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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.

All articles will be discussed by experts in the field of scholarly concern (peer reviewer) and will be edited by the editor. The editor reserves the right to add or subtract sentences, both abstracts, and scripts without changing the meaning. Manuscripts that are accepted for publication will become the property of the publisher. It is not allowed to be published in other media. The needed revised manuscripts will be returned to the author. Research articles must be approved by the health research ethics committee or consider the ethical aspects of research accounted for.

Article Writing

Typed the article in Microsoft Word format with paper size A4 (21.0×29.7 cm), 4 cm left and top margin, 3 cm down and right, not back and forth. The font is black Georgia with 12 pt size, typed justified except for a title with a spacing of two spaces. Typing a new paragraph 6 taps from the left edge of the line, unless the first paragraph is not typed indented. In one manuscript only in English. Typed italic the untranslatable terms in a foreign language or regional language. It is recommended to use a professional translator who understands the health field or software such as Grammarly in writing English manuscripts. The maximum script length is 20 pages (including images, tables, and photos). Each page is numbered typed on the bottom right page, sequentially starting from the title page to the last page.

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.

Typed center figure title with 11 pt font size, bold, numbered according to the appearance in the text and typed under the image. The source of the cited image and or table should be added to references if it is not the author's work.

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.

Articles Title

Maximum article title consists of 12 words (choose words and terms that are dense meaning and able to characterize the entire contents of the script). Typed with bold fonts, size 12 pt, one space, the initial letter of each word is written in capital letters (except the conjunctive), and center. The ownership row consists of 2 elements, the author name and origin institution. The author's name written with the initial fonts is capital and bold, size 11 pt, one space, and center. Institution name written with the initial fonts is capital, size 10 pt, one space, and center.

Abstract

The abstract is typed using 12 pt font size and one space. The abstract is written in one paragraph, one space, a maximum of 250 words, and should describe the entire contents of the article. The abstract should be suitable for the format of introduction, methods (contain method, place, and time of the study), results, discussion, and conclusion. Abstract be equipped with keywords consisting of 3–5 words.

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.

Results
The result is the core of scientific writing. This section presents data and information that will be used as the basis of the conclusion and is even expected to get a new theory. In results, listed the tables and or images, graphics, photos to explain and abbreviate the description should be given; numbered according to their appearance in the text. Results of the study and discussion should be written separately.

Discussion
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.

Books and Other Monographs
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Nriagu J, editor. Encyclopedia of environmental health. Michigan: Elsevier BV; 2011.

Organization as Author
World Health Organization. Guideline: neonatal vitamin A supplementation. Geneva: WHO Press; 2011.

Chapter in Book
Miller LG. Community-associated methicillin resistant *Staphylococcus aureus*. In: Weber JT, editor. Antimicrobial resistance. Beyond the breakpoint. Basel: Karger; 2010. p. 1–20.

Conference Proceeding
Nicholai T. Homeopathy. Proceedings of the Workshop Alternative Medicines; 2011 November 30; Brussels Belgium. Brussels: ENVI; 2011.

Journal Article from Internet
King P. *Haemophilus influenzae* and the lung (*Haemophilus* and the lung). Clin Transl Med. 2012;1:10 [cited 2015 August 15]. Available from: https://clintransmed.springeropen.com/articles/10.1186/2001-1326-1-10.

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RESEARCH ARTICLE

Determinants of Detectable Anti-hepatitis B in Fertile Age Women from Indonesia

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Abstract

Hepatitis B (HBV) is still a major health problem worldwide, as evidenced by the large number of people infected with hepatitis. There are around two billion people infected with HBV, and an estimated 350 million are in chronic conditions. Hepatitis B is a ninth-order disease that causes death in mothers and their babies. The HBV infection in pregnant women is critical because of vertical or perinatal transmission. This study's purpose was to analyze data of the HBsAg and anti-HBs rertile age women, pregnant women, and postpartum mothers from National Basic Health Research Data 2007. The method is a retrospective study using secondary data from the Basic Health Research in 2007. The number of samples in the form of data on respondents of fertile age women are women aged 15 to 49 years. Data screened and matched with that examined pregnancy/have had a postpartum examination/never checked neonates/had examined their toddlers. One thousand three hundred two (1,302) respondents were eligible to be sampled in this analysis. The variables analyzed were age and anti-HB titers in women of childbearing age 15 to 49 years who were not protected against hepatitis B, as much as 74.65% of the total 1,302 people. Three hundred thirty (330) respondents had anti-HBs titers. This study concludes respondents who are not married age 15–20 years showed relationship with negative anti-Hbs antibodies.

Keywords: Anti-hepatitis B titer, fertile age women, hepatitis B virus, postpartum mothers, pregnant women

Introduction

Hepatitis B is still a significant health problem in the world. It is proven by the large number of people infected with hepatitis.[1] The prevalence of chronic hepatitis B infection varies worldwide, ranging from <1% in low-endemism regions to 30% in highly endemic areas. There are around two billion people infected with HBV, and an estimated 350 million are in chronic conditions.[1] HBV is a ninth-order disease that causes death to mothers and their babies.[2] In Nigeria, despite effective vaccine administration, it is still declared an HBV hyperendemic area with an estimated prevalence of 12%.[2]

Regions declared endemic intermediate if the prevalence of HBsAg is around 1–17% and the risk of infection is approximately 20–60%, covering Southern Europe, Southern America, and Russia. Fertile age women (FAW) are women in a state of reproductive organs functioning properly between the ages of 20–45 years. The peak of fertility in women is in the age range of 20–29 years. At this age, women have a 95% chance of getting pregnant. At the age of 30–39 years, the percentage decreases to 90%, and after entering the age of 40 years, the chance of pregnancy becomes 40%, then it will reduce to 10% if women are over 40 years old.[3,4]

