laboratory	116,109	112,129	116,109	135,380	136,211	615,938
Anatomical pathology laboratory	1,110	1,336	1,110	1,122	1,105	5,783
Blood bank	3,976	3,133	3,976	5,301	4,667	21,053
						642,774

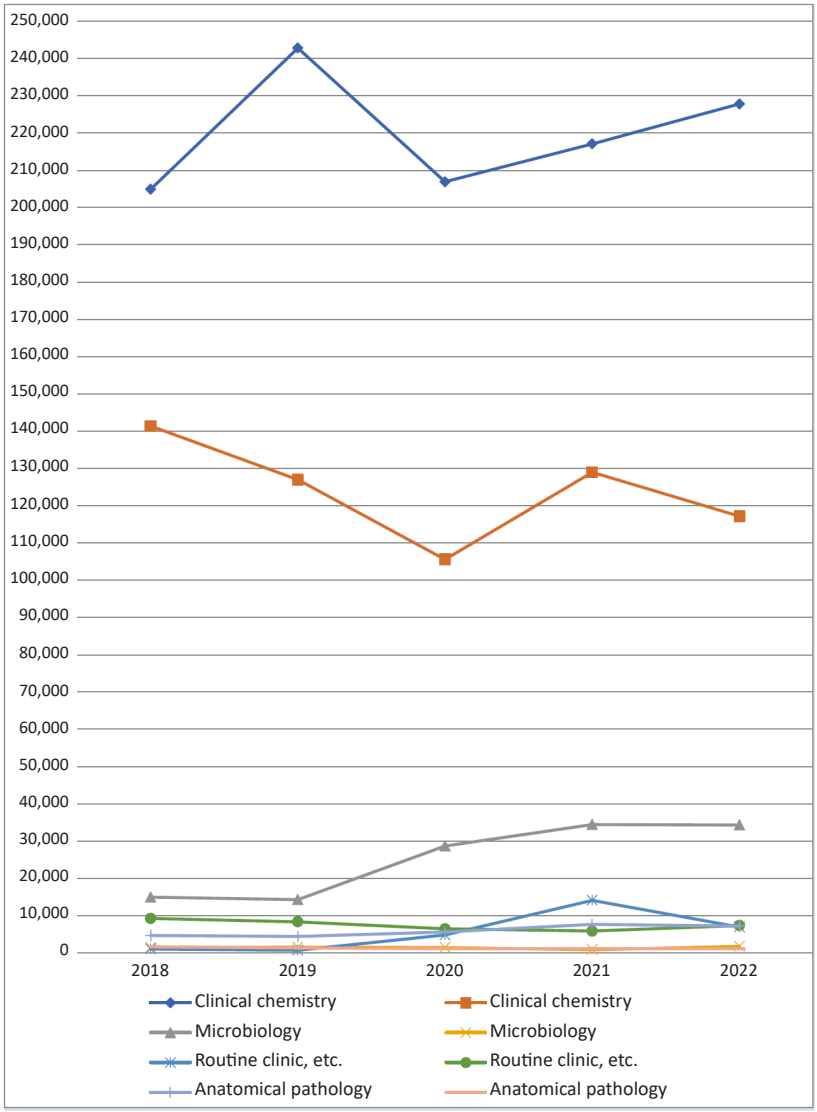

Figure 1 Laboratorium Inspection Type

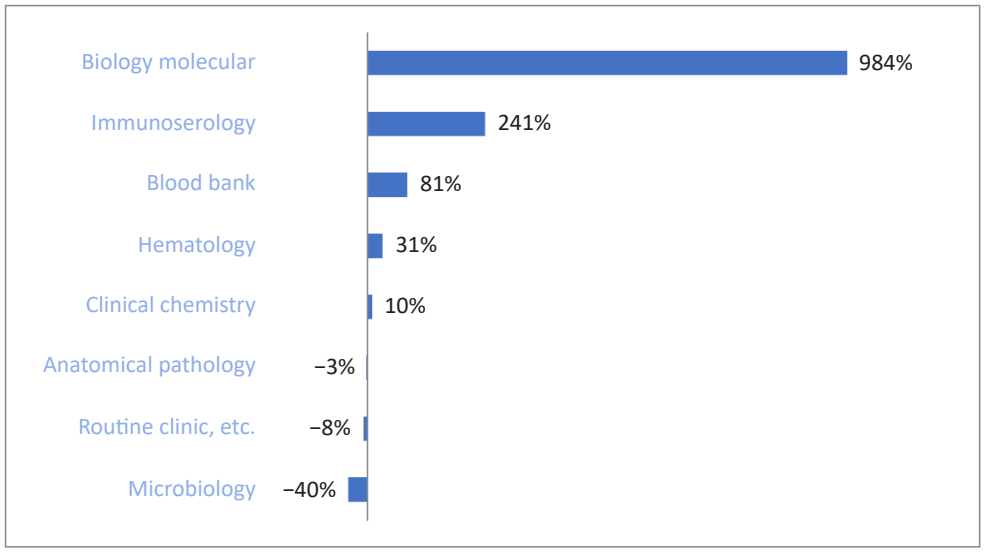

Figure 2 Differences Pre- and Post-COVID-19 Pandemic

pandemic (Figure 2). Like immunoserological examinations, molecular biology examinations also experienced a significant increase before and during a pandemic, as shown in Figure 3, even though in 2022, it decreased from the previous year

There are differences in laboratory examination services during the pre-pandemic and intra-pandemic periods (separation in March 2020), where laboratory services were decreased and added during the pandemic compared to before the pandemic. The decline in services in the anatomical pathology laboratory fell by 3%, and routine clinical laboratories and others decreased by 8%. Laboratory examination services that increased during the pandemic were the clinical chemistry laboratory, which increased by 10%. The hematology laboratory, which

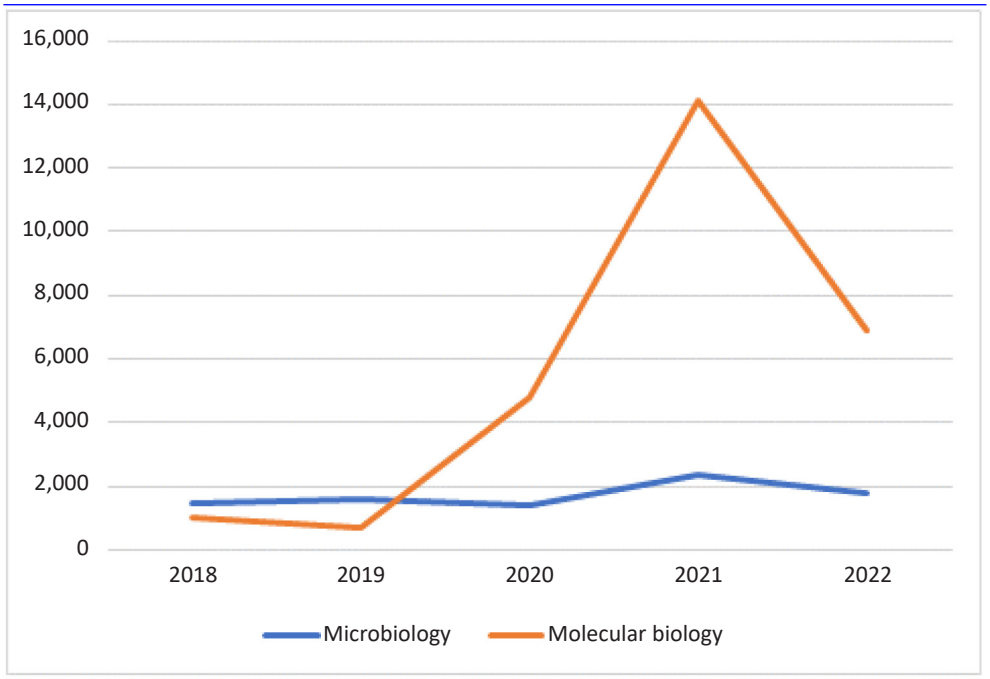

Figure 3 Comparison of Types of Pathogen Identification Tests

increased by 31%. The blood services laboratory, which increased by 81%. The immunoserology laboratory increased by 241%, and the molecular biology laboratory increased by 984%.

According to developments, types of laboratory examination services for diagnosing infectious diseases require changes in methods for identifying pathogens, as seen in Figure 3.

Examining pathogens grouped in the microbiology section at Al Islam Hospital consists of examining fungal preparations (KOH), gram staining, smear staining (with independent and DOTS programs), smear culture, and microorganism culture. In contrast, molecular biology examination consists of TCM TB and PCR SARS-CoV-2. Figure 3 shows a significant change in the number of molecular biology tests in 2020 when the pandemic occurred. A comparison of molecular biology examinations to microbiological examinations is shown in Table 2. Before the pandemic, molecular biology examinations were always less (ratio below 1). Still, at the beginning of the pandemic, molecular biology examinations were 3.37 times greater than microbiological examinations. During the pandemic, molecular biology examinations peaked almost six times more than microbiological examinations.

We found the highest services from each laboratory section, and each department varied. The ones that experienced the most changes were molecular biology services, immunoserology, and blood bank services, while laboratory examination services for other sections mostly stayed the same. Services ranked fifth most from the immunoserology examination, as seen in Table 3.

Discussion

The types of requests for clinical pathology laboratory examination services and blood banks have continued to increase from 2020 to 2023. The total number of laboratory patient visits differs from the number of laboratory

Table 2 Examination of Microorganism Identification

Types of Services	2018	2019	2020	2021	2022
Microbiology					
Fungi (KOH)	254	326	223	216	214
Gram	287	348	241	198	249
AFB stain	427	435	276	405	332
AFB culture	7	9	5	6	4
Microorganism culture	469	455	677	1,524	970
Molecular biology					
RT-PCR TB	1,037	706	187	680	939
RT-PCR SARS-CoV-2	0	0	4,615	13,407	5,988
Ratio molecular biology/microbiology service	0.71	0.44	3.37	5.99	3.91

Table 3 Services Ranked Five Most from Immunoserology Examination

Rank	2018	2019	2020	2021	2022
1	HBsAg	HBsAg	Rapid antibody SARS-CoV-2	Rapid antigen SARS-CoV-2	Rapid antigen SARS-CoV-2
2	Anti-HIV (screening)	Widal	HBsAg	Rapid antibody SARS-CoV-2	HBsAg
3	Widal	Anti-HIV (screening)	Anti-HIV (screening)	HBsAg	Widal
4	IgM *Salmonella typhi*	IgM *Salmonella typhi*	Widal	CRP	Rapid antibody SARS-CoV-2
5	CRP	NS1	CRP	Anti-HIV (screening)	Anti-HIV (screening)

examination services because a patient can perform more than one type of laboratory examination service. An average patient has 3 to 4 types of laboratory tests. This explanation can be seen in Table 1. During a pandemic, laboratory examination services increased the types of routine examinations carried out, as well as screening, diagnosis, therapy guidance, and follow-up therapy types of laboratory services for molecular biology examination services. Before the pandemic, the molecular biology examination service at the hospital was only for pathogen detection in diagnosing tuberculosis infectious disease, known as the molecular rapid test for tuberculosis, assisted by the provincial government in 2017. Since 2017, the Al Islam Hospital laboratory has begun providing molecular biology examination services. The molecular rapid test for tuberculosis (TCM TB) covered the eastern Bandung area and is the first private hospital in east Bandung to receive this equipment. At the beginning of the COVID-19 pandemic, molecular biology examinations for the identification of SARS-CoV-2 until December 2020 were still being referred to various nearby laboratories that already had RT-PCR equipment. Along with the increasing need for community services for the PCR SARS-CoV-2 examination, which is used in addition to diagnosing confirmed COVID-19 patients, it is also necessary for the community to conduct tracing if a family member has a COVID infection or travel requirements and follow-up for employee exit tests hospitals infected with COVID-19, this is the reason for the rapid increase in the number of molecular biology laboratory examinations.[7,8] This shows that the impact of the pandemic is not only on the type and number of examination services in the laboratory but also on innovation and creativity management, staffing arrangements, supervision of types of recommendation examinations, and availability of supplies in the laboratory.[1,5,9].

Procurement of molecular biology services during a pandemic requires increased knowledge and skills starting from the pre-analytical, analytical, and post-analytical stages. At the pre-analytical stage, specimen collection of oro swabs and nasopharynx of patients with COVID-19 infection was new in the laboratory. Still, during a pandemic, this became a routine examination. During a pandemic, compared to before the pandemic, immunoserology examination service of SARS-CoV-2 antigen is the most common from 2021–2022.[10,11] In addition to monitoring the mild degree of disease and therapeutic response, the interleukin-6 (IL-6) examination, an examination of inflammatory cytokines that is most in demand is also used.[12–14]

Laboratory examination services in the clinical pathology department that were dominant before and during the pandemic, namely hematology and clinical chemistry, were still the same. This is because these two laboratory examination sections are widely used to determine the patient's baseline condition, including whether with or without comorbidities and monitoring of a disease, both infectious and non-infectious.[15–17] This is due to the type of hematological examination other than routine hematology that is carried out (hemoglobin, leukocytes, platelets, hematocrit and specific count), hemostasis examination for PT, aPTT and D-dimer during a pandemic is the type of examination that is mainly carried out due to COVID-19 infection caused by a virus that has been shown to enter cells via binding to the angiotensin-converting enzyme 2 (ACE-2), found primarily in the alveolar epithelium and endothelium. Endothelial cell activation is a significant driver of the increasingly recognized complications of thrombosis. Viral inclusion bodies have been identified in endothelial cells in various organs, from the lung to the gastrointestinal tract.[11,18]

Conclusions

The COVID-19 pandemic has had a significant impact on laboratory performance. There have been changes and an increase in the number and types of laboratory examination services related to the diagnosis and management of COVID-19, and the type of laboratory examination that has undergone the most drastic changes in the type of molecular biology examination for the pathogens detection of SARS-CoV-2.

Conflict of Interest

All authors declared there was no conflict of interest.

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RESEARCH ARTICLE

Cytotoxicity of Combination Doxorubicin and *Garcinia picrorrhiza* Fruit Extract on Fibroblast Cell

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Abstract

Combining chemotherapeutic agents such as doxorubicin with herbal products or other compounds that can enhance cytotoxicity without side effects is required. Thus, we aimed to observe the cytotoxicity of doxorubicin and *sesoot* (*Garcinia picrorrhiza*) fruit ethanolic extract (GpKar) on human fibroblast cells, BJ. This study used a post-test-only control randomized group design with n=3 and a number group of 5. The method used in this research is cell number, and viability was measured with (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium assay. Treatments consisted of a combination of doxorubicin (0.02 µg/ml) and GpKar of 66.47 µg/ml (DES1), 132.94 µg/ml (DES2) and 265.89 µg/ml (DES3). The data were analyzed using a one-way ANOVA and Duncan post hoc tests. DES3 showed the lowest viability among treatments (89.32%). DES1 and DES2 showed high viability (>90%), 97.93%, and 95.08%, respectively. Thus, the combination of doxorubicin (0.02 µg/ml) and GpKar (66.47 µg/ml) was considered safe for further use in the following assay. In summary, the combination of doxorubicin and GpKar showed high viability in normal fibroblast cells.

Keywords: Cytotoxic, doxorubicin, *Garcinia picrorrhiza*, human fibroblast, MTS assay

Introduction

Cancer is a disease indicated by loss of control in cycle cell regulation and homeostasis in multicellular organisms. The deregulation of growth genes causes cancer and is insensitive to anti-growth signals.[1] According to the World Health Organization, cancer deaths have risen from 1.2 million to 1.8 million and are now the leading causes of death.[2] The incidence is thought to elevate in 2030 to 26 million people and 17 million deaths due to the disease. It grows faster in poor and developing countries. Report on Result of National Basic Health Research (*Riskesdas*) reported in 2007 that the prevalence of cancer in Indonesia was 4.3 out of 1,000 people.[3] Breast cancer is the most common cancer among women in Indonesia, with an incidence of 26 cases per 100,000 women, followed by cervix cancer, which has an incidence of 16 cases per 100,000 women.

Breast cancer has been commonly treated with chemotherapeutic agents, doxorubicin, yet it generates adverse effects such as dizziness, vomiting, and cardiac arrhythmias.[4] Therefore, a combination with herbal products or other compounds that can enhance cytotoxicity without side effects is required. Several studies utilized a combination of garcinol and doxorubicin that showed better performance compared to the single compound.[5] The cytotoxic effects of paclitaxel against breast cancer are enhanced by garcinol. Combination therapy, with a low dose of Taxol and garcinol, is a promising therapeutic strategy for managing advanced or metastatic breast cancer to determine the underlying mechanisms of these effects in vivo.[6] The synergistic combination therapy is recommended because it is safer and has a higher response rate than monotherapy.

Plant extracts have been widely used in anticancer therapy due to their high toxicity. Thus, it is essential to observe their toxicity on normal cells. A recent study shows that *Moringa oleifera* leaf extract synergistically enhanced the cytotoxic effect of cisplatin on PANC-1 cells.[7] Previous studies showed that the phytochemical of *sesoot* (*Garcinia picrorrhiza* Miq.) bark exhibited an antimutagenic effect on standard

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mutants, which has the potential to be used as an anticancer.[8] Combination of mandarin orange (*Citrus reticulata*) pericarp ethanolic extract-doxorubicin showed antiproliferative effects on Michigan Cancer Foundation-7 (MCF-7).[9] Combination of pyrophen fraction of endophyte fungus-doxorubicin showed a synergistic effect in antiproliferative, cell cycle, and apoptotic induction properties MCF-7.[10]

However, it remains unclear the effect of *Garcinia picrorrhiza* fruit ethanolic extract (GpKar) on normal cells except on Vero cells. The combination of doxorubicin and GpKar is expected to be toxic to cancer cells. Thus, we aimed to observe the cytotoxicity of GpKar and doxorubicin on human fibroblast cells, BJ.

Methods

Garcinia picrorrhiza Miq. fruit were obtained from Kebun Raya Bogor, LIPI. *Garcinia picrorrhiza* fruit is shown by the color of its seed, which is brown. The *sesoot*-ripe fruit was extracted using a maceration technique with 70% distillate ethanol for 24 hours and then filtered. The filtration was repeated until the colorless filtrate was further evaporated. The extract was stored at a temperature of −20°C.[11–13]

Biomolecular and Biomedical Research Center, Aretha Medika Utama, provided BJ cells [ATCC®CRL-2522]. Cells were grown in α-minimum essential medium Eagle (α-MEM) [Biowest L0475], 10% fetal bovine serum (FBS) [Biowest S181H], 1% penicillin-streptomycin [Biowest L0022], and maintained at 37°C in a humidified atmosphere and 5% CO_2 until the cells were 80–90% confluence. The growth medium was removed and washed with phosphate buffer saline (PBS) [Gibco 14200075]. Cells were added with trypsin-EDTA [Biowest L0931-500] and incubated at 37°C for 3 min. Tripsynization was stopped by adding a growth medium in equal volume. Cells were suspended and replaced into a tube, centrifuged at 500 xg for 4 min. The supernatant was removed, and the pellets were resuspended with 4–5 ml growth medium. The cell suspension was aliquoted into a T-flask containing a growth medium with a density of 8,000 cells/cm^2. Medium was replaced every two days. Cells were incubated at 37°C, 5% CO_2.[14]

This experimental study used a post-test-only control randomized group design with n=3, number group of 5. The treatment group consisted of negative control (normal cells), DMSO control, DSE 1 (doxorubicin of 0.02 µg/ml + GpKar of 66.47 µg/ml), DSE 2 (doxorubicin of 0.02 µg/ml + GpKar of 132.94 µg/ml), and DSE 3 (doxorubicin of 0.02 µg/ml + GpKar of 265.89 µg/ml).

The cells number and viability were measured with 20 µl (3-(4,5-dimethylthiazol-2-yl)-5-(3 carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) [Promega, Madison, WI, USA], and incubated at 37°C for 3 hours. Briefly, 100 µl cells were plated (5×103 cells per well) and incubated for 24 h at 37°C in a humidified atmosphere and 5% CO_2. The medium was then discarded and added with 90 µl of new medium and 10 µl of a combination of doxorubicin (0.02 µg/ml) and GpKar (66.47, 132.94, and 265.89 µg/ml) in DMSO in different plates in triplicate then incubated for 24 h. Untreated cells served as the control. The 20 µl MTS was added to each well. The plate was incubated in 5% CO_2 at 37°C incubator for 4 hours. The absorbance was measured at 490 nm on a microplate reader [MultiSkan Go Thermoscientific]. The data is presented as the percentage of viable cells (%). The viability assay determined the safe and non-toxic concentration for the following assay.[7,15]

Results

As shown in Figure, the combination of doxorubicin and *sesoot* extract was toxic to BJ cells compared to the control. Combining doxorubicin 0.02 µg/ml and an extract of 265.89 µg/ml showed the lowest viability among treatments (89.32%). Extracts of 66.47 µg/ml (DES1) and 132.94 µg/ml (DES2) showed high viability (>90%), which were 97.93% and 95.08%, respectively. However, DES1 was the only treatment comparable to the control, while DES2 showed a significant difference compared to the control. Thus, DES1 was considered safe for further use in the following assay.

Discussion

The present study showed that a combination of doxorubicin and *Garcinia picrorrhiza* extract showed high viability on normal fibroblast cells. This study used *Garcinia picrorrhiza* ethanolic extract and MTS assay for measuring cytotoxicity in human fibroblast cells, which are a novelty in experimental research. However, the limitation of this study is there need to be a characterization of the compounds in *Garcinia picrorrhiza*.

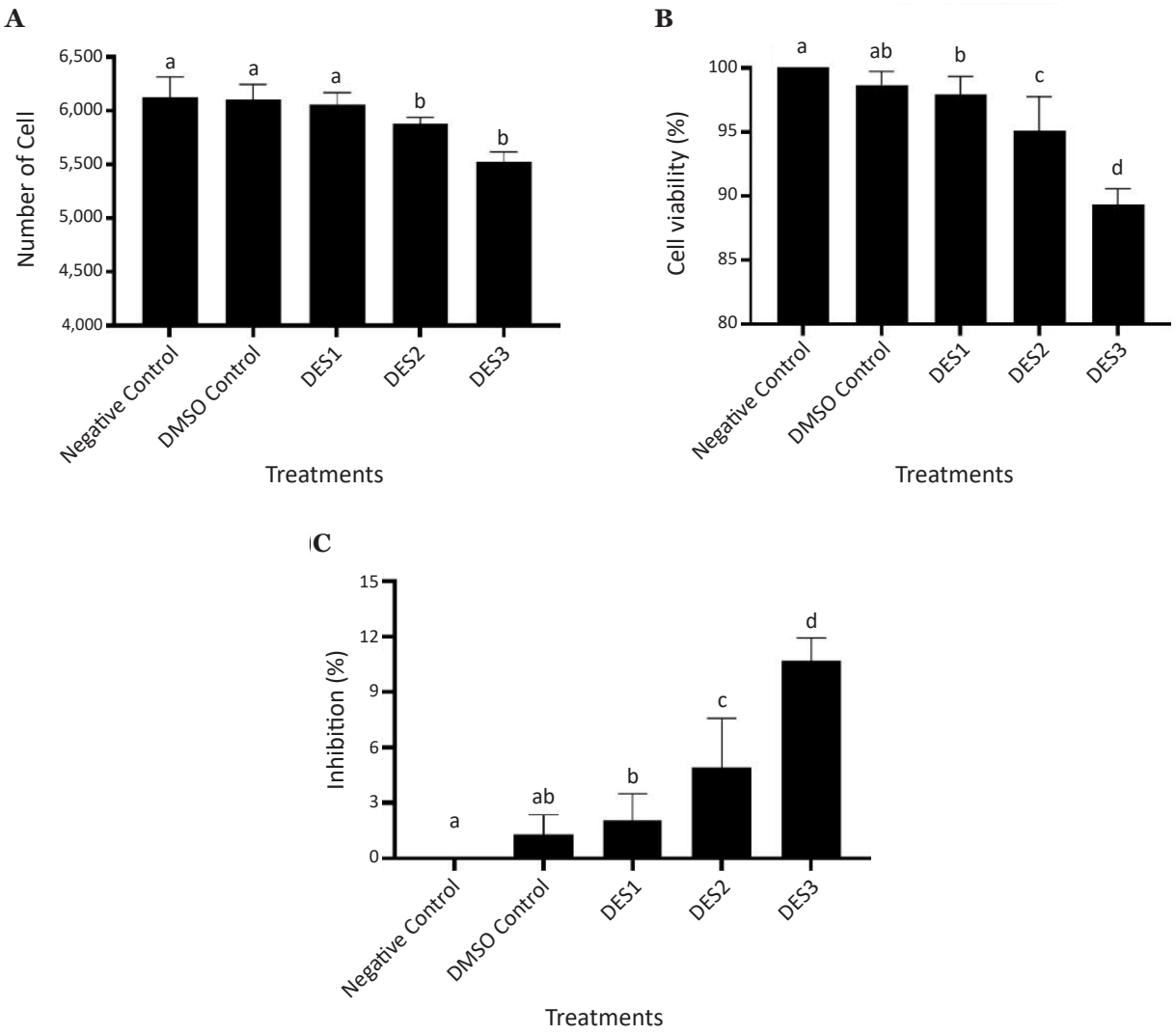

Figure Fibroblast Cells Treated with GpKar

Note: (**A**) Number of cell. (**B**) Cell viability (%). (**C**) Inhibition cell (%). DES1: doxorubicin 0.02 µg/ml and GpKar 66.47 µg/ml. DES2: doxorubicin 0.02 µg/ml and GpKar 132.94 µg/ml. DES3: doxorubicin 0.02 µg/ml and GpKar 265.89 µg/ml. The data is shown as means±SD with n=3. Different letters (a, ab, b, c, d) show significant differences among GTE doses based on the Duncan post hoc test (SPSS version 20.0) with p=0.05

Based on another study, the measurement of cell cytotoxicity of *Garcinia mangostana* used an MTT assay. Tannin compounds at 12.5%, 25%, 50%, and 100% in *Garcinia mangostana* extract show higher proliferation ability compared to the concentration of 6.25%. Tannins from mangosteen peel extract showed slightly toxic properties at a concentration of 6.25% and non-toxic at concentrations less than 6.25%, equivalent to 2.20% tannin isolation from mangosteen peel extract.[16]

Several studies utilized the combination of sulbactam and doxorubicin to enhance the cytotoxicity of doxorubicin in breast cancer cells.[17] These results indicate that combining both compounds can be used in cancer therapy without affecting normal cells. Therefore, previous studies utilized a combination of garcinol and doxorubicin that showed better performance compared to the compound alone.[19] Garcinol or Cambogia, a benzophenone derivative, can be obtained from *Garcinia indica* and *Garcinia picrorrhiza* Miq.[19] Furthermore, the higher concentration showed the lower cell proliferation rate described, namely the cytotoxic effect of flavin and EGCG on RL-34 cells, which states that all polyphenols will produce cytotoxicity at high concentrations.[20] Based on the results of this

study, tannins of *Garcinia mangostana* Linn. peel extract 0.78% compared with chlorhexidine gluconate 0.2% had better biocompatibility in BHK-21 fibroblast cells.[21]

Phytochemical compounds of Garcinia have been studied and showed the presence of prenylated xanthones, bioflavonoids, and benzophenones.[22] Garcinol on MCF-7, which has a positive estrogen receptor, and MDA-MB 231 with the negative receptor, showed growth inhibition and induced apoptosis on cancer-specific cells. Thus, garcinol alone can benefit as a chemopreventive agent, mainly in breast cancer.[23,24]

Conclusions

In conclusion, the combination of doxorubicin and GpKar showed high viability in normal fibroblast cells. These results indicate that combining both compounds can be used in cancer therapy without affecting normal cells.

Conflict of Interest

The authors declared that they have no competing interests.

Acknowledgments

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RESEARCH ARTICLE

Effectiveness of Machine Learning for COVID-19 Patient Mortality Prediction using WEKA

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Abstract

Timely detection of patients with a high mortality risk in coronavirus disease 2019 (COVID-19) can substantially improve triage, bed allocation, time reduction, and potential outcomes. A potential solution is using machine learning (ML) algorithms to predict mortality in COVID-19 hospitalized patients. The study's objective was to create and verify individual risk assessments for mortality using anonymous demographic, clinical, and laboratory findings at admission, as well as to assess the possibility of death using machine learning. We used a standardized format and electronic medical records. Data from 2,313 patients were collected from two Muhammadiyah hospitals from January 2020 to July 2022. Utilizing each patient's clinical manifestation state at admission and laboratory parameters, 24 demographic, clinical, and laboratory results were studied. The algorithms analyzed were AdaBoost, logistic regression, random forest, support vector machine, naïve Bayes, and decision tree, which were applied through WEKA version 3.8.6. Random forest performed better than the other machine learning techniques, with precision, sensitivity, receiver operating characteristic (ROC), and accuracy of 78.6%, 78.7%, 85%, and 78.65%, respectively. The three top predictors were septic shock (OR=21.518, 95% CI=4.933–93.853), respiratory failure (OR=15.503, 95% CI=8.507–28.254), and D-dimer (OR=3.288, 95% CI=2.510–4.306). Machine learning–based predictive models, especially the random forest algorithm, may make it easier to identify patients at high risk of death and guide physicians' appropriate interventions.

Keywords: Data mining, inpatient mortality, machine learning algorithm, prediction model

Introduction

In 2019, Wuhan province in China identified the first case of a novel coronavirus, which is considered to have been transferred from animals to humans.[1] The virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Originally known as the 2019 novel coronavirus (2019-nCoV), the disease is now known as COVID-19.[2] In March 2020, the World Health Organization declared COVID-19 a pandemic.[3]

When COVID-19 patients are first admitted, doctors frequently can only adequately determine their prognosis once the disease has worsened. Additionally, the course of COVID-19 can change abruptly, causing a patient with a stable status to develop a critical condition quickly.[4] Elderly age, male, and the presence of various comorbidities, such as diabetes, high blood pressure, high cholesterol levels, cardiovascular disease, and chronic kidney disease, have been linked to increased mortality rates and severe outcomes in individuals affected by COVID-19.[5,6]

Artificial intelligence (AI) is a discipline in computer science that aims to comprehend and construct intelligent entities, typically manifested as software programs.[7] AI research has utilized machine learning techniques, which can consider intricate relationships to detect patterns within the given data. Standard machine learning algorithms can be broadly categorized into two sorts based on the tasks they aim to solve: supervised and unsupervised.[7]

The study about mortality prediction in COVID-19 patients using supervised machine learning conducted in Korea shows that LASSO and linear SVM demonstrated ROC values of 94,6% and 97,7% in predicting mortality.[8] Another international study in India using eXtreme Gradient Boosting shows a ROC value of 85.8%.[9] Compared to the machine learning models, the numerous studies applying conventional statistical models have significant methodological weaknesses and provide a substantial risk of bias within multiple fields of study.[10]

PKU Muhammadiyah Yogyakarta and PKU

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Muhammadiyah Gamping General Hospital, Yogyakarta, are reference hospitals that applied structural electronic medical records; the electronic medical records can be easily and rapidly accessed compared to manual medical records.

The first aim of this study was to construct a model for predicting death from the first day of patient admission. The secondary purpose was to investigate predictors of COVID-19 mortality. Six machine learning models were employed, utilizing the Waikato Environment for Knowledge Analysis (WEKA) version 3.8.6. WEKA is open-source software, and compared to other software such as Rapid Miner and Orange, WEKA offers a broader range of machine learning methods and facilitates SMOTE, a technique used to address imbalanced datasets in machine learning. It also enables data mining activities by providing an extensive array of tools for data preprocessing, classification, attribute selection, and visualization. Several standard familiar file formats can be utilized with WEKA, such as xls and csv.[11]

Methods

This retrospective observational study included a total population of 2,882 patients, all consecutive COVID-19 patients admitted to the PKU Muhammadiyah Yogyakarta and PKU Muhammadiyah Gamping General Hospital, Yogyakarta, Indonesia, from January 2020 to July 2022. Of these, 68 patients were pregnant, 74 were children under 18, and 427 were missing or incomplete data. Then, the patients who met the inclusion criteria were 2,313 and applied for analysis.

The inclusion criteria were (1) SARS-CoV-2 infection confirmed by RT-PCR assays on material collected by a nasopharyngeal and oropharyngeal swab, (2) hospitalized patients, and (3) age above 18 years. Excluded from the analysis were patients who died during admission, patients who did not have primary data, pregnancies, and patients who were relocated to other designated hospitals while hospitalized.

The required patient data acquired from their medical records were age, gender, cardiovascular risk factors (high blood pressure, type 2 diabetes mellitus, and lipid disorders); primary comorbidities, including chronic renal disease; history of coronary artery disease, chronic obstructive pulmonary disease, and peripheral vascular disease; and laboratory results. Hospitalized COVID-19 patients who were deceased and those who lived were analyzed differently. Figure 1 shows the study design visualization.

The main objective of the study was to construct similar models with enhanced accuracy parameters to provide a mortality risk predictor.

Primary patient data, such as age and gender, were included within the clinical variables. A record of associated chronic diseases was

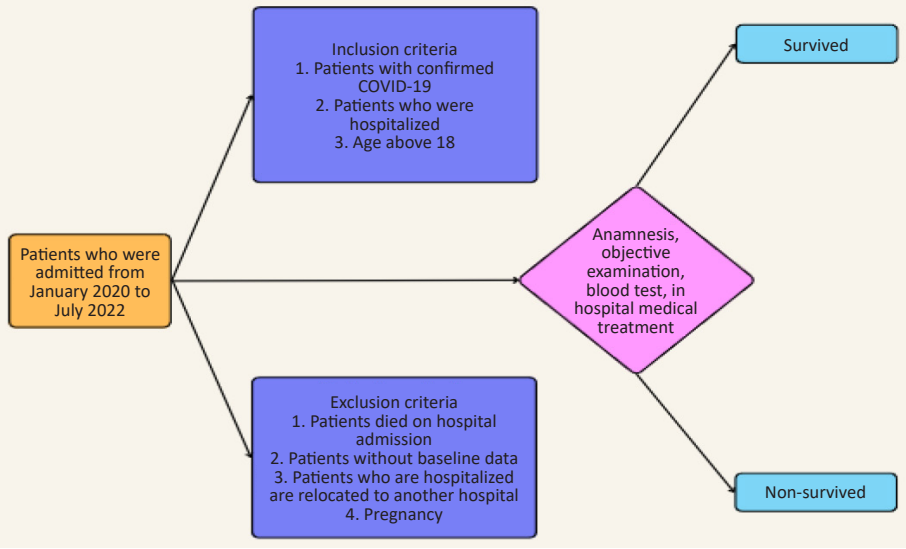

Figure 1 Study Design Visualization

collected, including diabetes, high blood pressure, cardiac and kidney disorders, and cancer. Laboratory parameters, such as lymphocytes, leukocytes, thrombocytes, neutrophils, D-dimer, glucose, creatinine, and hemoglobin, were evaluated. Out of 24 predictors, we selected these based on their odds ratio, p value, and relevance in clinical practice.