In countries with high HBV endemicity, where the prevalence of HBsAg is ≥8%, the transmission pattern is usually vertical at birth from a chronically infected mother or horizontally during early childhood from being caused by bites, skin lesions, or unhealthy habits. About 45% of the world's population, those living in African and Asian countries, the Amazon Basin, and parts of the Middle East, live in high endemicity areas with a lifetime risk of infection of more than 60%. Only about 12% of the world's population lives in low-endemicity regions, such as the United States, Western Europe, and Australia, where the prevalence of HBsAg is <1% and the lifetime risk of infection is <20%.[2,5]

Transmission in low-endemicity areas is generally horizontal in adulthood, usually through sexual transmission and contaminated needles in medical procedures or injection drug use. The results of the Basic Health Research in 2007 showed a prevalence of hepatitis of 9.4%.

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It can be said that every one person out of 10 Indonesians has ever been infected with hepatitis B.[6]

This paper describes the number of respondents (fertile age women)—including pregnant and postpartum mothers with neonates. Mothers with under-fives have a risk in their body because there is no anti-hepatitis B antibody titer, so they can be affected by hepatitis B.

Methods

The method used is a retrospective using secondary data from the Basic Health Research 2007 conducted by the National Institute of Health Research and Development of the Ministry of Health Republic of Indonesia. The data used are secondary data from the Basic Health Research 2007. It is in the form of biomedical data that can be linked to the data of public health. Samples are from respondents of fertile age women (FAW) at the Basic Health Research 2007 aged 15 to 49. Respondents in this study are the respondent in the last 12 months since the Basic Health Research 2007 data collection. Respondents have examined their pregnancy and had a postnatal health check. It also includes respondents who examined neonates under five years old. The data is linked to the biomedical data, the anti-hepatitis B antibody titer data. After the screening process, the information is FAW aged 15 to 49. Data can be matched with those who have examined pregnancy/have had a postpartum examination, checked neonates/had examined their toddlers; 1,302 respondents were eligible in this analysis. In comparison, the number of samples of women of childbearing age who have anti-hepatitis B antibody titers was 7,325 respondents.

This study had received ethical approval from the Health Research Ethics Committee of the National Institute of Health Research and Development of the Ministry of Health Republic of Indonesia, number: KS.02.01.2.1.4739.

Results

The results of anti-hepatitis B antibody titer examination from 7,325 respondents were negative for 5,451 and positive for 1,873 respondents. The percentage of the antibody results can be seen in Figure.

Table 1 shows the relationship FAW between individual characteristics and anti-hepatitis B antibodies by the age group of fertile women

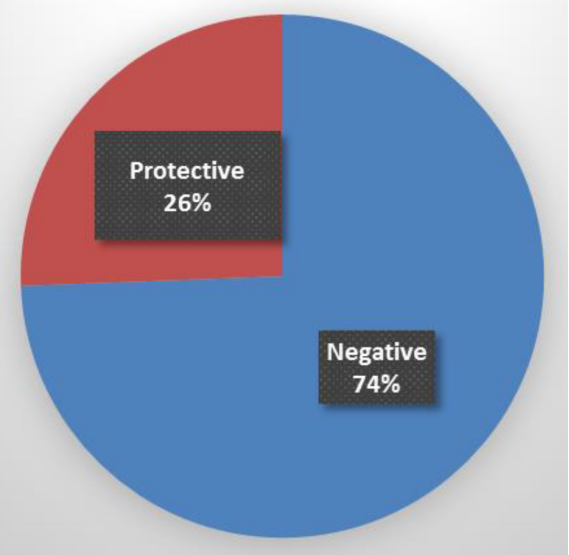

Figure Results of the Anti-HBs Antibody Examination

(15–49 years), showing that several variables have a statistically significant relationship. In the work variable, it was found that women of fertile age who did not work had a risk of 1.367 times (OR=1.367) not having antibodies/negative and statistically significant (p=0.000). Education women of high reproductive age risk 1.129 times (OR=1.129) not having antibodies/negative and statistically significant (p=0.016). The following variables are significant: women of childbearing age who are not married have a risk of 1.458 times (OR=1.458) of not having antibodies/negative and statistically significant (p=0.000). The age group (20–49 years old), the socio-economic variable of the poor, and the variable of women who did not check their health were statistically unrelated.

Multivariate analysis of independent variables is marriage, education, occupation, age group, socioeconomic level, and health checked. Multivariate analysis using binary logistic or logistic regression by a stepwise method including all independent variables and then corresponding p>0.25 were excluded in the analysis.