New variables were initially derived using Microsoft Excel 2013 to analyze the original data. Descriptive statistics for categorical variables used in this study are presented as absolute numbers (percentages). Since the study only used categorical variables, percentages were used to describe the data using chi-square tests to examine for correlations. The chi-square test was performed in bivariate analysis. The Pearson chi-square test or Fisher exact test was used, depending on which was suitable for analysis, and the odds ratio was computed. If $p<0.05$, it was considered significant. SPSS version 25.0 was used to analyze the data.

Data preprocessing is an essential part of the data mining process. It includes cleaning, transforming, and integrating raw data for analysis. The steps of data preparation are cleaning the data, integrating the data, reducing the amount of data, and changing the data. Data cleaning is getting clear of wrong, missing, or inaccurate information from a dataset. Integrating data involves combining information from different sources into a single file.

Data reduction is the process of making a dataset smaller by getting rid of duplicate or unimportant data. Changes are made to the format or layout of data to be used in the mining process.

We evaluate the predictors of hospitalized mortality using a set of machine learning algorithms that were adjusted. Six supervised machine learning algorithms were used in WEKA version 3.8.6 to construct mortality prediction models utilizing the preprocessed data: AdaBoost, logistic regression (LR), random forest (RF), support vector machine (SVM), naïve Bayes, and decision tree (DT).

For this research's categorization problem, supervised machine learning was selected among different methods. The nonlinearity in the data was clarified by supervised machine learning, which also constructs a performance that maps the input (predictor variables) to the output (mortality). As input data are processed, the outcomes of supervised machine learning become more accurate, and the predictions are more likely to fall throughout the allowed range.[12]

Researchers used the synthetic minority oversampling technique (SMOTE) to make more examples for the surviving class, which is in the minority group. SMOTE oversamples the minority class by making more artificial samples, and this increases the size of the class with fewer samples. After that, the researchers implemented the spread subsample to decrease the number of subjects in the majority class or surviving class, thus reducing it to balance with the minority class. When we oversample the minority class and undersample the majority class or cut off several samples in the class with more samples, the classifier will work better.[13]

The optimum hyperparameters for each model were obtained using WEKA's explorer module. The selected hyperparameters were those with the highest performance values. The effectiveness and general error of the comprehensive classification models were assessed using a tenfold cross-validation process system. All models were tested ten times using WEKA's experimenter module, and repeating ten-fold cross-validation was utilized to make comparisons of the performance-based prediction.

To produce the performance metrics (sensitivity, specificity, accuracy, precision, and ROC) generated from testing alone, the validation findings from ten experimental models were combined.[14]

Building an accurate machine learning model requires a fundamental component called model performance evaluation. Utilizing performance metrics for the confusion matrix, the predictive models were assessed (Table 1).

We used assessment indicators comprising accuracy, specificity, precision, sensitivity, and ROC chart criteria to assess the performance of the predictive models. To determine the best model for predicting COVID-19 mortality, All of these evaluation measures were contrasted based on their performance (Table 2).

The Research Ethics Committee of PKU Muhammadiyah Gamping Hospital approved the study protocol with exemption number 144/KEP-PKU/VII/2022). Additionally, because the study was retrospective, informed consent was not required.

Results

Between January 2020 and July 2022, a total

Table 1 Confusion Matrix

Output	Predicted Values	
	Non-survival (+)	Survival (–)
Actual value		
Non-survival (+)	TP	TN
Survival (–)	FP	FN

Note: TP: true positive is the number of cases the algorithm correctly classifies as positive; FP: false positive is the number of cases the algorithm incorrectly classifies as positive; FN: false negative is the number of cases the algorithm incorrectly classifies as negative; TN: true negative is the number of cases the algorithm correctly classifies as negative

Table 2 Performance Evaluation Measures

Performance Criteria	Item
Accuracy	(TP+TN)/(TP+TN+FP+FN)
Precision	TP/(TP+FP)
Sensitivity/recall	TP/(TP+FN)
Specificity	TN/(TN+FP)

Note: TP: true positive, TN: true negative, FP: false positive, FN: false negative

of 2,313 consecutive PCR-confirmed COVID-19 patients were retrospectively analyzed. Six hundred and thirty-eight COVID-19 patients (27.6% of the total) died at the time of their hospitalization, while the remaining 1,675 patients (73% of the total) survived. Table 3 provides more information on the symptoms, comorbidities, vital signs, and laboratory findings. Significantly, the three top odds ratios were septic shock (21,518), respiratory failure (15,503), and D-dimer (3,288). Type 1 diabetes mellitus was the top predictor among comorbidities (1,453).

In Table 3, 3 datasets were created. The first is the original dataset, which has 1,675 instances of the class that survived and 638 instances that did not survive.

Following the processing of the SMOTE algorithm, the number of cases belonging to the minority class was increased by generating synthetic samples, and the resulting dataset was then saved in the second dataset. This dataset contains 1,675 cases that related to the survived class and 1,276 cases that related to the updated non-survived class.

The researchers then executed the spread subsample technique, which undersamples the majority class to create a balanced dataset, which was then saved in the third dataset. By executing the SMOTE and Spread Subsample steps, the researchers created a balanced dataset, which was then used to train and test the COVID-19 predictor (Figure 2).

Figure 3 overviews the machine learning models' final testing results. The random forest algorithm was the best machine learning, with a precision of 78.6%, sensitivity of 78.7%, ROC of 85%, and accuracy of 78.65%. The 85% ROC value indicates good accuracy. The ROC needs to be higher than 0.5 for a diagnostic test to be considered meaningful. ROC≥0.8 is typically regarded as acceptable.[15]

Discussion

We use a ten-fold cross-validation technique to increase data utilization for training and

Table 3 SMOTE and Spread Subsample Methods' Results

Dataset Number	Technique Used	No. of Cases from the Surviving Class	No. of Cases from the Non-survived Class
1	–	1,675	638
2	SMOTE	1,675	1,276
3	Spread subsample	1,675	1,276

Table 4 Baseline Characteristics of Study Participants According to Mortality (Survival Vs Non-survival)

Parameters	Survival		Non-survival		OR (95% CI)	p
	n	%	n	%		
Total sample	2,126	72.4	638	27.6		
Comorbidity						
Pneumonia	47	2.0	10	0.4	0.552 (0.277–1.098)	0.086
Hypertension	422	18.2	163	7.0	1.019 (0.826–1.259)	0.861
Septic shock	2	0.1	16	0.7	21.518 (4.933–93.853)	0.000*
Chronic kidney disease	36	1.6	18	0.8	1.322 (0.745–2.345)	0.339
Acute kidney disease	3	0.1	3	0.1	2.633 (0.530–13.080)	0.356
Type 2 DM	235	10.2	115	5.0	1.347 (1.055–1.721)	0.017**
Type 1 DM	176	7.6	93	4.0	1.453 (1.110–1.903)	0.006**
Asthma	39	1.7	6	0.3	0.398 (0.168–0.945)	0.031**
Anemia	40	1.7	13	0.6	0.850 (0.452–1.600)	0.615
Respiratory failure	13	0.6	69	3.0	15.503 (8.507–28.254)	0.000*
COPD	7	0.3	2	0.1	0.749 (0.155–3.617)	1.000
Cerebral infarction	20	0.9	4	0.2	0.522 (0.178–1.533)	0.229
CHF	14	0.6	11	0.5	2.081 (0.940–4.609)	0.065
Myocardial infarction	8	0.3	2	0.1	0.655 (0.139–3.094)	0.736
Vital signs/laboratory result						
High blood pressure	1,092	47.2	477	20.6	1.582 (1.289–1.942)	0.000*
SPO_2<90%	1,329	57.5	563	24.3	1.954 (1.494–2.556)	0.000*
Lymphocytes	885	38.3	485	21.0	2.830 (2.304–3.475)	0,000*
Leukocytes	447	19.3	261	11.3	1.902 (1.571–2.303)	0.000*
Thrombocytes	339	14.7	149	6.4	1.201 (0.965–1.494)	0.101
Neutrophils	1,069	46.2	534	23.1	2.911 (2.307–3.673)	0.000*
D-dimer	1,192	51.5	568	24.6	3.288 (2.510–4.306)	0.000*
Glucose	667	28.8	357	15.4	1.915 (1.593–2.303)	0.000*
Creatinine	787	34.0	403	17.4	1.935 (1.137–2.334)	0.000*
Hemoglobin	772	33.4	303	13.1	1.058 (0.881–1.270)	0.546
Demographics						
Gender (male)	877	37.9	383	16.6	1.367 (1.136–1.645)	0.001**
Age>65 years	72	3.1	54	2.3	2.059 (1.429–2.966)	0.001**

Note: *p<0.001 and **p<0.05 considered significant, DM: diabetes mellitus, SPO_2: peripheral oxygen saturation, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, OR: odds ratio, CI: confidence interval

validation instead of overfitting or data overlaps between the test and validation sets. Furthermore, this technique helped to decrease the deviation in prediction error and frequently used and recommended validation methodology in machine learning and data mining.[16]

Random forest was an effective machine learning algorithm to categorize the mortality risk in a study population of patients admitted to the PKU Muhammadiyah Gamping and PKU Muhammadiyah hospitals in Yogyakarta. This study was similar to other international studies, such as a study in Italy suggesting that random forest was the best machine learning with an ROC score of 88%,[17] and another study in Iran showed an ROC score of 83.6%.[18] The random forest algorithm is a popular ensemble learning method that exploits the combination of numerous decision trees in order to create accurate predictions. Employing an ensemble technique helps reduce overfitting problems and enhance the overall generalized performance. Random forests have been observed to exhibit computational inefficiency and prolonged training times when used to huge datasets.[19] Several international studies have shown different results on the best machine learning algorithm. A study conducted on the Korean population suggests that the decision tree algorithm is more effective at predicting the probability of death among COVID-19-infected patients compared to different algorithms, such as the support

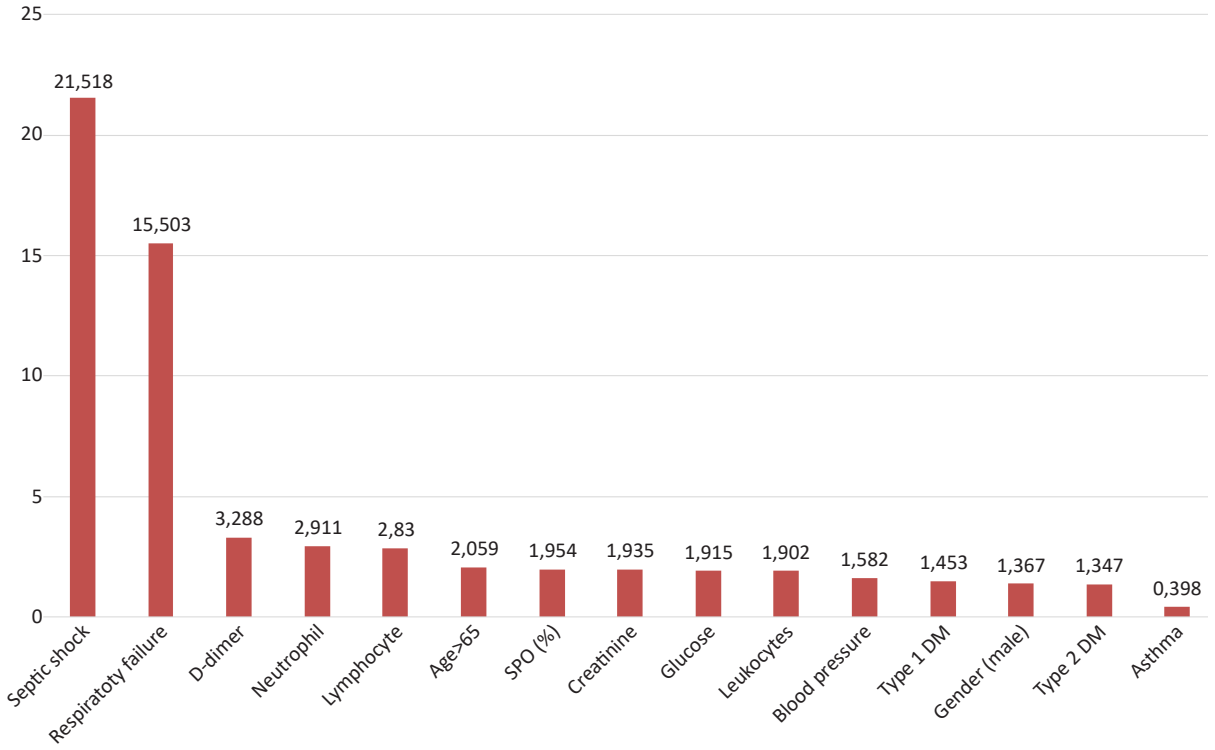

Figure 2 Odds Ratios of Top 15 Predictors based on Bivariate Analysis (p<0.05)

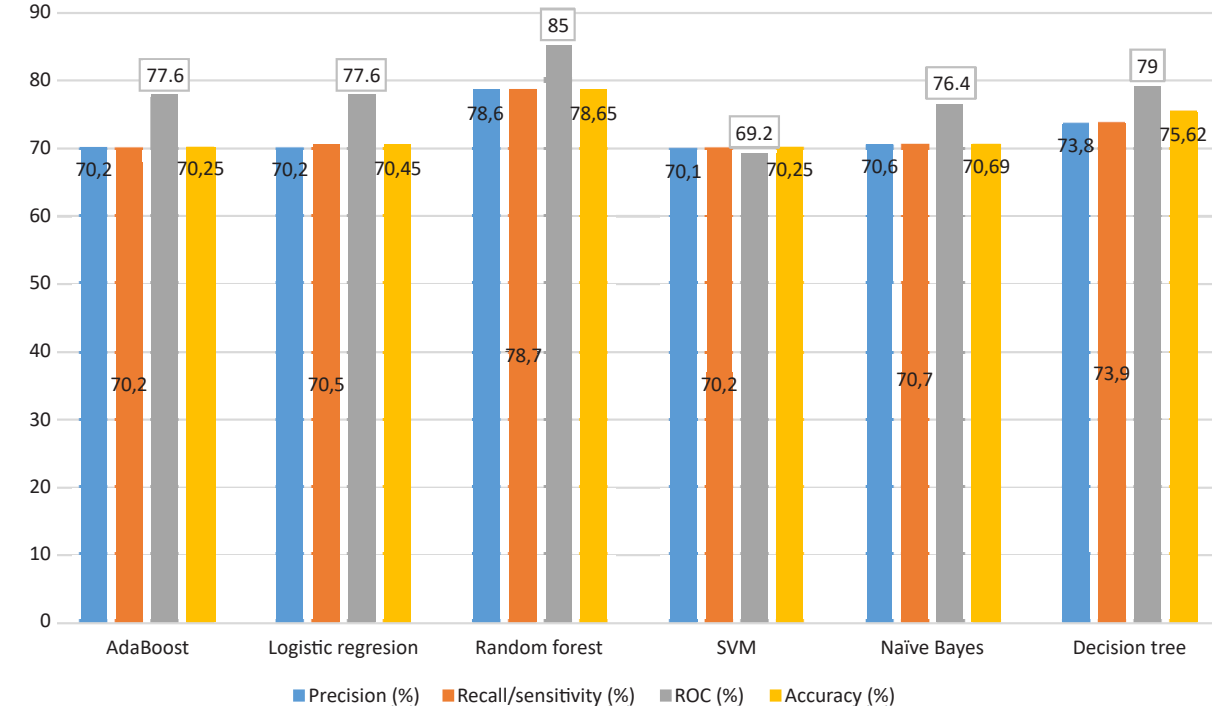

Figure 3 Visual Comparison of Machine Learning Algorithm Capabilities for COVID-19 Mortality Prediction

vector machine, naïve Bayes, logistic regression, random forest, and K-nearest neighbor.[20] The results could differ due to the differences in the datasets used and the features selected.[21]

In this study, the patient's age over 65 years was the main predictor and high mortality risk, significantly indicated here with a high odds ratio (OR=2.059, 95% CI=1.429–2.966). Other studies also suggest that older age predicts an increased mortality risk.[22] Comorbidities that are common among the elderly, including type 2 diabetes mellitus, high blood pressure, coronary artery disease, and pulmonary disease, are indicators of a poor prognosis, more significant mortality, and morbidity rates. The absence of symptoms in the older population and their ability to carry a significant viral load renders them a viable vector for viral transmission.[23] Additionally, odds ratios (OR=1.367, 95% CI=1.136–1.645) for men indicate a greater risk of mortality, which is consistent with a study conducted by Doerre and Doblhammer[24] that death rates are twice as high for men than for women in every age group. The expression of angiotensin-converting enzyme 2 (ACE2) receptors, which have a role in facilitating the entry of the SARS-CoV-2 virus and its transmission between humans, exhibits variations across individuals of various sexes. Estradiol has the potential to exert an effect on the expression of ACE2, a gene that is situated on the X chromosome. This chromosomal location may confer susceptibility to evading X-inactivation in females.