Table 2 shows the results of multivariate analysis, where all variables were included and analyzed simultaneously. It turned out that only one significant variable, the unmarried in marriage variable, had a significant relationship with anti-hepatitis B antibodies with a risk of 1.459 times compared to those who were married and statistically significant (p=0.000). Furthermore,

Table 1 Relationship Characteristic of Individuals with Titer Antibody Anti-hepatitis B in Fertile Age Women (15–49 Years)

Individual Characteristics	Anti-hepatitis B Antibodies			OR	95% CI	p
	Negative	Protective	Total			
Age (years)						
20–49	4,606	1,667	6,273	0.673	0.572–0.791	0.000
15–19	846	206	1,052			
Occupation						
Not work	1,149	306	1,455	1.367	1.190–1.571	0.000
Work	4,303	1,567	5,870			
Education						
Higher	3,569	1,174	4,743	1.129	1.012–1.259	0.016
Lower	1,883	699	2,581			
Marriage						
No	1,423	365	1,787	1.458	1.281–1.660	0.000
Yes	4,029	1,508	5,537			
Socioeconomic						
Poor	3,245	1,076	4,321	1.090	0.980–1.212	0.060
Rich	2,207	797	3,003			
Women checks health						
No	5,244	1,800	7,044	1.022	0.779–1.342	0.460
Yes	208	73	281			

Table 2 Multivariate Analysis the Determinants of Individual Characteristics with Anti-hepatitis B Antibody Titers in FAW

Variables	Value	Sig	Exp (B)	95% CI	Percentage Correct
Marriage	0.378	0.000	1.459	1.282–1.661	
Constant	–1.739	0.000	0.176		
Overall percentage					74.4

the overall percentage was 74.4% of marriage variables could answer the relationship between individual characteristic variables and anti-hepatitis B antibodies, whereas other variables determined the rest.

Discussion

The analysis of maternal risk factors checked for pregnancy, delivery, puerperium, neonates, and toddlers; the anti-HBs antibody titer examination results showed no significant relationship. At the same time, the age variable had a significant association with p=0.010. It proves that age prioritizes managing the hepatitis B virus (HBV). Age factors influence the presence of anti-hepatitis B antibody titers (anti-HBs). The results of the Basic Health Research, 2007, the relationship between the age of respondents with anti-hepatitis B antibody titer data is significantly related to the group of respondents aged 46–49 years.[6] Other research shows that anti-HBs titers decrease with increasing human age, especially after age 15. The research about pregnant women infected with hepatitis B can transmit the virus to their baby during pregnancy or delivery, so screening is necessary to determine the prevalence of pregnant women with hepatitis B in Malang.[7] The screening was carried out in two public health centers of Malang city, i.e., Dinoyo and Kedungkandang, two public health centers of Malang regency, i.e., Sumberpucung and Gondanglegi, and Hermina Hospital. Participants were given counseling, anamnesis, vital signs

checks, and blood sample collection. The serum of participants was tested for HBsAg and Anti-HBS. The method used was ELISA.[7]

In another study, 156 pregnant women participated in the screening. The mean age of participants was 28,5±5,8 years old, and the mean age at marriage was 22 years. Hepatitis B prevalence was 1%, and 8% positive anti-HBs were found in patients with negative HBsAg. The other research is about a centrifuge to produce serum. The serum is issued in HBsAg examination with the immunochromatography method, while HBsAg examination is based on double-antibody sandwich immunoassay for HBsAg determination. Sampling was carried out for one month. The studies of hepatitis B antigen surface (HBsAg) and anti-HBs in pregnant women are screening for vertical transmission of hepatitis B.[8,9]

The research by Sinaga et al.[10] aimed to determine the results of HbsAg and anti-HBs examination in pregnant women in Sentani. The serum sample of pregnant women in this research was 60. The method of HBsAg and anti-HBs examination used is the Immunochromatography method. Beginning with taking venous blood in pregnant women, then doing was carried out using HBsAg rapid test brand SD Bioline with sensitivity >99% specificity >99% and anti-HBs test strip brand Answer with sensitivity >99% specificity >99.5%. This research used a descriptive analysis method to determine the results of HBsAg and anti-HBs examination in pregnant women. HBsAg and anti-HBs examinations were conducted for 13% HBsAg positive infected with hepatitis B, and as many as 87% showed negative results. The anti-HBs examination showed that 15% had hepatitis B antibodies, and 85% were negative.

The results of our analysis have the same results from research on seroprevalence from pregnant women who attend routine antenatal care in South Ethiopia and Uganda. The study in South Ethiopia aimed to estimate seroprevalence and associated factors of HBV infection among pregnant women attending the Antenatal Clinic (ANC) of Arba Minch Hospital. The overall seroprevalence of HBV infection was 4.3% (95% CI=2.2–6.9%). Multivariate analysis showed a history of abortion (AOR=7.775; 95% CI=1.538–39.301) and having multiple sexual partners (AOR=7.189; 95% CI=1.039–49.755) were independent predictors of HBsAg seropositivity. In conclusion, the prevalence of HBV infection is intermediate. Therefore, screening for HBV infection should be a routine part of ANC.[11,12]

Anti-hepatitis B titer (anti-HBs) is formed from the results of immunization or individuals who have suffered from hepatitis and recovered so that the body has developed immunity against hepatitis B. It is also necessary to analyze the relationship between immunization with anti-hepatitis B antibody titer. In this study, the age of respondents and antibody titer increased. It is likely that older respondents had hepatitis B but were cured. Studying the relationship between ever having hepatitis B with an antibody titer is necessary. The results of the study by Chibwe et al.[13] showed that anti-HBs were detected using enzyme immunoassays. Health workers must emphasize routine HBV screening among pregnant women, plus appropriate management in developing countries.