Septic shock was a high predictor in this study (OR=1.518, 95% CI=4.933–93.853). It is consistent with several international studies. An increased risk of death has been associated with respiratory symptoms, including respiratory failure and low oxygen levels (SPO_2<90%, see Table 3). It has been extensively researched in United States populations.[26]

In this study, comorbidities also had a minor impact on mortality risk prediction. These results are similar to another study[27] but only partially consistent with international studies, which have demonstrated that comorbidities play a significant role in risk prediction.[28]

Diabetes mellitus was the only comorbidity with an implication on mortality in this study. The odds ratios of types 2 and 1 diabetes mellitus were 1.347 (95% CI=1.055–1.721) and 1.453 (95% CI=1.110–1.903), similar to the meta-analysis carried out by Kumar et al.[29] Even though all types of diabetes mellitus have been linked to an elevated risk of in-hospital COVID-19-related mortality, our findings revealed that the risk was higher in type 1 diabetics than in type 2 diabetics. Various factors could explain this finding. Types 1 and 2 diabetes mellitus differ in terms of COVID-19-related mortality for a variety of reasons, including their distinct causes and pathophysiologies, patterns of complications or iatrogenic harms (such as hypoglycemia), treatments, intensity and duration of glycemia, and the effects of comorbidities either not taken into account in these analyses or were not appropriately considered.[30]

Among the laboratory features tested during admission, lymphopenia (<1 mg/dl) had an OR of 2.830 (95% CI=2.304–3.475), which matches the findings of a systemic review and meta-analysis.[31] Other significant factors including increased leucocytes (≥11 mg/dl), neutrophils (≥6 mg/dl), creatinine (≥1.2 mg/dl), and D-dimer (≥0.5 mg/dl) were shown to be mortality risk factors. These findings were similar to another international study.[32]

Conclusions

Independent predictors of mortality in patients with COVID-19 were age above 65 years, male, and diabetes mellitus. They have vital signs and laboratory tests: septic shock, respiratory failure, O_2 saturation, higher leucocytes, neutrophils, creatinine, and D-dimer. These parameters could be combined in a random forest machine learning model to provide a moderate-accuracy predictor of mortality with an ROC of 85%.

Conflict of Interest

None declared.

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RESEARCH ARTICLE

Development of a Qualitative Assessment Instrument for Cognitive Processes in Gaming Decision

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Abstract

Indonesia ranks 6th with the highest number of online gamers in Asia and 12th in the world gaming market. When online gamers become addicted, they lose the ability to halt or control their gaming behavior, leading to problematic behavior. Decision-making processes at the cognitive level are considered relevant in various addictive behaviors, including inappropriate gaming behavior. Exploratory research can be conducted using a qualitative technique, with data collected through in-depth interviews, to acquire an in-depth understanding of the comparison of the interaction process of each cognitive component in decision-making to play online games. This research was conducted in Bandung from December 2021 to December 2022. Steps are needed to develop guidelines that explore the functioning of affective and cognitive responses (coping, cognitive and affective bias, and craving and urge) and executive and inhibitory control. The guideline used a cognitive theoretical framework in addictive behavior, namely the I-PACE model, with a multidimensional theoretical basis. Through theoretical deepening, it was derived as a guideline divided into three main aspects, four sub-aspects, 32 main questions, and 36 probing questions.

Keywords: Cognitive process, decision-making, depth-interview guideline, qualitative method

Introduction

Indonesia ranks 6th with the highest number of online gamers in Asia and 12th in the world gaming market.[1] A report from DFC Intelligence showed that nearly 3.1 billion people, or about 40% of the world's population, play online games.[2] In addition, data from the Indonesia E-Sport Premier League (IESPL),[1] Indonesia's active online game players in 2019 were 62.[1] million people. This fantastic number shows that online gaming behavior has evolved into a social phenomenon. Online games are modern game that provides limitless winning and losing experiences, sophisticated narratives and characters to investigate, enormous open worlds to explore, and possibilities to communicate with other players.[3] Online games are intended to be long-playing applications, with game creators creating extremely engaging features that encourage players to stay involved in the game and limit their likelihood of abandoning the field. According to Ng and Wiemer-Hastings,[4] online game players spend more time playing games than offline game players, with the majority of the underlying reasons being that the gameplay characteristics of online games are perceived as more fun and satisfying, and they sometimes prefer playing online games to doing other activities in real life. Nowadays, many new types of games have more immersive, socially integrated, and financially rewarding features than previous games. In psychologically vulnerable people, these features open up opportunities for problematic gaming behavior or even addiction.[5]

A variety of factors influence a person's decision to play online games. King and Delfabbro[5] stated that there are three main factors behind the emergence of gaming behavior in enthusiasts (non-problematic) and harmful (problematic) gamers. Individual differences, external influences, and gaming-related factors are the three categories. As the only internal factor, individual differences are essential in developing problematic online gaming behavior. These include gender, age, personality traits and personal characteristics, comorbidities, low self-regulation and decision-making deficits, low self-esteem and self-efficacy, low levels of education, and interest in other things. The psychological traits of a person underlie vulnerability and can develop problematic gaming behavior.

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However, not all people who play games are susceptible to becoming addicted to all games. Problematic gaming behavior will emerge due to the interaction between the characteristics of the vulnerable player and the characteristics of the game properties.[6] One of the perspectives considered capable of understanding this problematic behavior is the multidimensional theoretically grounded Interaction of Person-Affect-Cognition-Execution (I-PACE) model, a synthesis of a wide range of theoretical approaches and empirical research results and is considered the most comprehensive to explain the emergence of problematic online behavior.[5]

Because this paradigm explains the importance of psychological and social elements in addition to biological factors. Brand et al.[7] underline the importance of diverse cognitive and affective processes in influencing recurrent decisions to play games despite long-term detrimental repercussions. There are four main components in examining the emergence of problematic gaming behavior based on the I-PACE model, namely predisposition (P), affective and cognitive responses (A and C), executive function, inhibitory control, and decision-making to play games (E) and the consequences of playing games. Predisposition refers to an individual's core characteristics that remain relatively stable throughout life. This component includes biopsychological constitution, psychopathological features, personality, social-cognitive, and motives for using the internet. Affective and cognitive responses to internal and external stimuli refer to changes in mood and thinking that follow exposure to gaming stimuli. This section comprises coping, internet-related cognitive biases, cue-reactivity, craving, the urge to regulate mood, and attentional biases. Executive function, inhibitory control, and gaming decision-making refer to the executive function deficits and response control that determine an individual's decision to play. Finally, the consequences of gaming pertain to positive experiences, satisfaction, and compensation arising from playing online games. The core idea of this theoretical model is that individuals who have a predisposition for addiction (to gaming) will seek gratification from gaming, which causes significant changes in the individual's emotional and cognitive responses to gaming activities. This then leads to habitual gaming behavior to compensate for the changes (arising from regular gaming), resulting in negative consequences. Various results from literature studies show that multiple determinants make gamers maintain their behavior to play games despite knowing the harmful consequences, such as impulsivity, weak self-regulation, and differences in personality type.[8–10] However, research exploring the potential of cognitive mechanisms in problematic online gaming behavior has yet to be widely conducted for clinical application.[11] This is reinforced by Nuyenz et al,[12] who stated that it is necessary to study cognitive processes in two groups of online game players (problematic and non-problematic) as a suggestion for further research. Based on literature studies conducted by the author, cognitive processes are widely measured through cognitive tasks such as the Stroop task, go/no-go task, cue reactivity task, negative priming task, and game of dice task.[13–17] In the author's view, an in-depth explanation of how the process of individual cognition and affective mechanisms in the emergence of gamers' decisions to play games is essential data. King and Delfabbro,[5] stated that mixed observations with qualitative studies and clinical case studies are needed to develop online game addiction research, strengthening the author's consideration of this study.

A qualitative approach will be used to gain an in-depth understanding of comparing the interaction process of affective and cognitive response (A and C) and executive and inhibitory control (E) on decision-making to play online games in problematic and non-problematic online game players. The purpose of the qualitative approach was to obtain a thorough and complete understanding of the phenomenon under study.[18] Of the many data collection techniques in the qualitative approach, interviews are the most frequently used technique for primary data collection because they provide a natural and comfortable atmosphere for participants.[19] Interviews in a qualitative approach are used to obtain in-depth information about participants' perceptions, thoughts, and meanings, where participants can express their points of view personally and freely. In this case, the interviewer must encourage participants to be fully involved through an interpersonal approach. However, if well prepared, the content of the interview can be on-topic and efficient. Qualitative researchers need to identify an appropriate line of questioning to stay on track and get to the main object of a research study.[20] To get in-depth, meaningful

data, the researcher chose a semi-structured interview format. Through this format, interviews will be conducted based on predetermined questions (guidelines). However, the interviewer can also ask more questions to clarify information. Thus, a master guide is required, which contains the questions to be asked. The interviewer can modify the questions' wording and order of questions and explore new avenues to obtain data according to the research objectives. In line with Taherdoost's[19] statement,this interview format allows rich data collection and new concepts to emerge. This means that the in-depth interview data collection method will provide a greater opportunity for researchers to explore the experience of playing online games. Identify the flow of questions, starting with designing a guide that meets the research objectives. There are three types of interview questions: main questions, planned follow-up questions (probes), and follow-up questions. Main questions focus on the main objective of the research and are usually the first question after the interviewer opens the interview. Planned follow-up questions, or probes or probing, are used to get more specific and detailed answers. These questions can also lead to important research concerns. Finally, follow-up questions are questions that the interviewer asks after hearing the participants' initial responses. This is also done to gain validity by encouraging participants to prepare more clarification on what the question/ issue means to them.[20] Specifically, six points serve as guidelines in designing the interview guide conducted by the researcher, namely: 1) relevance, that the researcher should dedicate sufficient time to analyze the required questions that are appropriate to answer the research objectives accurately; 2) phrasing the questions in simple and short sentences; that the researcher should phrase the questions in simple and short sentences to avoid any misunderstanding from the participants, for example by considering the participants' education level. Therefore, jargon and technical language are not recommended; 3) use language that is easy to understand; the use of language that is easy to understand can avoid the emergence of questions and bias; 4) use questions that are prompts and probes; these questions encourage participants to elaborate or provide further explanation. Probing questions can be applied with follow-up questions to get more details and clarifications, 5) writing final questions; these can be designed like "Is there anything else you want to say?" which can help add final details or forgotten points to the answer. These answers can be very open-ended, and adding these questions is very important. 6) starting with easy questions placing more challenging questions that may discourage participants from continuing at the end of the interview.[19–22]

Thus, based on the explanation above, it can be said that an instrument in the form of a guideline containing a list of open-ended questions is required to gather the information needed by the researcher so as not to get out of the original purpose of conducting the interview. This study compiled an interview guideline for qualitative assessment of the cognitive process in making online games to get an in-depth description of the decision-making process for playing games.

Methods

The qualitative research was conducted in Bandung from December 2021 to December 2022. It was approved by the Committee on Research Ethics at the Faculty of Psychology, Universitas Indonesia, with a Research Ethics Approval number 069/FPsi.Komite Etik/ PDP.04.00/2021.

The preparation of this in-depth interview guideline used the theoretical framework of the I-PACE model by Brand et al.,[7] and the characteristics of problematic online gaming behavior using the internet gaming disorder criteria based on the American Psychiatric Association,[23] as the primary reference to be derived into several question items.

The components of the I-PACE model are 1) predisposing, 2) affective and cognitive response, 3) executive and inhibitory control, and 4) consequences of gaming behavior or other internet activities. The characteristics of internet gaming disorder include 1) preoccupation, 2) withdrawal, 3) tolerance, 4) loss of control, 5) loss of non-gaming interest, 6) gaming despite harm, 7) deception of others about gaming, 8) gaming for escape or mood relief, and 9) conflict/ interference due to gaming.[5,23]

After compiling the question items, a content validity test was conducted to ensure researchers' accuracy in reducing related theoretical concepts into question items. This test was conducted by consulting and discussing with two experts. One

expert has experience in clinical psychology and qualitative research, while the other has cognitive process expertise. The input provided was in the form of assessment and feedback regarding the relevance of the theory to the items, word selection, and sentence construction. Researchers used this input data to refine the instrument.

The subsequent step was to conduct a pilot study with a small group of participants with similar characteristics to the research participants, specifically five individuals who enjoy playing online games. The comments and feedback obtained by the researcher from the small group helped the researcher develop the interview guidelines. In line with Doody and Noonan,[21] Bolderston,[20] and Turner III,[22] comments from the pilot group can be utilized, such as the researcher's accuracy in sentence construction or confusing question wording. The researcher then examined the questions by question, considering these comments, and made modifications (if necessary).[20–22]

To determine whether the questions covered the aspects of the theoretical construct, the researcher followed and answered the following points of the pretesting protocol: 1) whether the questions can provide the data needed to answer the research questions, 2) whether the questions are easy enough to understand, 3) whether the flow of questions within the same topic or from one topic to another is appropriate, 4) whether the language used is appropriate for the educational level of the participants, 5) whether the set of questions is comprehensive, or whether any topics are missing.[20]

Results

Researchers carried out several stages in developing this qualitative assessment instrument. First, the researchers employed the internet gaming disorder classification concept to generate an interview guide comprising eight primary questions. Next, utilized the I-PACE framework to construct the question items, with the measured components including 1) predisposition, 2) affective and cognitive responses, 3) executive function, and 4) consequences of playing games. Overall, we developed 32 main question items and 38 probing questions in this qualitative assessment design.

Specifically, the theoretical framework of question item references, aspects, sub-aspects, and question items are presented in Table.

Discussion

The interview guide, as an instrument for qualitative assessment of cognitive processes in decision-making to play online games, was divided into two main aspects, namely 1) information related to gaming behavior, 2) information related to aspects of the I-PACE model, and was prepared using the principles of interview guide preparation from Taherdoost[19] and pretesting protocol from Bolderston.[20]

In the first aspect, information related to online gaming behavior, was derived from the classification of internet gaming disorder; namely 1) preoccupation: constantly thinking about gaming activities and internet gaming becomes a dominating activity every day, 2) withdrawal: feeling angry, anxious or sad when unable to play games, 3) tolerance: increased need to play games, 4) loss of control: failure to control oneself not to play games, 5) loss of non-gaming interest: loss of interest in hobbies or other pastimes due to gaming, 6) gaming despite harms: continuing to play online games despite knowing the risk of problems that will arise, 7)deception of others about gaming: lying to family, therapists and others about the amount of time used to play games, 8) gaming for escape or mood relief: using online games to avoid or reduce negative moods/ feelings, 9) conflict/interference due to gaming: losing meaningful relationships, work, education or career opportunities due to playing online games.

Furthermore, various research results related to risk factors for problematic gaming behavior were used, namely individual differences and gaming-related factors. As the only internal factor, individual differences are essential in developing problematic gaming behavior. These include gender, age, personality traits and personal characteristics, comorbidities, low self-regulation and decision-making deficits, low self-esteem and self-efficacy, low levels of education, and interest in other things. The external factors explain how social and environmental factors can lead a person to display problematic online gaming behavior. These include peer influence, accessibility to online games, family influence, and traumatic events, on factors directly related to the online game itself (gaming-related factors), including the type of game and game features. Based on these classifications and theories, eight main questions and 18 probing questions were derived.

Table Depth Interview Guideline Cognitive Processes in Decision-Making to Play Online Games

Aspect	Sub-aspect	Main and Probing Question	Theoretical Framework Reference
Information related to gaming behavior		1. How did you get to know and start playing online games? 2. How long have you been playing? 3. What games (type and name) have you played? • From these games, what do you like the most? • What are the reasons for this? 4. What is the average length of time spent gaming in a session? 5. How often do you play games? • In one day? • Do you log in every day? • In a week? 6. What time of day do you usually choose to play games? • Is it morning/afternoon/evening? • What is the reason? 7. What feelings do you experience when playing online games? 8. Has playing online games affected your life positively or negatively in this aspect? • Self-care: bathing, eating • Social relations: • Do you have a new circle of friends in online games? • How do you perceive the difference between making friends in the game and the real world? • Purpose of life • Has it changed your goals? • How does it affect focus in life? • Productivity • Is it as a student? • Is it as a worker?	1. Classification of Internet Gaming Disorders from DSM-5[23] • Preoccupation • Withdrawal • Tolerance • Loss of Control • Loss of non-gaming interests • Gaming despite harms • Deceptions of others about gaming • Gaming for escape or mood relief • Conflict/interference due to gaming 2. Problematic gamers Theories related to risk factors of problematic gamers: Individual differences • Peer influences: Kowert et al.[24] • Personal characteristics: Billieux et al.,[8] Lee and Chao,[25] Rho et al.[26] • Self-regulation in managing both timing and amount of play: Seay and Kraut[27] Gaming related factors • Types of games: Eichenbaum et al.[28] • Game features: Wood and Griffiths[29]
I-PACE	Affective and cognitive bias	1. What comes to your mind when you hear about online gaming? 2. When you are enjoying playing a game, what do you feel? 3. Can you tell me how gaming affects your mood or feelings? 4. Do you have other hobbies/favorite activities besides gaming? • How do you balance playing online games with these other activities? 5. How do you deal with/counter other people's judgments about your gaming habits? 6. Do you accept them, or do you counter them? What are the reasons for this?	The main framework used is the Interaction of Person-Affect-Cognition-Execution (I-PACE) model of internet use disorders developed by Brand et al.[7] To deepen these aspects, the researcher used the following literature: Cognitive processes, in general • Cognitive and behavioral model in problematic internet use: Davis[30] • Cognitive approach to gaming: King and Delfabbro[31] • Cognitive psychology in internet gaming addiction: King and Delfabbro[31] • Irrational thinking regular gamblers: Delfabbro and Winefield[32] • Cognition: Kahnemann[33] • Cognitions in problematic game behavior: Haagsma et al.[34] • Mind at play: Loftus and Loftus[35] • Dysfunctional cognition in online gaming: Marino et al.[36] Cognitive bias • Cognitive bias pada gamers: Decker and Gay[37] • Role of cognitive bias in gamblers: Griffiths[38] • Cognitive distortion: Huanhuan and Su[39] • Attentional bias and disinhibition: Van Holst et al.[40] Decision making • Deficient decision making: Liu and Peng,[9] Schiebener and Brand[41] • Poorer decisions under risky conditions: Yao et al.[42] • Less able to delay gratification for a larger reward: Pawlikowski and Brand[17] • Decision-making style in internet gaming disorder: Ko et al.[43] • Impaired decision making in internet gaming addiction: Wang et al.[44] • Decision making and related process: Schiebener and Brand[41] Coping strategy • Kardefelt-Winther[45] • Snodgrass et al.[46] • Boyd[47] • Blinka and Smahel[48] Inhibitory control • Tiego[49] • Wilcockson and Pothos[50] Craving and urge • Abstinence-induce IGD symptoms: Kaptsis et al.[51] • Craving for internet gaming: King and Delfabbro[31] • Motivation for gaming: Yee[52] • Cognitive-behavioral models: Dong and Potenza[53]
	Specific coping style	1. What do you usually do when you have a problem (stress, demands, or many tasks)? • What is the reason? 2. Is online gaming an option to do when you are experiencing uncomfortable feelings? • What is the reason for this? • Can you tell us when? 3. When your game session happens, can you tell us how you feel? • How did you overcome that feeling? 4. Have you ever felt judged or stigmatized (negatively) as a gamer? • How do you respond to that?	
	Craving and urge	1. When did you want to play a game? • What made you want it so much? • How did you respond to that? 2. When you are in a situation where it is not possible to play games (e.g., traveling, exam week, sick) • What comes to your mind? • And then what happens? 3. Have you ever had a situation where you felt like you could not stop gaming, even though you wanted to? • What was going through your mind at that time? • What did you feel at that time? 4. Have you ever felt that gaming was taking up time in your life? Can you tell me? • Can you tell me what happens to you and how you feel when you hear stories about other people's experiences playing games or advertisements for new games?	
Executive and inhibitory control	Executive function and response control	1. Does that prevent you from playing games? 2. Has it ever crossed your mind to stop gaming? • If Yes, when and why • If No, why 3. Did you take a break or even stop playing games? 4. Have these things ever made you break or even quit? Such as feelings, situations, or other influences? 5. How do you manage your time between gaming and other priorities like school or work? • Have you ever had trouble managing that time? Can you tell me? 6. Are there any ways that you monitor your gaming habits, such as keeping track of your playing time or setting a limit on the money you spend? • If so, can you tell us about it? • If not, what is the reason?	
Decision to gaming		1. What usually makes you want to play games? Is it a feeling/situation/hearing a sound/seeing a picture? Are there any other influences? 2. What are some things that could cause you to decide to stop playing the game even though you could have continued playing it at that time? What were the influencing factors? 3. What are some of the things that could have caused you to decide to keep playing the game even though you could have kept playing the game at that time? 4. What were the influencing factors? 5. How do you balance your desire/liking to play online games with the negative impacts you will face?	

In the second aspect, information related to aspects of the I-PACE model was derived from the I-PACE model framework.[7] The components of this model are 1) predisposition (P), which refers to the main characteristics (core) of individuals that are relatively stable throughout their lifespan. These include the biopsychological constitution, psychopathological features, personality, social-cognitive and internet use motives, and 2) affective and cognitive responses (A and C) to internal and external stimuli, which refers to changes in mood and thinking that follow exposure to gaming stimuli. This component includes coping, internet-related cognitive biases, cue-reactivity and craving, the urge to regulate mood, and attentional biases; 3) executive functioning, inhibitory control, and decision-making to game (E); refers to deficits in executive functioning and control over responses that determine an individual's decision to game, 4) consequences of gaming. Refers to positive experiences, satisfaction, and compensation arising from playing online games, which was divided into four sub-aspects, namely attentional and cognitive bias, specific coping style, craving and urge, executive function and inhibitory control, and decision to game. The predisposing component was assumed to be measurable from the first aspect (individual differences and gaming-related factors) described in the previous paragraph.

Attentional and cognitive bias is the behavioral tendency to more quickly, efficiently, or accurately remember, recognize, and respond to stimuli associated with a particular behavior; based on this definition, two main questions and two probing questions were derived.

Furthermore, specific coping styles are repeated cognitive and behavioral responses to manage stressful situations and related emotions; based on this definition, four primary and five probing questions were derived.

On craving and urge: craving refers to the affective experience of image and verbal thought accompanied by the sensation of urge; based on this definition, five primary and six probing questions were derived.

Then, in the sub-aspect of executive function and inhibitory control, executive function is defined as cognitive control over thoughts, actions, and emotions directed at a goal. At the same time, inhibitory control is the ability to inhibit responses to irrelevant stimuli while cognitively pursuing a goal. Based on this definition, six main questions and five probing questions were derived.

The last sub-aspect, decision to game, is choosing whether to game or not; based on this definition, four primary and four probing questions were derived.

The researcher developed 32 main question items and 38 probing questions to qualitatively assess cognitive processes in gamers' decision-making to play online games. This guideline was developed as a guideline for conducting semi-structured interviews. Thus, the interviewer can modify the wording of questions and the order of questions and develop the interview until in-depth data is obtained and the initial objectives of the interview can be achieved. Prior research primarily relied on explicit measures, including various cognitive tasks, to gain insight into the cognitive processes involved in gamers' decision-making when choosing to play games.[13–17] However, qualitative research methods such as interviews are also essential to achieve a comprehensive understanding of these processes. By utilizing qualitative studies, a more profound comprehension of experiences in the context of real-life situations can be garnered.[54] This aligns with past research findings indicating that utilizing qualitative methods provides a more comprehensive understanding of gaming behavior.[34] Therefore, the guideline developed in this study offers an alternative approach to gathering qualitative research data on online gaming behavior.

Conclusions

The need for a thorough evaluation of the factors influencing an individual's decision to play games has become increasingly pressing, given the rise in the number of online gamers in Indonesia. Researchers have developed a qualitative assessment tool as an alternative method of measuring the cognitive processes of online gamers. The development process of this evaluation instrument involved several stages. First, researchers compiled eight main questions into an interview guide using the concept of internet gaming disorder classification. Next, the I-PACE framework was utilized to construct the question items, with the measured components including 1) predisposition, 2) affective and cognitive responses, 3) executive function, and 4)

consequences of playing games. This qualitative assessment design had 32 primary question items and 38 probing questions.

Conflict of Interest

There is no conflict of interest in this study.

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RESEARCH ARTICLE

Relationship between Self-Management Behavior on the Severity of Artery Coronary Disease

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Abstract

Coronary artery disease (CAD) is a non-communicable disease that is the main cause of death and loss of disability-adjusted life years (DALYs) globally. Patients can experience various complications that affect the severity of the disease. Various factors, especially self-management behavior, can influence the severity of CAD patients. This study aimed to determine the relationship between self-management behavior and the severity of CAD in Dr. Zainoel Abidin Regional General Hospital Banda Aceh. This study used a cross-sectional design from March 28 to May 19, 2023. The sample consisted of 221 CHD patients who had undergone coronary angiography, were selected using purposive sampling, and met the inclusion and exclusion criteria. Data was collected through guided interviews using the self-management scale (CSMS) and syntax score. Data were analyzed descriptively and inferentially. Data analysis showed a significant relationship between self-management behavior and the severity of CAD. Daily life management (p=0.000, OR=5.334), disease management (p=0.000, OR=2.633), and emotional management (p=0.000, OR=2.047) were associated with the severity of CAD. Logistic regression indicated that daily life management was the most dominant factor associated with the severity of CAD (OR=5.334). Good daily life, disease, and emotional management can help reduce the risk of complications and improve the prognosis of CAD patients. Self-management behavior, particularly daily life management, is significantly related to the severity of CAD in Dr. Zainoel Abidin Regional General Hospital patients.

Keywords: Behavior, CAD, self-management

Introduction

Coronary artery disease (CAD) is the most common cardiovascular disease. CAD is the leading cause of death and loss of disability-adjusted life years (DALYs) globally. A large number of CAD problems occur in low- and middle-income countries, with nearly 7 million deaths and 129 million DALYs each year. In 2021, CAD accounted for 8.9 million deaths and 164.0 million DALYs.[1]

Furthermore, data from the medical records of the Aceh Regional General Hospital show that in 2020, the number of cardiac catheterization patients was 667 patients, increasing in 2021, reaching 899 patients, and this number decreased in 2022 to 777 patients but those diagnosed with CAD and having coronary examinations angiography in 495 patients. Heart disease services at the hospital have been carried out using adequate facilities and health workers, and pharmacological and medical management has also been excellent. However, the number of patients with CAD is still high, and many suffer co-morbidities such as diabetes, hypertension, and increased low-density lipoprotein (LDL). The behavior of CAD patients in independent self-management at home can influence this condition.

The severity of CAD can be reduced with good self-management by the sufferer. Self-management is a dynamic process in which sufferers actively manage chronic disease independently. Many people with chronic illnesses have poor self-management skills. It will lead to poor disease control and quality of life.[2]

Several studies related to self-management in chronic diseases, such as research on the effectiveness of self-management on the quality of life of patients with type 2 diabetes mellitus, show that self-management effectively improves the quality of life among diabetes patients.[3] Other research on self-management and self-efficacy in chronic kidney failure patients undergoing hemodialysis. This research shows that good self-management behavior can increase self-efficacy

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for the better, too.[4] Furthermore, research on self-management to improve the quality of life of people living with HIV also found that self-management programs improve the overall welfare of people living with HIV.[5]

Referring to several studies on self-management in chronic diseases that have been described above, the same thing applies to patients with CAD because they are also chronic diseases. Good self-management can reduce the risk of recurrent CAD attacks. There are many risk factors for CAD. Modifiable risk factors are high blood pressure, high blood cholesterol levels, smoking, diabetes, being overweight or obese, lack of physical activity, unhealthy diet, and stress. The non-modifiable factors are age, sex (men are generally more at risk for coronary artery disease), family history, and race.[6]

Self-management behavior in CAD patients is based on three main aspects: managing daily life, disease management, and emotional management, and combined with specific disease management skills that need to be mastered by CAD patients, such as first aid technology and management of angina symptoms. Daily life management includes managing habits, such as smoking, alcohol, and diet, and general life management, such as regular work and rest or activity. The disease management domain includes symptom management, first aid management, disease knowledge acquisition management, and medication adherence management—emotional management domains such as relaxation, self-direction methods, and others.[7]

Many studies on self-management in patients with chronic diseases have been carried out. However, there is very little research on self-management in patients with CAD. This study aims to determine the relationship between the components of self-management behavior and the severity of CAD.

Methods

This study used a cross-sectional study design. The samples are CAD patients who have undergone coronary angiography at Aceh Regional General Hospital. The sample size is determined based on the proportion formula, and a total of 221 people is obtained. The sample selection technique used a purposive sampling method, which was then determined based on the inclusion criteria were CHD patients who had undergone coronary angiography, patients in a stable and compos mentis condition, patients who agreed to be studied, and were cooperative, able to read and write and had good hearing. Meanwhile, the exclusion criteria were patients who experienced shortness of breath, chest pain, and impaired mobility.

The data collection instrument used was the coronary artery disease self-management scale (CSMS), which was carried out using guided interviews and syntax scores to measure the severity of CHD as seen from the patient medical record. CSMS was adapted from Zhu et al.,[7] and the score syntax was adapted from Askin and Tanriverdi.[8]

This research was carried out at the Catheterization Laboratory and Cardiac Clinic at Dr. Zainoel Abidin Regional General Hospital Banda Aceh. Data was collected from March 28 to May 19, 2023. The data collection results were analyzed using descriptive statistics followed by inferential statistics and the chi-square test to determine the partial relationship between one independent and dependent variable. Another inferential statistic is the binary logistic regression with the stepwise method, which is to know the simultaneous relationship of all independent variables with the dependent variable and to find out the most dominant independent variable related to the dependent variable.

This research was carried out after obtaining a certificate of passing the ethical test from the Ethics Committee of Dr. Zainoel Abidin Regional General Hospital Banda Aceh on March 2, 2023, with research code 23-02-038.

Results

Characteristics of CAD patients treated at Dr. Zainoel Abidin Regional General Hospital Banda Aceh can be seen in Table 1.

Table 1 shows that of the 221 CAD patients who did coronary angiography, as many as 159 people (71.9%) aged 41–65 years (mid-adult), 175 people (79.2%) were men, 104 people (47.1%) had secondary education, 73 people (33, 0%) work as entrepreneurs, 156 people (70.6%) earn <Rp3,280,000, 180 people (81.4%) are married, 175 people (79.2%) had CAD >5 years, 94 people (42.5%) had >2 rings installed, 129 people (58.4%) had diabetes mellitus as a co-morbidity, 78 people (35.3%) had high total cholesterol

Table 1 Sociodemographic Characteristics of CAD Patients

Characteristics	n=221 (%)
Age (years)	
Young adults: 19–40	12 (5.5)
Mid-adult: >40–65	159 (71.9)
Elderly: > 65	50 (22.6)
Gender	
Male	175 (79.2)
Female	46 (20.8)
Last education	
High	92 (41.6)
Intermediate	104 (47.1)
Basic	25 (11.3)
Occupation	
Civil servant	30 (13.6)
Contract employee	1 (0.5)
BUMN employee	1 (0.5)
Retired	34 (15.4)
Self-employe	73 (33.0)
Farmer	45 (20.4)
Housewife	37 (16.7)
Income (rupiah)	
≥3.280.000	65 (29.4)
<3.280.000	156 (70.6)
Marital status	
Married	180 (81.4)
Divorced alive	4 (1.8)
Divorced dead	37 (16.7)
Long suffered from CAD (years)	
≤5	46 (20.8)
>5	175 (79.2)
Number of rings	
≤2	127 (57.2)
>2	94 (42.5)
Associated disease	
Diabetes	129 (58.4)
Hypertension	42 (19.0)
Diabetes and hypertension	38 (17.2)
Other	12 (5.4)
Total cholesterol	
Normal	74 (33.5)
Close to normal	69 (31.2)
High	78 (35.3)
Body mass index	
Underweight	1 (0.5)
Normal weight	35 (15.8)
Overweight	123 (55.7)
Obesity	62 (28.1)

values, 123 people (55.7%) were overweight and 191 people (86.4%).

Table 2 shows that the majority of components of self-management behavior daily life management are very good with 140 people (63.3%), disease management with 116 people (52.5%), and emotional management with 94 people (42.5%).

Table 2 Distribution of Self-Management Behavior Components in CAD Patients

Components Self-Management Behavior	n=221 (%)
Daily life management	
Very good	140 (63.3)
Good	41 (18.6)
Enough	32 (14.5)
Bad	8 (3.6)
Disease management	
Very good	116 (52.5)
Good	68 (30.8)
Enough	31 (14.0)
Bad	6 (2,7)
Emotional management	
Very good	72 (32.6)
Good	94 (42.5)
Enough	49 (22.2)
Bad	6 (2.7)

Table 3 shows that most coronary artery disease severity is low, with 191 people (86.4%) and moderate 30 people (13.6%). Table 4 shows the relationship between daily life management, disease management, and emotional management with the severity of CAD.

Table 3 Distribution of Coronary Arterial Disease Severity in CAD Patients

Coronary Arterial Disease Severity	n=221 (%)
Low	191 (86.4)
Moderate	30 (13.6)

Table 4 Relationship between Self-Management Behavior Components and CAD Severity in CAD Patients

Components Self-Management Behavior	CAD Severity
Daily life management	0.000
Disease management	0.000
Emotional management	0.000

Table 5 Results of CAD Severity Predictor Analysis

Factors	B	OR	p	95% CI	
				Lower	Upper
Daily life management	1.674	5.334	0.001	2.003	14.201
Disease management	0.968	2.633	0.050	0.999	6.939
Emotional management	0.717	2.047	0.048	1.007	4.163
Constant	5.758	0.003	0.000		

Table 4 shows that daily life management (p=0.000), disease management (p=0.000), and emotional management (p=0.000) are associated with CAD severity. Table 5 shows an analysis to determine the simultaneous relationship between daily life management, disease management, and emotional management with the severity of CAD using binary logistic regression with the stepwise method.