Acute hepatitis B can become chronic depending on when someone is infected. If an infection occurs as a baby, then the possibility of acute hepatitis B developing into a chronic disease in about 90% of the total infants infected with HBV. The risk goes down when we get older. About 25–50% of children between 1–5 years infected with the hepatitis B virus are also at risk of becoming chronic. The risk decreases to 6–10% when someone over five years old is infected. Most people with chronic hepatitis B are infected at birth or early childhood. If someone has been infected with chronic hepatitis B since childhood, then it is likely that 25% of infected people will die if they do not get treatment. Whereas if someone is infected with hepatitis B during adulthood, chances are 90% of patients will recover, and the virus will disappear in 6 months.[14,15]

Hepatitis B can be prevented by vaccination. Anti-HB antibodies can appear in response to hepatitis B vaccination. One series of vaccinations can produce enough antibodies in 95% of healthy people. Anti-HBs antibody titers will decrease along with the age of immunization. At an older age, immune disorders will decrease anti-HB titer. Hepatitis B immunization giving will form active immunity against infections caused by the hepatitis B virus in infants, toddlers, and adults. Giving hepatitis B immunization when newborns are born for up to 7 days to break the chain of transmission from mother to baby during delivery.[16,17]

The cross-sectional study results were

conducted in Southeastern Turkey between January and April 2013 with a representative sample of community-based agriculture (n=705). The results obtained are the prevalence of HBsAg, anti-HBs, anti-HBc, anti-HBe antibodies, and seropositive, respectively 5.7%, 25.9%, 28.9%, 28.9%, 16.4%, and 36.7%. There was no relationship between HBsAg and household size, age, education level, parity, and place of birth. In contrast, HBsAg prevalence was higher in seasonal migrant workers and people living in urban areas. The prevalence of anti-HB antibodies was significantly higher in women ≥35 years old, those with high parity, and those who gave birth without the help of a health professional ($p<0.05$). The risk for HBV infection in the seasonal migration group was 4.3 times higher compared to local workers ($p=0.00$; OR=4.3; 95% CI=2.2–8.4), with a prevalence rate of 11%.[18]

The importance of the HBV screening test of pregnant women was also carried out by Yi et al.[19] and Kambuno et al.[20] Their study suggested screening pregnant women to find out whether they are infected with hepatitis B. Early immunization of babies born to women infected with hepatitis B is highly recommended, and check HbsAg for those women going to marry.

Conclusions

In this analysis, there was no relationship between FAW, who examined their pregnancy and postpartum health, and FAW, who examined neonates and infants with HBs antibody titers. However, there was a significant relationship between FAW age groups and antibody titers anti-HBs. That is in the age group 15–20 years, and respondents who are not married have a relationship with negative antibodies anti-Hbs.

Conflict of Interest

The authors declare that there are no competing interests. All authors read, approved, and have the same contribution to the manuscript.

Acknowledgments

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RESEARCH ARTICLE

Effect of Massage and Bathing or Swimming toward Baby Weight Improvement

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Abstract

Body weight or anthropometric measure is the most important and most frequently used measure to see the development of infants. Stimulating the growth in infants aged 4 to 6 months can be done in two ways: massage the baby's body and continue by bathing or swimming. This study aimed to analyze the effect of massage and bathing or swimming on an infant's weight gain in Kinara Mom and Baby Spa, Kerkep village, Gurah district, Kediri regency. The research design is quasi-experimental, with one group pre-test-post-test design approach, carried out in August–October 2021. The sample was babies aged 4–6 months using purposive sampling with a sample size of 20 babies—independent variables were baby massage and bathing or swimming on infants, and the dependent variable was weight gain. The instrument used is a weight-monitoring sheet. Data were analyzed using pairs sample t-test analysis. The results showed that all 20 babies experienced weight gain. The conclusion is that massage and bathing or swimming affect weight gain in infants aged 4–6 months.

Keywords: Baby, bathing, massage, swimming, weight gain

Introduction

According to the 2019 Indonesian Health Profile, 15.2% of infants still have malnutrition problems, with malnutrition being the main factor causing stunting. The prevalence of stunting in Indonesia in 2018 was 30.8% which is very high.[1]

A baby aged 4 to 6 months provides an excellent opportunity for parents to strive for optimal growth and development. During this age, children experience rapid growth and generally reach two times their weight at birth. Nutritional disorders at 4 to 6 months are permanent and cannot be reversed even though dietary needs in the next period were met. Good nutrition and a healthy body are the keys to preventing stunting. Monitoring the baby's weight is very important because weight gain indicates whether the baby has developed optimally or not. Special efforts to improve nutritional status can be made through baby massage, bathing, or swimming. An update from previous research monitoring baby growth and development is not only in weight gain but also in the length of the baby's.[2]

Baby massage is also known as touch therapy, one of the most effective techniques that combine the physical benefits of human touch with emotional benefits such as an inner bond. Baby massage is also an alternative and straightforward way to improve health. It can be done at home and create an internal bond between children and parents.[3] The benefits of baby massage are to develop communication, reduce stress, relieve symptoms of pain, and reduce pain.[4]

Doing a baby spa regularly can increase the weight of babies with low body weight aged 4 to 6 months.[5–8] Swimming is the first safe sport to be introduced to babies. Therefore, swimming and massage can help improve a baby's growth and development. In addition, children can gain new skills such as swimming and floating through activities in the water environment. The primary mechanism that can explain the effect of baby massage on increasing infant weight is the release of beta-endorphins and an increase in vagus nerve tone, which can increase the baby's appetite and stimulate suction. In addition, massage can stimulate photonic nerves, such as the smooth muscles of the intestines. Photonic nerves stimulate the release of hormones that help absorb food in the intestines so that nutrients are well absorbed.[5] Therefore, babies aged 4–6 months need to be massaged, bathed, or swam to increase the baby's appetite, so that the baby's weight can increase. The paper analyzes the effect of massage and bathing or swimming on weight gain in infants aged 4 to 6 months at Kinara Mom and Baby Spa in Kerkep village, Gurah district,

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Kediri regency, East Java province.