The results of the analysis in Table 5 show that daily life management (p=0.000, OR=5.334), disease management (p=0.000, OR=2.633), and emotional management (p=0.000, OR=2.047) were simultaneously associated with CAD severity. Daily life management is the most dominant factor associated with CAD severity with OR=5.334, or daily life management is associated with CAD severity of 5 times.

Discussion

CAD severity is influenced by various sociodemographic factors, namely age, gender, and education. Old age is an independent risk factor for cardiovascular disease in adults, but this risk is accompanied by additional factors, including frailty, obesity, and diabetes.[9–11] In addition, socioeconomic factors such as income, occupation, and education level contribute to the general population's risk of adverse cardiovascular events.[12] Low educational background is an independent predictor in CAD patients undergoing angiography.[13] In addition, many risk factors influence CAD severity,[6] especially diabetes mellitus, which increases the risk of CAD.[14] Habits or daily lifestyles significantly affect the health of individuals. Lifestyle has been shown to influence the risk of CAD severity in patients with irreversible CAD risk factors.[15] This study found that, for the most part, CAD patients have carried out daily life management very well. Furthermore, it is also known that CAD patients who carry out daily life management well experience low CAD severity. Based on these results, it can be concluded that there is a significant relationship between daily life management and the severity of CAD.

Other research has suggested a relationship between self-management behavior and the incidence of CAD. Most CAD patients have low self-management scores. Daily life management has the highest average score compared to disease and emotional management.[16] Aspects of daily life management most often not adhered to by CAD patients are physical activity, maintaining a healthy diet, and weight loss.[17]

A healthy lifestyle, modifying risk factors, and medication adherence are critical to preventing death and recurrence in individuals with CAD. Previous studies have revealed the preventive effects of lifestyle modifications, including smoking cessation, exercise, healthy diet, and exercise, on mortality among patients with CAD. Another systematic review also reported that smoking cessation can reduce the risk of death and myocardial infarction in CAD patients by 30%.[18]

Healthy lifestyle behavior can reduce the risk of CAD severity, which has been proven through various studies. Risk reduction through behavior in CAD patients is essential in mediating health conditions after coronary angioplasty. By maintaining healthy physical activity, CAD patients who engage in physical activity can significantly reduce mortality and other cardiovascular risks.[19]

Based on the results of this study and the discussion that has been described, good daily life management will affect the severity of CAD. In contrast, increased non-compliance in carrying out good day-to-day life management will increase the severity of CAD.

Disease management is the concept of reducing health care costs and improving the quality of life of individuals with chronic conditions by preventing or minimizing the effects of disease through integrated care.[20] The results of this study show how CAD patients carry out

disease management very well. Furthermore, it is known that CAD patients who carry out disease management well experience low CAD severity. Based on these results, it can be concluded that there is a significant relationship between disease management and CAD severity.

Related research suggests a relationship between disease management, namely adherence to taking medication and controlling risk factors for cardiovascular disease.[21] A high level of adherence to antihypertensive therapy and controlled blood pressure is a form of disease management to prevent the severity of CAD.[22] Cardiovascular medications are essential for the secondary prevention of CAD. However, the cardiovascular effects of drugs may depend on optimal patient adherence. Compliance with taking medication is defined as the extent to which a patient takes medication as prescribed by a health care provider. In clinical practice, medication nonadherence is one of the main factors reducing the effectiveness of drug therapy in CAD patients.[23]

The main factors for preventing CAD recurrence are health behavior practices in disease management in CAD patients, such as regular and continuous drug therapy, low-fat, low-sodium, and low-cholesterol diets, regular exercise, smoking cessation, follow-up examinations, and adherence to treatment plans.[24] Based on the results of this study and the discussion described, it can be concluded that disease management is related to the severity of CAD patients through the level of adherence of CAD patients to treatment and medical examinations.

The management of problematic emotions (including anger and anxiety) plays a significant role in physical ailments such as cardiovascular disease. Many studies have examined the relationship between personality influences and heart disease.[25] The results of this study show CAD patients carry out emotional management well. Furthermore, it is known that CAD patients who carry out emotional management well experience low CAD severity. There is a relationship between emotional management and the severity of CAD.

The conclusion of this study is in line with studies that say one of the factors that influence the severity in patients with heart disease is negative emotions such as anger, which can exacerbate the disease.[25] Intense emotions, significantly negative emotions such as hostility, anger, depression, and anxiety, can trigger CAD.[26] Stress is also one of the most common predisposing factors experienced by people with CAD. The relationship between anxiety and CAD has been the subject of several studies, most of which show that stressful events are associated with CAD. Sudden and profound emotional stress can precipitate acute heart failure in individuals with CAD.[27]

Furthermore, emotional management in CAD patients is also influenced by co-morbidities such as diabetes. The results of the study said that patients with type 2 diabetes mellitus had a higher risk of depression and suffered from high levels of emotional stress.[28] Anxiety and fear are the most common emotional disturbances in diabetes patients, which the results of many studies have confirmed. Studies also show that depression in diabetes patients has been associated with an increased risk of vascular complications, poor glycemic control, and nonadherence to medication and self-management behaviors.[29]

Behavioral risk reduction in CAD is essential in mediating health conditions after coronary angioplasty. However, many patients with CAD need more critical knowledge about the role of behavioral management (e.g., physical activity) in the secondary prevention of CAD severity.[19]

CAD patients who engage in physical activity can achieve a significant reduction in the risk of death from cardiovascular disease. This statement shows that of the three constructs of self-management behavior, daily life management is the most important thing to prevent the severity of CAD.[16]

Daily life management in CAD patients is related to maintaining daily living habits, including physical activity. However, the vast majority of patients with CAD do little of this. CAD patients often do not engage in sustained physical activity or other health behaviors consistently over time and have high levels of poor adherence to health maintenance.[30]

Nearly two-thirds of patients with CAD do not engage in physical activity. Studies show that among people hospitalized for CAD, physical activity levels increase initially after discharge and decrease around 2–4 months after discharge. CAD patients participating in exercise-based cardiac rehabilitation programs in all age groups experienced a decreasing trend in exercise over time—only 22% of people adhered to the guidelines after 12 months.[31]

Conclusions

The results of this study conclude that daily life management is most related to severity in CAD patients undergoing coronary angiography. Good daily life management will reduce the severity of CAD patients. CAD patients need to make lifestyle modifications to be healthier by not smoking, eating a healthy diet, and exercising while adhering to the treatment program.

Conflict of Interest

There is no conflict of interest among all the authors in this study.

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RESEARCH ARTICLE

Arbovirus Detection of Adult Female *Aedes aegypti* for Dengue Surveillance: a Cohort Study in Bandung City, Indonesia

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Abstract

Dengue surveillance is an important activity to prevent dengue outbreaks. This activity becomes a significant challenge for the region with limited logistic capabilities. Developing a simple mathematical model to predict the possibility of dengue incidence provides a reliable early warning system. This study compared the correlation between vector (adult female *Aedes aegypti*) and arbovirus detection on a vector to dengue incidence, which generalized linear mixed models tested. The incidence of adult female *Aedes aegypti* and dengue fever cases were interpolated through third-power inverse distance weighting (IDW). A spatial correlation between female *Aedes aegypti* incidence and dengue incidence was obtained from polynomial regression. Collection sites were 16 villages in Bandung city, one of the significant dengue endemic areas in January–December 2017. A total of 8,402 mosquitoes of *Aedes aegypti*, *Aedes albopictus*, and *Culex* sp., with 17% belonging to *Aedes aegypti* as the subject of the dengue virus (DENV) infection test. Data analysis only showed a weak correlation between the numbers of adult female *Aedes aegypti* and dengue incidence. On the other hand, there is no correlation between positive dengue infection of vector and dengue incidence. This study highlights the importance of constant arbovirus surveillance and integrated surveillance methods on all possible dengue vectors to develop an early warning system for dengue incidence.

Keywords: *Aedes aegypti*, arbovirus detection, dengue, Indonesia, surveillance

Introduction

Over the tropical and subtropical regions, *Aedes aegypti* mosquitoes are widely distributed as the vector of arboviruses such as dengue, chikungunya, Zika, and West Nile virus.[1–3] *Aedes aegypti* is endemic throughout the tropical and subtropical regions. However, the insect started invading new geographic locations such as Europe for the last 50 years.[4,5] The transmittance of the dengue virus through *Aedes aegypti* caused approximately 390 million infections a year in 128 countries,[6] especially Asia,[7] and caused a significant economic and social burden.[8] In Indonesia, dengue has been endemic since the first case in 1968, and it has been spreading to all regions in Indonesia, including West Java.[9] Among Indonesian cities, dengue incidences in Bandung city of West Java are considered higher than in other cities. The total number of reported dengue cases in Bandung city ranged from 3,000 to 6,000 cases annually between 2007 and 2016.[10] The proportion of confirmed serology from febrile episodes ranged from 7.6 to 41.8% annually, while the average incidence rate of dengue lies was 17.3 cases/1,000 per person (43 times higher than the national average).[11]

Dengue cases could be reduced by improving detection and prediction through active surveillance.[12] However, instead of active surveillance, passive surveillance has been a widely accepted standard for dengue surveillance in many countries. Since passive surveillance highly depends on the individual seeking clinical treatment, under-reporting dengue cases is highly common for regions with limited medical facilities.[4] Thus, to overcome monitoring and evaluation problems, developing surveillance methods with predictive power on epidemic risk based on entomological information is needed.[13]

The dengue virus is transmitted through the bites of several vector mosquitoes infected. It transmits the virus through the ovarium, transovarial transmission, or the salivary gland.[14] The virus is infectious and transmissible to humans bitten by mosquitoes in adulthood.[15]

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arbovirus surveillance is one of the most vital components in dengue mitigation.[16] This method has been applied for the early detection of potential outbreaks and to identify new arbovirus agents.[17,18] Detecting the circulation of the dengue virus in mosquitoes could prevent future outbursts of dengue disease, especially in regions with the co-circulation of multiple arboviruses.[19,20]

Initially, arbovirus detection in mosquitoes was based on the viral antigen, using enzyme-linked immunoabsorbent assay (ELISA) or immunofluorescence assay (IFA). However, it takes time to analyze the samples from remote locations immediately and logistical and cost issues. Molecular-based assays to detect viral RNA in mosquitoes have been preferable as they allow the detection of viruses even after seven days under tropical conditions.[16] Therefore, our study prefers arboviral RNA detection for arbovirus surveillance in mosquitoes.

This paper aims to provide background information on the distribution and impact of *Aedes aegypti* mosquitoes as vectors for arboviruses, particularly dengue, in tropical and subtropical regions. It emphasizes the global spread of *Aedes aegypti* and its invasion into geographic locations. In this study, we compared the spatial incidence of female *Aedes aegypti* and dengue fever cases from 16 villages in Bandung city, Indonesia, to find the correlation between them. The collected female *Aedes aegypti* mosquitoes from those 16 villages were further analyzed for the presence of arboviral RNA to test the hypothesis on the correlation of arbovirus infection on *Aedes aegypti* with the number of dengue cases in the villages. We hope the result of this study could be applied as an alternative approach for mitigating dengue cases.

Methods

This study was conducted in Bandung city, West Java, Indonesia (107°36' east longitude and 6°55' south latitude) with a total area of 16,729.65 ha, 791 m above sea level (ASL). The highest and lowest points are 1,050 m ASL and 675 m ASL, respectively. Bandung has an average annual temperature of 26.8°C and 2,120 mm annual rainfall.[21] The area is surrounded by mountains that border the region. The city comprises 30 sub-districts and 151 villages, with approximately 2.4 million inhabitants.[22] For this study, sampling areas were selected by the stratified random sampling approach.[23]

Sixteen villages out of 151 villages in Bandung city were stratified and selected based on altitude, area, population, and the number of dengue cases (Table 1).

We collected mosquitoes from 16 villages across Bandung city using a modified light-type trap and a mosquito attractant solution. Mosquitoes were collected daily for one year and were identified at the Parasitology Laboratory of the Universitas Padjadjaran. Separated adult female *Aedes aegypti* was preserved in RNA later solution at the Parasitology Laboratory of the Universitas Padjadjaran.

We collected dengue hemorrhagic fever cases from primary healthcare posts at the village level (called *puskesmas*) from January to December 2017 from the Bandung City Health Office. The information in the report was based on WHO standard criteria, including age, sex, address, and diagnosis, which were used in this study. The data is contained in the program holder institution.

After the female *Aedes aegypti* mosquitoes were submerged in RNA later solution, ten mosquitoes from each village were pooled into one 1.5 ml microtube. In each microtube, 800 µl of PBS (Takara Bio Phosphate buffered saline (PBS) tablets, Cat# T900) were added. Mosquitoes were then ground and homogenized.

Viral RNA was extracted from each mosquito pool using the Magmax Viral/Pathogen Nucleic Acid Isolation Kit, Cat. No. A48310 and the KingFisher Flex Purification System, KingFisher with 96 Deep-well Head, Cat. No. 5400630. The purified RNA was used for further analysis through multiplex quantitative RT-PCR (qRT-PCR).

Multiplex qRT-PCR was applied to target the RNA of three arboviruses: Zika, dengue, and chikungunya. The qRT-PCR amplification of the targeted viral RNA sequence was done in a 15 µl reaction consisting of 10 µl of Oasig OneStep MasterMix, 1 µl of Multiplex primer/probe mix, and 4 µl of RNAse/DNAse free water. Samples were incubated in the thermocycler at the following conditions: 55°C for 10 minutes for the reverse transcription process, 95°C for 2 minutes for the enzyme activation process, then repeated for 50 cycles at 95°C for 10 secs and 60°C for 60 secs for denaturation and data collection, respectively.

The incidence of adult female *Aedes aegypti* and dengue fever cases were interpolated through third-power inverse distance weighting (IDW). A spatial correlation between female *Aedes aegypti*

Table 1 Sampling Villages

Villages	Altitude (ASL)	Area (km²)	Population	Dengue Case
Antapani Wetan	690	115	16,966	47
Ciateul	686	45	10,810	18
Cibaduyut Wetan	689	97.35	6,145	14
Cigadung	750	264.4	26,176	75
Cigondewah Kaler	709	140	22,781	11
Cijawura	670	119.7	22,291	80
Cikutra	706	139.34	22,584	34
Cipedes	891	51	29,415	15
Lebak Siliwangi	792	100	4,238	11
Nyengseret	695	38	11,001	9
Pasteur	790	119	19,132	13
Suka Asih	694	92	21,100	5
Sukabungah	801	51	23,067	15
Sukamaju	730	41.5	10,208	19
Sukapada	720	103	19,526	17
Tamansari	751	102	26,302	26

incidence and dengue incidence was obtained from polynomial regression.

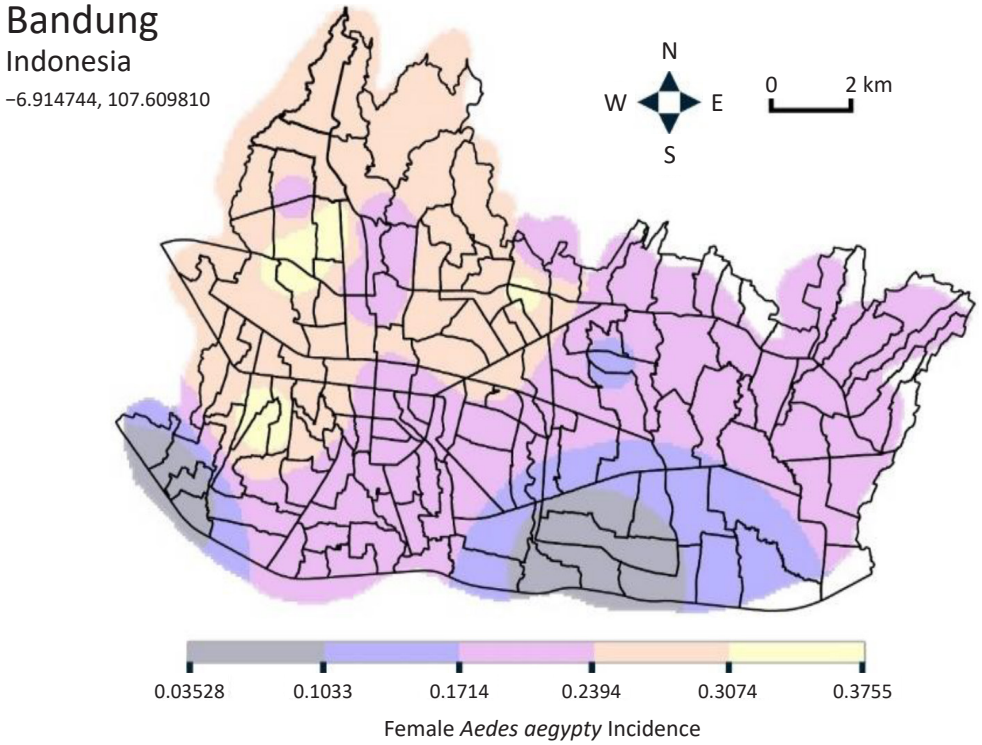
Results

We collected 8,402 mosquitoes of *Aedes aegypti*, *Aedes albopictus*, and *Culex* sp., with about 17% female *Aedes aegypti*, the main subject of this study. The most abundant female *Aedes aegypti* was collected from Nyengseret village (6.9305° S, 107.6016° E), although the highest incidence occurred in Pasteur village (6.8913° S, 107.5993° E). Both are located near the center of Bandung city, an urban area—the lowest abundant female *Aedes aegypti*, 58, was recorded in Cigondewah Kaler village (Table 2).

We analyzed the feasibility interpolation method and found that IDW is suitable instead of the geostatistical approach of Kriging. This is important since the sampling data does not fit any of the semivariogram models of Kriging, which is circular, spherical, exponential, Gaussian, or linear. Moreover, we found that the mapped variable (female *Aedes aegypti* and dengue fever

Table 2 Mosquito Collection from 16 Villages in Bandung City

No.	Region	*Aedes* Female	Total Mosquito	% of Total
1	Antapani Wetan	89	614	14.50
2	Ciateul	102	591	17.26
3	Cibaduyut Wetan	71	413	17.19
4	Cigadung	56	212	26.42
5	Cigondewah Kaler	58	1,645	3.53
6	Cijawura	68	1,043	6.52
7	Cikutra	90	285	31.58
8	Cipedes	104	481	21.62
9	Lebak Siliwangi	64	305	20.98
10	Nyengseret	156	595	26.22
11	Pasteur	95	249	38.15
12	Suka Asih	113	366	30.87
13	Sukabungah	83	245	33.83
14	Sukamaju	132	511	25.83
15	Sukapada	104	541	19.22
16	Tamansari	68	306	22.22
	Total	1,453	8,402	17.29



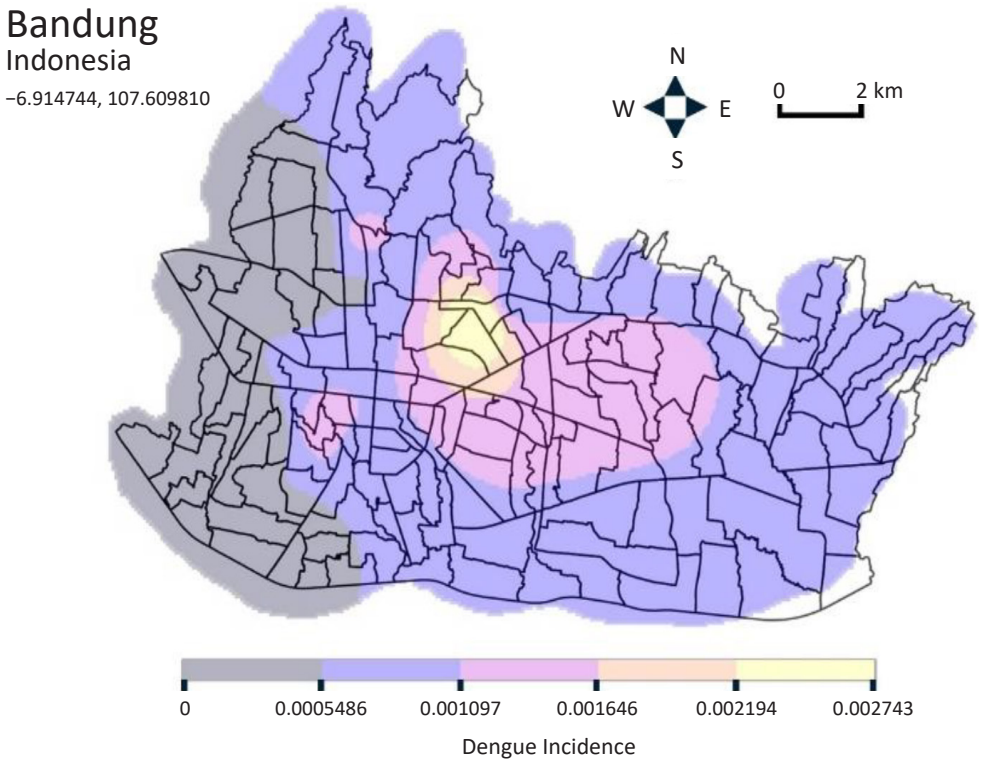


Figure 1 Top: the Interpolated Incidence of Female *Aedes aegypti*, Bottom: Dengue Fever Incidence
Note: Brighter areas represent higher incidence

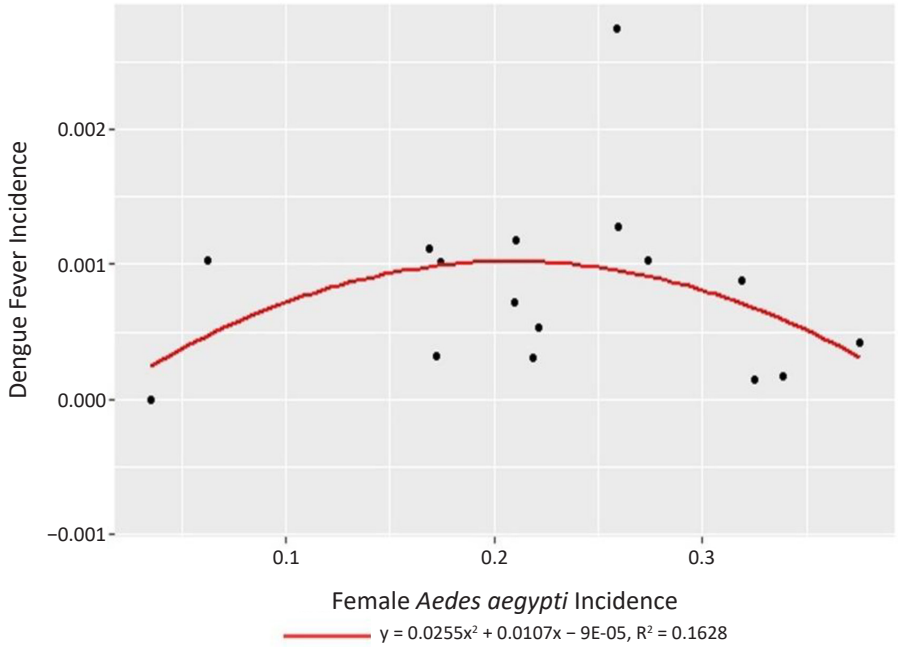


Figure 2 Polynomial Regression between Female *Aedes aegypti* and Dengue Fever Incidence Arbovirus Surveillance

incidence) has an inherent assumption that they will decrease in influence with distance from its initial sampling location. Another parameter defined is the power on which IDW relies. The power of 3 (three) used in this study emphasizes the nearest points. However, the determination of the power threshold is mainly attributed to when it gives the lowest mean absolute error.

The mapped interpolation in Figure 1 showed higher dengue-infected female *Aedes aegypti* numbers in the northwest of Bandung, while they were lower in the southeastern part. However,

Table 3 Sampling Villages

Villages	Population	Dengue Case	Incidence Rate (%)	Arbovirus Case		
				DENV[a]	ZIKV[b]	CHIKV[c]
Antapani Wetan	16,966	47	0.28	–	–	–
Ciateul	10,810	18	0.17	–	–	–
Cibaduyut Wetan	6,145	14	0.23	–	–	–
Cigadung	26,176	75	0.29	–	–	–
Cigondewah Kaler	22,781	11	0.05	–	–	–
Cijawura	22,291	80	0.37	–	–	–
Cikutra	22,584	34	0.15	–	–	–
Cipedes	29,415	15	0.05	–	–	–
Lebak Siliwangi	4,238	11	0.26	–	–	+
Nyengseret	11,001	9	0.08	–	–	–
Pasteur	19,132	13	0.07	+	+	+
Suka Asih	21,100	5	0.02	–	–	–
Sukabungah	23,067	15	0.07	–	–	–
Sukamaju	10,208	19	0.19	–	–	–
Sukapada	19,526	17	0.09	–	–	–
Tamansari	26,302	26	0.10	–	–	–

Note: [a]DENV: dengue virus, [b]ZIKV: Zika virus, [c]CHIKV: chikungunya virus

the interpolation mapping showed contradictory results to dengue case mapping as dengue cases concentrated in the central region of Bandung city. On the other hand, the prediction of different areas is consistent with the hypothesized correlation.

Further correlation analysis showed curvilinear dependence between several female *Aedes aegypti* and dengue fever. A maximum threshold of mosquito incidence in the region affects dengue fever incidence (Figure 2).

We pooled ten mosquitoes per village out of 17% female *Aedes aegypti* of 8,402 mosquitoes collected (1,453 mosquitoes). It was found that arbovirus could be detected in viral RNA extracted from 2 pools of mosquitoes originating from 2 villages (Table 3). The mosquito pool collected from Pasteur village tested positive for Zika, dengue, and chikungunya viruses, while the mosquito sampled from Lebak Siliwangi village tested positive for the chikungunya virus. However, no arbovirus RNA was detected from the mosquitoes obtained from the remaining 14 villages.

Discussion

This report is on the dependence analysis between female and adult *Aedes aegypti* mosquitoes and the incidence of dengue fever in a large urban setting, to our knowledge. Other research reports mainly on the nature of variation from locally acquired dengue cases,[24,25] dependence from other forms of variables, such as socio-economic factors,[26] and the timing of case emergence.[27]

In this study, the weak spatial correlation between female *Aedes aegypti* and dengue fever cases implies that other governing factors may significantly impact the number of cases that emerged in Bandung. From previous studies and other viewpoints, human settlements are among the most critical factors affecting dengue cases.[28] Reasonably, if there is some correlation between human settlements and mosquito incidence in the specific region, there should be notable dependence between variables tested in this study. The proximity of the relationship between humans and mosquitoes is a well-known matter, supported by the notion that blood-requiring insects evolved to prefer the most available and stable source, humans.[29] As a result, the approach taken on the factor inference should be more comprehensive than human settlements, which are environmental aspects, but also other factors from the mobile elements of the system. These include human mobility[30] and connectivity between two regions of these studies where the highest incidence of female *Aedes aegypti* and dengue fever cases occurred.

Non-linear dependence from the variables of these studies suggests that mechanisms are yet to be explored. The result was not intuitively obvious, showing that further continuation of mosquito incidence increase in a specific region does not necessarily mean an increase in dengue fever cases. However, the dengue fever case incidence reaches the maximum value at a certain point. There are some reasons to explain this kind of result; one of them is little evidence of quantifiable associations between vector factors and dengue transmission. On the other hand, this can be compared to previous studies on malaria, another mosquito-borne disease with similar onset characteristics. A phenomenon is exhibited in southern Tanzania, where the risk of human infection increased with the entomological inoculation rate (EIR) and vector indices when the parasite prevalence was low. But, when the parasite prevalence was high, an increase in EIR did not appear to increase human infection.[31] Lastly, another variable that needs to be considered is the herd immunity of the sample. Regardless of the magnitude of entomological indices, the probability of disease transmission will be low if herd immunity is high. Contrarily, if herd immunity is low, any measure of vector incidence will result in an epidemic.

Previous studies have shown that early detection of potential outbreaks of arbovirus through mosquito surveillance is an effective method for dengue mitigation.[17–20] In this study, we highlight the possibility of mosquito surveillance for arbovirus as an approach for dengue mitigation in Bandung city, West Java, Indonesia. Results showed that arboviral RNA can be detected in mosquitoes captured from two villages, one of which tested positive for dengue. Interestingly, our findings found no correlation between the positive finding and the number of dengue cases in a village. The mosquito pools collected from the villages with the most dengue cases tested negative for arbovirus. In contrast, the mosquitoes that tested positive for arbovirus infection were collected from the village with a relatively lower number of reported dengue cases.

The positivity rate of mosquitoes infected with

the dengue virus is not the sole factor affecting the number of dengue infections in one region. Higher density of *Aedes aegypti* was not associated with higher dengue infection risk,[22] and transmission of the dengue virus can still occur efficiently when the population of *Aedes aegypti* is low.[23] One of the factors affecting dengue virus transmission is the mosquito mortality rate, which changes between seasons. Dengue transmission depends on the probability of whether the mosquito infected with dengue lives long enough for the virus to incubate and further transmit it to susceptible hosts.[24,25] Environmental conditions and prevention measures are taken to minimize the mosquito population and decrease the livelihood of the mosquitoes, thus affecting the dengue virus transmission rate. The population demographic of each village may also determine their dengue infection rate, as factors such as the age and sex of the hosts affect their susceptibility to dengue infection.[26] The trend for dengue infection in Indonesia in the last 22 years showed that the adult population aged 15 years and above is more prone to dengue infection than children, which shifted from the previous trend, where children were more susceptible.[27] Therefore, even if the number of infected mosquitoes in a region increases, the number of dengue incidences will not necessarily increase, depending on the host's susceptibility. Another possible explanation of the result is the possibility of *Aedes albopictus*, which is not included in this study, as a vector of dengue. Studies showed the increasing role of *Aedes albopictus* as a dengue vector in various countries,[28,29] and their population is correlated to the lack of sanitation in Indonesia's high human population density region.[30] Although the level of dengue virus infection in *Aedes albopictus* is usually significantly lower than in *Aedes aegypti*, the higher population of this species may improve the chance of dengue virus infection. However, this hypothesis should be assessed by future studies.

Mosquito incidence is also one of the determinants of virus transmission efficiency. A higher biting rate was observed in smaller mosquitoes in contrast to larger ones, thus increasing the probability of infecting hosts. Adult mosquitoes with higher incidence have a lower positivity rate, which was also implied by the results of this study. Consequently, it is less effective for larger female mosquitoes to be targeted in dengue mitigation. Since this study only considered adult female mosquitoes as the target for the surveillance, further advancement in arbovirus surveillance in mosquitoes to mitigate dengue outbreaks should also consider the potential of mosquito larvae as the target for surveillance and mitigation. Due to the transovarial transmission of the dengue virus in mosquitoes, controlling mosquito larvae could be essential as immature stages have the potential to be a virus reservoir.[15]

Due to the complexity of vector-host interaction in dengue transmission, the correlation between vector incidence and positive infection rate could be determined more accurately if mosquito surveillance for arbovirus is performed over multiple periods.[22] However, it could be very time consuming and not cost-effective as a routine for dengue surveillance. Arbovirus surveillance in mosquitoes described in this study has shown the possibility of a more cost-efficient and less laborious approach for routine mosquito surveillance for circulating arbovirus in urban areas such as Bandung city.

Conclusion

This study highlights the importance of constant arbovirus surveillance and integrated surveillance methods on all possible dengue vectors to develop an early warning system for dengue incidence.

Conflict of Interest

No conflicts of interest.

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RESEARCH ARTICLE

Clove Extract and Grape Seed Oil Nanoemulsion for Oral Diseases Therapy: Antibacterial and Antioxidant Activities

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Abstract

The growth of micro-organisms that acquire resistance to most commercially available antibiotics is occurring rapidly. Consequently, a pressing necessity exists to identify and detect new antimicrobial substances. This study aimed to analyze the antioxidant and antibacterial activity of nanoemulsion clove extract and grape seed oil. This research was conducted in June 2023 using experimental methods at the Research Laboratory of the Universitas Islam Bandung Pharmaceutical Study Program by developing a nanoemulsion preparation containing clove extract (*Syzygium aromaticum* L.) and grape seed oil (*Vitis vinifera* L.). Antioxidant activity was tested using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. Antibacterial activity was tested using the agar diffusion method by measuring the growth inhibitory diameter of *Staphylococcus aureus* and *Streptococcus mutans* bacteria and divided into four groups formulas based on the addition of clove extract with different concentrations in the nanoemulsion base (FA=0.25%, FB=0.5%, FC=0.75%, and FD=1%) to see the best results. The result shows nanoemulsion preparations have antioxidant properties in the DPPH test. The FA formula has the highest IC_{50}, namely 1,117.56 ppm. The antibacterial activity of *Staphylococcus aureus* and *Streptococcus mutans* has an inhibition zone, although it is still in the category of inhibiting bacterial growth, but does not kill growth. The nanoemulsion formulation, comprising clove extract and grape seed oil, has exhibited exceptional antioxidant properties and substantial antimicrobial efficacy against prevalent oral bacterial strains.