Methods

This research is a quantitative, quasi-experimental design with a one-group pre-test-post-test design approach, starting from August–October 2021. The study was carried out at Kinara Mom and Baby Spa in Kerkep village, Gurah district, Kediri regency, East Java province. The sampling technique used was purposive sampling with a sample size of 20 respondents (11 boys and nine girls). The criteria are that the baby's age is 4–6 months and can lift the head without assistance (show optimal growth and development). The research variables observed included baby massage and bathing or swimming in infants. In addition, the weight gain in infants was observed using an observation sheet. Statistical analysis used the pairs sample t-test (test of two samples in pairs). The ethics committee approved the study from the Research Ethics Committee of Universitas Kadiri with letter number 006/07/VII/EC/KEP/UNIK/2021.

This research was conducted for three months. Each baby was given the intervention twice a week, so the total treatment for each was six times. Every treatment visit, an evaluation of the child's weight and length is recorded. The spa staff carries out this treatment. The time of massage treatment is 30 minutes, while the swimming treatment is a maximum of 20 minutes. Each of these treatments was carried out on children in a state that was not fussy or quiet so that all babies received the same treatment time. Then observations were made in the treatment group without using the control group. So the observations were recorded and compared with the World Health Organisation's normal growth standards for boys and girls.

Results

Based on Table 1, it can be seen that the number of respondents was 20, with details of male sex as many as 11 babies, while female sex as many as 9 babies. The baby's age was taken at an average age of 4 months.

Based on Table 2, it can be seen, after being given massage therapy and bathing or swimming, there were changes in the baby's weight as many as 20 babies experienced weight gain.

Table 3 shows there are improvements in the weight gain of babies who are given massage and bathing or swimming The results showed that body weight before massage and bathing or swimming was 6.96 kg, with a standard deviation of 0.36. While body weight after massage and

Table 1 Frequency of Age and Gender of Babies

Number	Babies	
	Age	Sex
1	4 months 2 days	Boy
2	4 months 24 days	Girl
3	4 months 1 day	Girl
4	4 months 5 days	Boy
5	4 months 7 days	Boy
6	4 months 11 days	Girl
7	4 months 8 days	Boy
8	4 months 5 days	Girl
9	4 months 1 day	Boy
10	4 months 8 days	Girl
11	4 months 12 days	Girl
12	4 months 1 day	Boy
13	4 months 8 days	Boy
14	4 months 9 days	Boy
15	4 months 12 days	Girl
16	4 months 3 days	Boy
17	4 months 2 days	Girl
18	4 months 9 days	Boy
19	4 months 10 days	Girl
20	4 months 7 days	Boy

Table 2 Distribution of Respondents' Frequency based on Changes in Baby Weight Gain

Weight Change	n=20
Weight gain	20
No weight gain	0

Table 3 Frequency of Baby's Weight before and after Baby Massage and Bathing or Swimming

Weight	Mean (kg)	SD	Min–Max
Before intervention	6.96	0.36	6.50–7.80
After intervention	7.94	0.29	7.50–8.70

Table 4 Statistical Test Results in the Effect of Massage and Bathing on Baby Weight Improvement

	95% CI		t	df	Sig (2-tailed)
	Lower	Upper			
Baby weight at the first meeting (kg)–baby weight at the next meeting (kg)	−1.09220	−0.86780	−18.281	19	0.000

bathing or swimming mean 7.94 kg, with a standard deviation of 0.29. The average increase in body weight before and after is known to be 0.98 kg. This shows that more routine massage therapy is given and bathing or swimming is always followed by an improvement in the baby's weight.

The results of the t-test obtained p=0.000 (p<0.05), which means that statistically it shows there is the effect of massage and bathing or swimming on increasing the weight of babies aged 4–6 months (Table 4).

Discussion

The data obtained have been analyzed using the pairs sample t-test analysis. The results obtained are −18.281, with a significance value of p<0.05. These results indicate the effect of massage and bathing or swimming on weight gain in infants aged 4–6 months. From the results of the pairs sample t-test, it is known that Sig (p)=0.000, Sig (p)<α, then H_1 is accepted, H_0 is rejected, it means that there is an effect of baby massage and bathing or swimming on increasing the weight of babies aged 4–6 months. Furthermore, the significance of massage and bathing or swimming can be seen from the results of the confidence interval. The significant effect of increasing the baby's weight is 0.8678–1.0922 kilograms or growing between 0.9–1.1 kilograms.

The results of the difference in the average body weight after massage and bathing or swimming are that there is an average first weight (pre-test) of 6.995 kg with a standard deviation of 0.35759 and an average post-test weight of 7.935 kg with a standard deviation of 0.29069 and an average mean −0.98000. The results of the pairs sample t-test test obtained a t value of −18.281 with p=0.000 (p<0.05), which means that statistically, it shows the effect of massage and bathing or swimming on increasing the weight of infants aged 4–6 months.

It is similar to research by Prastiani and Setyaningrum[5] regarding the relationship between the frequency of baby spa and an increase in baby weight at the Oemah Moengil Baby Spa Clinic, Tegal city. There is a relationship with p=0.01 (p<0.05) between the frequency of baby spa with an increase in baby weight. This study is in line with research conducted by Marni,[9] which stated that there is an effect of baby massage on increasing infant weight in Giripurwo village, Wonogiri district, with p<0.025. In addition, this research is in line with the study conducted by Ekasari and Arum[7] regarding the relationship between the frequency of baby spa visits with the increase in body weight of babies aged 3–12 months at the Luqi Medika Clinic. The study results showed a significant relationship with p=0.001.