Keywords: Antibacterial, antioxidant, clove extract, grape seed oil, nanoemulsion

Introduction

Antibiotic-resistant microbes are a global issue. The utilization of medicinal plants as phytochemical sources is being developed to circumvent this issue. Many benefits come from active substances. One phytochemical that inhibits *Streptococcus mutans* has been found by studying many plant-derived substances and their active components for years.[1]

The gold standard for *Streptococcus mutans* treatment is chlorhexidine; however, adverse oral effects limit its usage. Worse, most antibacterials cause bacterial resistance. Current therapeutic research should focus on naturally available, safe medications, especially for oral disorders with few side effects, and can fully treat patients. Clove and grape oils have been examined for dental health. Several research studies show that this plant extract has antioxidant and antibacterial abilities.[2] Natural ingredients contain many biologically active chemical molecules.[3,4] Nanoemulsions are being developed as drugs. Nanoemulsions made from natural oils have been extensively studied for oral health issues.[5,6]

Clove (*Syzygium aromaticum*) is a plant native to the Maluku islands in Eastern Indonesia.[7] Clove oil contains essential oils such as β-caryophyllene, eugenol, and eugenol acetate.[8] Grape seed oil (GSO) is rich in bioactive components with health benefits. GSO possesses antioxidant, anti-inflammatory, and metabolic disease-fighting capabilities.[9] GSO contains several phenolic components, including flavonoids, carotenoids, phenolic acids, tannins, and stilbenes.[10] Jafri and Ahmad[11] found that clove oil and eugenol may fight dangerous bacteria biofilms alone or together. Microscopy confirmed

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the outstanding results of the combination treatment on preexisting *Staphylococcus aureus* and *Streptococcus mutans* biofilms. Grape seed extract was found to be antibacterial against *S. aureus* and *S. mutans* in another study.[12]

According to the explanation, phytodentistry does not currently use clove-grape seed oil nanoemulsion. This formulation is claimed to absorb antioxidants and antibacterials better. This study examines a nanoemulsion's antibacterial and antioxidant properties with clove extract and grape seed oil against bacterial-induced oral diseases.

Methods

This experiment was conducted in June 2023 at the Research Laboratory of the Universitas Islam Bandung Pharmaceutical Study Program by developing a nanoemulsion preparation combining clove extract (*Syzygium aromaticum* L.) with grape seed oil (*Vitis vinifera* L.). Clove samples (*Syzygium aromaticum* L.) were taken from the West Java agricultural area via a company, Friends of Indonesian Spices. The clove samples were determined at the Herbarium Bandungense, School of Life Sciences and Technology, Institut Teknologi Bandung, with registration number 3470/IT1.CC11.2/TA.00/2023. Grape seed oil was obtained from PT Tamba Sanjiwani, Tabanan regency, Bali, using the TSb product brand.

Fresh cloves obtained in packaged form have gone through a washing and drying process in the sun using the natural air-dried method. The clove samples were then ground using a blender until they became simplicia powder.[13] The preparation was made into four different formulas based on adding clove extract with different concentrations on the nanoemulsion basis (FA=0.25%, FB=0.5%, FC=0.75%, and FD=1%).

The method used for the antioxidant test begins with preparing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution and determining the maximum wavelength. A total of 6 mg of DPPH powder was weighed and then dissolved in 100 ml of ethanol p.a. (60 ppm).[14] Preparation of blank solution was done as follows: a total of 2 ml of DPPH solution (60 ppm) was pipetted and put into a test tube, then added with ethanol p.a. to 2 ml and homogenized.[15] Preparation of test solutions for nanoemulsion preparations of grape seed oil and clove ethanol extract was done as follows: a nanoemulsion stock solution was made by weighing 500 mg of the nanoemulsion sample and then dissolving it in 50 ml of ethanol p.a. (10,000 ppm), a concentration of 400 was made; 600; 800; 1,000; and 1,200 ppm. 2 ml of each dilution concentration was taken into a test tube then 2 ml of 60 ppm DPPH solution was added.

The reaction tube was homogenized using a vortex and then incubated in the dark for 30 minutes. Preparation of clove ethanol extract test solution was done as follows: weighed 50 mg of clove extract, then dissolved it in 50 ml of ethanol p.a. (1,000 ppm), concentrations then made in 2, 4, 6, 8, and 10 ppm. 2 ml of each dilution concentration was taken into a test tube then 2 ml of 60 ppm DPPH solution was added. The reaction tube was homogenized using a vortex and then incubated in the dark for 30 minutes. Absorption measurements were done using a UV-Vis spectrophotometer; the blank solution, the test sample solution, and the comparison solution for vitamin C preparations were measured for absorption at a wavelength of 516 nm. Lastly, the calculation of % inhibition and IC_{50} was done as follows: The free radical inhibition activity of DPPH with the test solution of nanoemulsion preparation of grape seed oil and ethanol extract of guava leaves and DPPH with the comparison solution of vitamin C preparation was calculated using the formula:

$$\%\text{inhibisi} = \frac{\text{a DPPH} - \text{a sample}}{\text{a DPPH} \times 100}$$

The inhibitory concentration (IC_{50}) value is the antioxidant concentration (μg/ml), which can provide a radical scavenging percentage of 50% compared to the control via the line equation. The IC_{50} value is obtained from the line intersection between 50% resistance power and the concentration axis, then enter the equation y=a+bx. Where y=50 and the x value shows IC_{50}.[16]

The antibacterial activity of nanoemulsion preparations of grape seed oil and ethanol extract of guava leaves was tested using the agar diffusion method by measuring the growth inhibitory diameter against *Staphylococcus aureus* and *Streptococcus mutans* bacteria. Making tryptone soya agar (TSA) media was done as follows: a total of 20 grams of TSA, which will be used as a medium in the antibacterial test, is dissolved in 500 ml of distilled water, then heated while stirring with a hotplate stirrer. The media was

sterilized by autoclaving at a temperature of 121°C and a pressure of 1.5 atm for 15 minutes.[17] Equipment preparation and sterilization were done: the tools used were prepared, washed, cleaned, and dried. After that, the tools and media are wet sterilized using an autoclave.[18] Bacterial rejuvenation tests were done as follows: rejuvenation of the test bacteria is done by taking one cycle of the initial microbial culture and then planting it on TSB media. Next, it was incubated at 37°C for 24 hours.[19]

Preparation of bacterial suspension was done as follows: making a bacterial suspension is done by measuring the results of bacteria that have been incubated using a UV-Vis spectrophotometer at a wavelength of 625 with an absorbance range of 0.08–0.12.[20] Inhibitory power test of nanoemulsion preparations was done as following; the test bacteria were inoculated as much as 100 µl into 20 ml of agar media in a petri dish then aseptically, the inoculated media was made with a hole of 8 mm. Comparative preparation of 1% antibiotic solution as a positive control, test samples of grape seed oil nanoemulsion and clove flower ethanol extract, grape seed oil nanoemulsion base were dropped 45 µl each in the wells that had been made in the test medium. After that, the media was incubated at 37°C for 18–24 hours. Then, measure the diameter of the obstacle area around the hole using a caliper.[20]

This study was approved by the Health Research Ethics Committee of Universitas Islam Bandung (110/KEPK-Unisba/XI/2023).

Results

The preparation formulation begins with preliminary grape seed oil nanoemulsion optimization, and then the percent transmittance test is evaluated. The optimum formula is F6, with the highest transmittance percentage, 99.65%±0.17. The preliminary research formula can be seen in Table 1.

After obtaining the optimum preliminary formula, optimization was done by adding clove extract, namely 0.25%, 0.5%, 0.75%, and 1% (Table 2).

Antioxidant activity tests were carried out on nanoemulsion preparations of formulas A, B, C, and D and also on ethanol extract of clove flowers to determine the inhibitory power and IC_{50} value of nanoemulsion preparations and ethanol extract of clove flowers against DPPH radical compounds. The IC_{50} value and antioxidant activity test curve results can be seen in Table 3. In testing antioxidant nanoemulsion preparations, the FA formula had the highest IC_{50}, 1,117.56 ppm, followed by the FB formula, 949.14 ppm, FC 874.58 ppm, and FD 811.28 ppm. Based on the test results, adding the concentration of clove flower ethanol extract affects the antioxidant strength of the preparation. The more extract added, the lower the IC_{50} value, meaning the higher the antioxidant strength.

The free radical scavenging activity of DPPH is based on the ability of the test material to reduce or capture DPPH radicals, which can be

Table 1 Optimization Nanoemulsion Formulas

Material	Formulas (%w/w)					
	F1	F2	F3	F4	F5	F6
Grape seed oil	4	4	4	4	4	4
Tween 80	20	22	24	26	28	30
PEG 400	20	22	24	26	28	30
Aquadest	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100

Table 2 Nanoemulsion Formula of Clove Extract and Grape Seed Oil

Material	Formulas (%w/w)			
	FA	FB	FC	FD
Clove extract	0.25	0.5	0.75	1
Grape seed oil	4	4	4	4
Etanol	10	10	10	10
Tween 80	30	30	30	30
PEG 400	30	30	30	30
Aquadest	ad 100	ad 100	ad 100	ad 100

Table 3 Antioxidant Test Results

Samples	Unit	Value IC_{50} (ppm)	Description
Sample FA	Ppm	1,172.56	DPPH
Sample FB	Ppm	949.14	DPPH
Sample FC	Ppm	874.58	DPPH
Sample FD	Ppm	811.28	DPPH
Clove extract	Ppm	8.18	DPPH

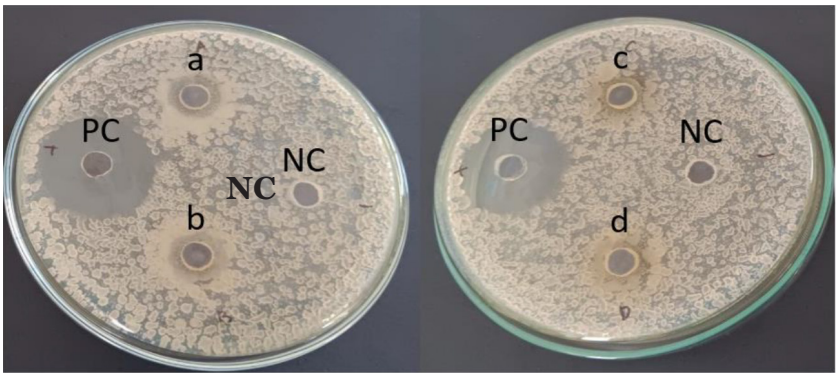

Figure 1 Inhibition Zones *Staphylococcus aureus*
Note: PC: positive control, NC: negative control, a: formula A, b: formula B, c: formula C, d: formula D

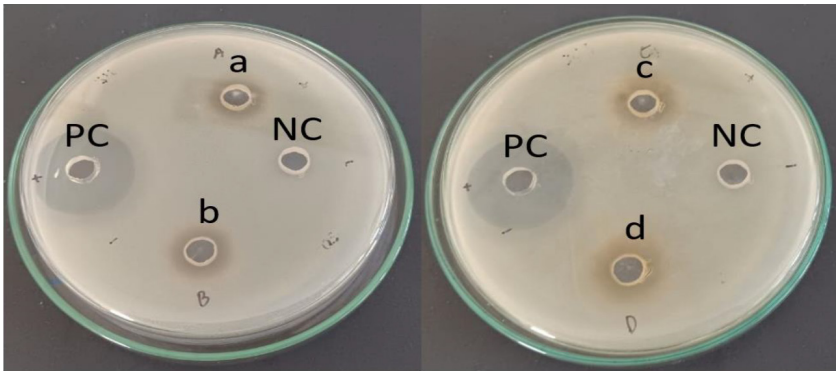

Figure 2 Inhibition Zones of *Streptococcus mutans*
Note: PC: positive control, NC: negative control, a: formula A, b: formula B, c: formula C, d: formula D

seen from the purple color change of the DPPH solution after being mixed with the test sample to yellow. Thus, the ethanol extract of clove flowers and the nanoemulsion preparation have antioxidant properties in the DPPH test.

The IC_{50} value was obtained based on the linear regression equation derived by plotting the percent reduction of DPPH as a parameter of antioxidant activity against the concentration of the test solution (ppm). The abscissa represented the concentration of the test solution along the X-axis, while the ordinate represented the percent reduction value along the Y-axis. Determination of the potential DPPH free radical scavenging activity of ethanol extract of clove flowers and nanoemulsion preparations is expressed by the IC_{50} parameter, namely the concentration of the test compound, which causes free radical scavenging of 50%.

The antibacterial activity test of the nanoemulsion preparation was carried out against *Staphylococcus aureus* bacteria. The diffusion method uses wells.

The test was carried out using an 8 mm diameter perforator by adding up the horizontal and vertical diameters of the inhibition zones (Figure 1 and Figure 2). Antibacterial activity testing was carried out on nanoemulsion base formula (F6), FA formula with an extract concentration of 0.25%, FB formula with an extract concentration of 0.5%, FC formula with an extract concentration of 0.75%, and FD formula with an extract concentration of 1%. The results of testing the antibacterial activity of microemulsion preparations can be seen in Table 4.

Based on Tables 4 and Table 5, the results of the antibacterial tests that have been carried out, it was found that each nanoemulsion formulation of FA, FB, FC, and FD has a fragile antibacterial activity for *Staphylococcus aureus* because the inhibition zone is almost invisible, however

Table 4 Results of Antibacterial Testing for *Staphylococcus aureus*

Groups	Inhibition Diameter *S. aureus* (mm)	Categories based on Inhibition Zones
FA	4.03	Very weak
FB	4.17	Very weak
FC	4.6	Very weak
FD	4.3	Very weak
Base	4	Very weak
Positive control	21.9	Very strong
Negative control	–	It has no antibacterial activity

Note: very weak: <5 mm, weak: 5–10 mm, strong: 10–20 mm, very strong: >20 mm

visually there is the potential to reduce growth in the area around the *Staphylococcus aureus* bacterial media just doesn't kill the bacteria. Meanwhile, in the results of the antibacterial activity of *Streptococcus mutans*, the inhibition zone was more visible. However, it was still inhibiting bacterial growth, not to the point of killing growth.

The inhibition zone results for the positive control of clindamycin, FA, FB, FC, and FD formulas were 13.93 mm, 4.03 mm, 4.17 mm, 4.27 mm, and 4.63 mm, respectively. The concentration of the extract in the preparation influences the results of the inhibition zone. In the negative control in the form of a nanoemulsion base without adding extracts, no clear zone was formed around the disc. The positive control group was included in the solid bacterial inhibition zone category. This weak inhibitory power is caused by the low concentration of clove flower ethanol extract, which has yet to be tested for its minimum concentration of antimicrobial substances.

Discussion

In this study, testing antioxidant nanoemulsion preparations, the FA formula had the highest IC_{50}, 1,117.56 ppm, followed by the FB formula, 949.14 ppm, FC 874.58 ppm, and FD 811.28 ppm. Based on the test results, adding the concentration of clove flower ethanol extract affects the antioxidant strength of the preparation. The more extract added, the lower the IC_{50} value, meaning the higher the antioxidant strength. However, a sample with an IC_{50} value of more than 200 ppm must be more substantial than a clove flower ethanol extract sample.

This study, by the statement of Partayasa et al.,[21] states that the antioxidants contained in

Table 5 Results of Antibacterial Testing for *Streptococcus mutans*

Groups	Initial Inhibition Diameter *S. mutans* (mm)	Perforator Diameter (mm)	Inhibition Diameter *S. mutans* (mm)	Categories based on Inhibition Zones
FA	12.03	8	5.03	Weak
FB	12.17	8	5.17	Weak
FC	12.27	8	5.6	Weak
FD	12.63	8	5.3	Weak
Base	There are no inhibition zones	–	–	There are no inhibition zones
Positive control (clindamycin for *S. aureus*; gentamycin for *S. mutans*)	21.93	8	13.93	Strong

Note: very weak: <5 mm, weak: 5–10 mm, strong: 10–20 mm, very strong: >20 mm

the sample decrease because the antioxidants are easily oxidized by the external environment, thereby reducing their activity in reducing DPPH free radicals.In testing the antioxidants of clove extract, the IC_{50} value was 8.18 ppm, which means it has antioxidant power in the strong category.

Based on the IC_{50} strength table, according to Leksono et al., a sample with an IC_{50} value of less than 50 ppm has antioxidant activity in the very strong category.[22]

The results of a good inhibition zone in the nanoemulsion dosage form are because the resulting nano-sized particles can penetrate bacterial cell membranes. The antibacterial effect of nanoparticles is attributed to their significant surface area, facilitating optimal interaction with microbes.[23,24] Apart from that, the bioactive compounds contained in clove flowers, such as flavonoids, phenols, and tannins, can also inhibit the activity of living bacteria.[25]

Referring to the antibacterial inhibitory power classification of Dewi et al.,[26] the positive control has very strong antibacterial effectiveness with an inhibitory diameter value of >20 mm, and the negative control has no antibacterial activity because there is no inhibition zone around the well. Factors that influence antibacterial activity include the bacteria being inhibited, the content of antibacterial compounds, the concentration of the extract, the diffusion ability of an extract, and differences in the structure of bacterial cell walls, which will influence the activity, penetration, and binding of antibacterial compounds.

According to research by Daulay,[27] in clove flower ethanol extract nanoemulsion, extract concentrations of 1.25% and 2.5% have a weak inhibitory category, and at 5%, it has a weak category. This study's highest extract concentration was 1%, with a transmittance percentage of 82,874. If the extract concentration is increased, the transmittance percentage will likely be smaller.

Further research needs to be carried out in vivo to clinically test the ability of nanoemulsion preparations containing clove extract and grape seed oil in their activity as antioxidants and antibacterials.

Conclusion

The nanoemulsion of clove extract and grape seed oil has exhibited exceptional antioxidant properties and substantial antimicrobial efficacy against prevalent oral bacterial strains.

Conflict of Interest

All of the authors have declared that they have no conflicts of interest.

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