The results are supported by the research conducted by Utami et al.,[10] on the effect of baby massage and spa on weight gain. This is also under the results of Margiana and Muflihah's[8] research, which states that there is a relationship between a baby spa and baby weight at *Rumah Sehat Kita*, Purwokerto.

The results showed that after being given massage therapy and bathing or swimming, there were changes in the baby's weight. As many as 20 babies experienced weight gain. The babies were given massage stimulation therapy and bathed or swam regularly (every two weeks for three months, the treatment was carried out six times). Several previous studies state that baby massage is an alternative effort to improve health status, which is the simplest thing at home.[2,3,9] Besides, baby massage can also cause an inner bond between parents.[3,4] In addition, babies are often given massage at home, which makes the baby's sleep pattern regular.[10–14] There is a decrease in the stress hormone cortisol, and it creates a sense of comfort and well-being affection.[15] Babies can feel relaxed through baby spa activities with massage stimulation, bathing, and swimming.

Relaxation for the baby is not only to relieve stress but also an important thing for the baby's growth and development process. In addition, the increased growth that occurs in babies who have taken massage and bathing or swimming can also increase the baby's appetite, so that the baby's weight increases and the baby looks healthy. This is associated with vagal nerve stimulation, which can increase the absorption of nutrients by the digestive tract. Massage therapy can improve sleep patterns, circulation, and more stable brain activity. Massage and bathing or swimming in infants make the baby calmer, so it is not often fussy.[10,15]

Based on the results of the study, it can be seen that there are differences in the weight gain of babies who are given massage and bathing or swimming infants. The results showed that body weight before massage and bathing or swimming was 6.96 kg, with a standard deviation of 0.36, with a minimum body weight of 0.50 kg to a maximum weight of 7.80 kg. Meanwhile, body weight after massage and bathing or swimming means 7.94 kg, with a standard deviation of 0.29, with a minimum body weight of 7.50 kg to a maximum weight of 8.70 kg. The average increase in body weight before and after is 0.98 kg for three months of treatment. While the effect can be seen in the confidence interval, the significant impact of increasing the baby's weight is 0.8678 kg to 1.0922 kg, or the baby's weight grows between 0.9 to 1.1 kg. It shows that the more routine massage therapy is given, the increase always follows bathing or swimming in the baby's weight.

Babies with no increase in weight, possibly because the baby has a history of low birth weight. Low birth weight is also possible because the baby is sick with coughs and colds, so the frequency of breastfeeding is reduced.[16] The baby's weight gain can also be hampered if the mother does not give breast milk and the nutrition is not fulfilled.[17,18] Several factors can affect a baby's weight, namely child nutrition, child health status, immunization, genetics, housing, environmental sanitation, chromosomal abnormalities, socioeconomic status, and drugs.[17–21] Therefore, health workers should provide counseling about the importance of the child's growth and development period and apply infant massage therapy and bathing and swimming to help improve the baby's growth and development so that it is more optimal. And for the community to optimize baby growth by increasing baby weight through baby massage and bathing or swimming because massage and bathing or swimming can improve baby's weight.

Conclusion

It can be concluded that there is an improvement in the baby's weight gain after massage and bathing or swimming.

Conflict of Interest

There are no conflicts that occur in this study.

Acknowledgments

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RESEARCH ARTICLE

Role of T2-weighted and Diffusion-weighted Imaging in Cervical Malignancy in Developing Countries

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Abstract

Cervical cancer is the second most common gynecologic malignancy in Asia and is the leading cause of death in women in developing countries. The cervical cancer stage will significantly affect the prognosis and management. Based on the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification of cervical cancer, magnetic resonance imaging (MRI) has a crucial role in determining cervical cancer staging. This study aimed to evaluate the role of T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI) sequences in assessing cervical carcinoma, with the pathological diagnosis being taken as the standard for cervical cancer diagnosis. This study was conducted on seven patients diagnosed with cervical cancer from pathological examination in January 2020 to March 2021 in the Department of Radiology Dr. Hasan Sadikin General Hospital Bandung. We detect the presence of locoregional lesions and extensions of cervical carcinoma using MRI with T2WI and DWI sequences in patients who have previously been diagnosed histopathologically. This study involved seven cervical cancer patients. Pelvic MRI with T2WI and DWI sequences was performed. The imaging results in these patients show that one patient has stage IB1 cervical cancer, four patients have stage IIB, one patient has stage IIIA, and one has stage IIIC1 cervical cancer. This study concluded that T2WI and DWI sequences in MRI are essential and sufficient for diagnosing cervical cancer.

Keywords: Cervical malignancy, diffusion-weighted imaging, magnetic resonance imaging, T2-weighted imaging

Introduction

Cervical cancer is Asia's second most common gynecologic malignancy after uterine and ovarian malignancies. According to 2020 Globocan data, in developing countries such as Indonesia, cervical cancer is the second most common cancer after breast cancer and is the leading cause of death in women.[1]

Radiology plays a vital role in the diagnosis of cervical cancer and determining the staging of cervical cancer.[2] Cervical cancer staging will significantly affect the prognosis and management.[3,4] Based on the revised classification from the International Federation of Gynecology and Obstetrics (FIGO) in 2018, cross-sectional imaging, especially magnetic resonance imaging (MRI), has a vital role in determining the staging.[4] MRI can determine the origin of the mass, the size of the masses more accurately, invasion of the parametrium, pelvic wall, vagina, bladder, ureter, and rectum, and see the presence of lymph node involvement.[5–7] The necessary MRI sequences in cervical cancer are T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI). In T2WI, we can determine if there is tissue edema or necrosis due to cervical cancer. DWI can be used to see the presence of cervical cancer lesions and to evaluate quantitatively the diffusion properties based on the value of the apparent diffusion coefficient (ADC).[8–10]

This study aimed to evaluate the role of T2WI and DWI in assessing cervical carcinoma, with the pathological diagnosis being taken as the standard for cervical cancer diagnosis.

Methods

This study was conducted on seven patients diagnosed with cervical cancer from pathological examination in January 2020 to March 2021 in the Department of Radiology Dr. Hasan Sadikin General Hospital Bandung. They underwent pelvic MRI with T2WI and DWI sequences and had not yet undergone therapy. The processed data is secondary data from patient medical records and picture archiving and communication

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systems (PACS) in Dr. Hasan Sadikin General Hospital Bandung. The Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung approved this study with a number: LB.02.01/X.6.5/330/2020.

Results

This study consisted of seven cases of cervical cancer, confirmed by histopathological examination. Only one patient who underwent an immunohistochemistry (IHC) examination showed positive for P16 and CK, consistent with cervical cancer. The median patient's age was 49 years. All patients were married, with two having been married twice. The median duration of complaints experienced by patients until diagnosis was four months. MRI examination using T2WI and DWI sequences showed that one patient has stage IB1 cervical cancer, four patients have stage IIB, one patient has stage IIIA, and one patient has stage IIIC1 cervical cancer (Table).

Case 1. A 47-year-old woman came with complaints of vaginal bleeding, especially after sexual intercourse, five months ago. History of using implant contraception dan injections for two years. The patient had menarche at 15 years old and menopause at 45 years old. The patient had 6 children. The patient had never received a cervical cancer vaccination (Figure 1).

Case 2. A 51-year-old, nulliparous, woman with chief complaints of vaginal bleeding for four months accompanied by vaginal discharge, lower abdominal pain, and postcoital bleeding. The patient has menarche at 14 years old and is married at 18 years old. The patient had never received a cervical cancer vaccination (Figure 2).

Case 3. A 57-year-old woman came with chief complaints of vaginal bleeding for ten months. A foul-smelling vaginal discharge accompanies complaints, lower abdominal pain radiating to the waist. The patient had a history of being married twice, the first marriage when the patient was 17 years old. The patient had menarche at 13 years old and menopause at 49 years old. The patient uses injection contraception every three months. The patient had never received a cervical cancer vaccination (Figure 3).

Case 4. A 40-year-old woman, P1A0, presented with vaginal bleeding for seven months. Complaints are accompanied by pain in the lower left abdomen, radiating to the left thigh, and vaginal discharge mixed with blood. The patient had a history of bilateral ovarian cysts. The cyst was removed in October 2020 with the results of bilateral mucinous ovarian cystadenoma. The patient had menarche at 16, got married at 19, and is not currently menopausal. The patient had no history of contraceptive use. The patient had never received a cervical cancer vaccination (Figure 4).

Case 5. A 60-year-old woman complained of vaginal discharge for four months accompanied by lower abdominal pain. The patient had menarche at 12 years, menopause at 45 years, and there was no history of using contraception. The patient had never received a cervical cancer vaccination (Figure 5).

Case 6. A 60-year-old woman complained of vaginal bleeding for two months. Patients with menarche and married at 14 years old and

Table Patients Characteristics

Characteristics	n=7
Age (years)	
<45	2
46–64	5
>65	0
Marital status	
Married	7
Divorced	0
Not married	0
Total parity	
Have no children	1
Have one children	2
Have children >1	4
Menarche (years)	
<12	0
>12	7
Contraception	
No contraception	0
Hormonal	7
Non-hormonal	
Pathology report	
Adenocarcinoma	1
Squamous cell carcinoma	5
Non-Keratinizing epidermoid cell carcinoma	1
Stage of cervical cancer	
Early (IA, IB, IIA)	5
Advanced (IIB, IIIA, IIIB, IIIC, IVA, IVB)	2
Vaccination	
Yes	0
No	7

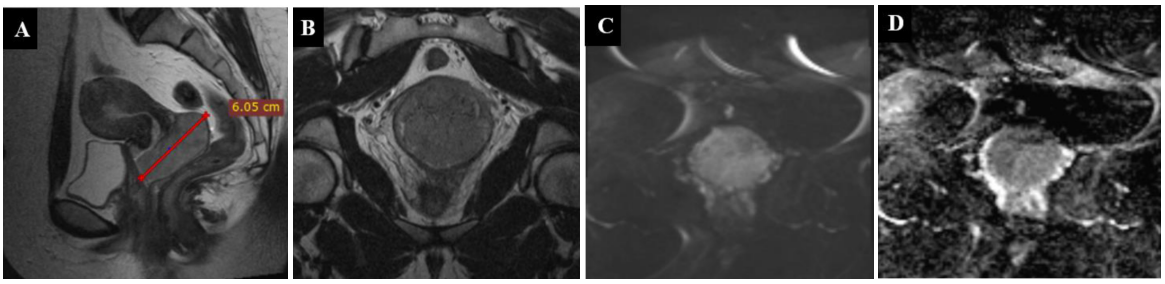

Figure 1 Pelvic MRI Examination of Case 1

The patient showed stage IIB cervical cancer based on the 2018 FIGO. (**A**, **B**) Sagittal and axial T2WI showed a 6.05 cm hyperintense lesion in the cervical region that appeared to infiltrate the left parametrium. Superior vaginal structure, pelvic wall, bladder, and rectum are still intact. Superior vaginal structure, pelvic wall, bladder, and rectum are still intact. (**C**, **D**) DWI and ADC show a restricted area in the cervical region

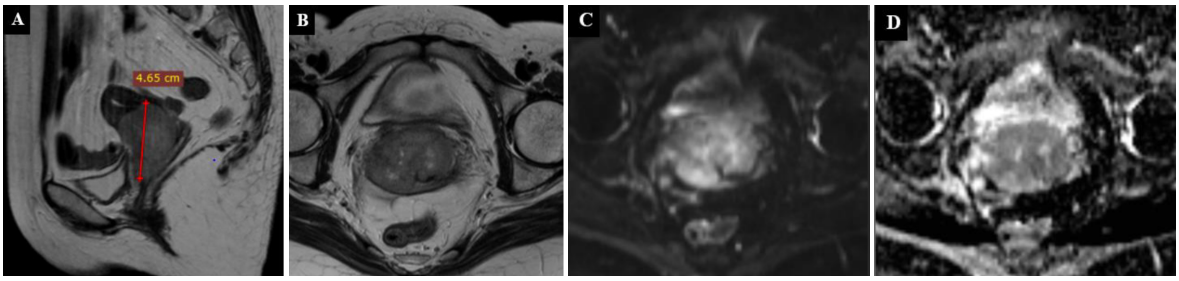

Figure 2 Pelvic MRI Examination of Case 2

The patient showed stage IIB cervical cancer based on the 2018 FIGO. (**A**, **B**) Sagittal and axial T2WI showed an inhomogeneous hyperintense lesion measuring 4.65 cm in the cervical region that appeared to be infiltrating the uterine corpus, superior ⅔ of the vagina, and the right-left lateral parametrium. The ⅓ inferior of the vagina, pelvic wall, bladder, and rectum are still intact. (**C**, **D**) DWI and ADC sequences show it is restricted in the cervical region

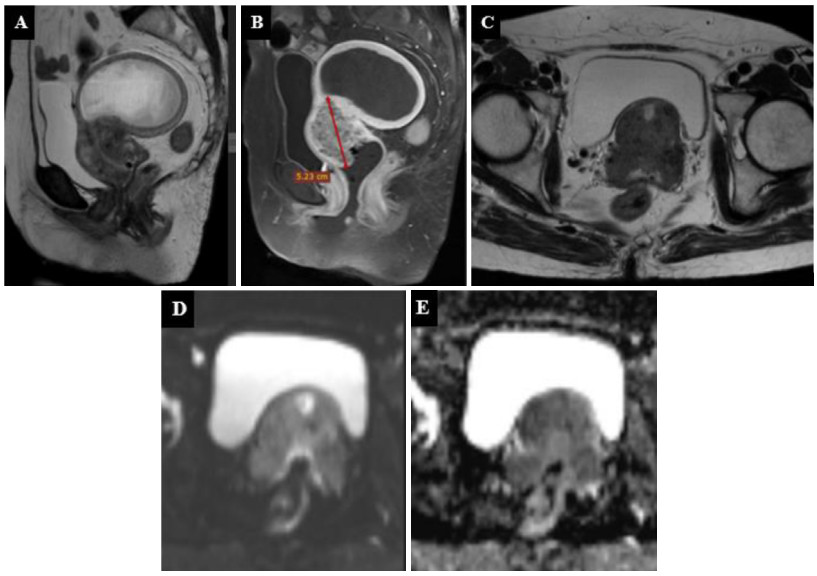

Figure 3 Pelvic MRI Examination with Contrast in Case 3

The patient showed stage IIB cervical cancer based on the 2018 FIGO with endometritis and cervical canal stenosis due to mass effect. (**A**) Sagittal T2WI showed an inhomogeneous mass in the cervical region measuring 5.23 cm, which partially gave a hyperintense signal. The superior vagina, rectum, ureters, and urinary bladder seem intact. (**B**) There was an enhancement in contrast administration. (**C**) The hypodense line that separates the cervix from the parametrium was no longer visible, consistent with parametrium infiltration. (**D**, **E**) DWI and ADC sequences showed restricted areas

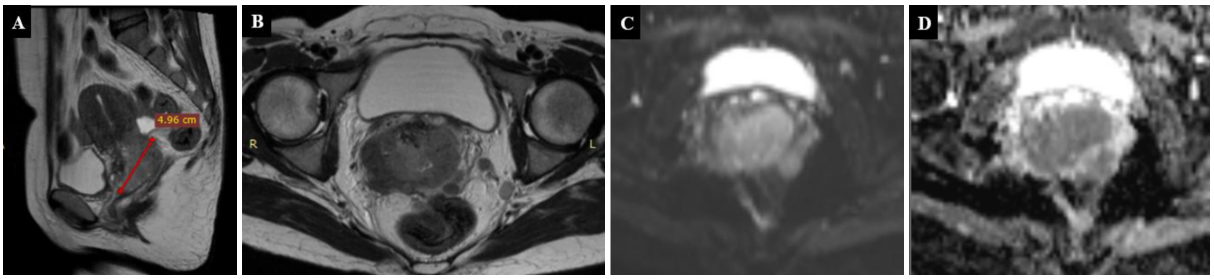

Figure 4 Pelvic MRI Examination of Case 4

The patient showing stage IIIC1 cervical cancer based on the 2018 FIGO. (**A**, **B**) Sagittal and axial T2WI showed an inhomogeneous hyperintense lesion measuring 4.96 cm in the cervical region that infiltrated the uterine corpus, superior ⅔ of the vagina, and parametrium. There were also multiple enlarged lymph nodes in the pelvic area. (**C**, **D**) DWI and ADC sequences showed a restricted area in the cervical region

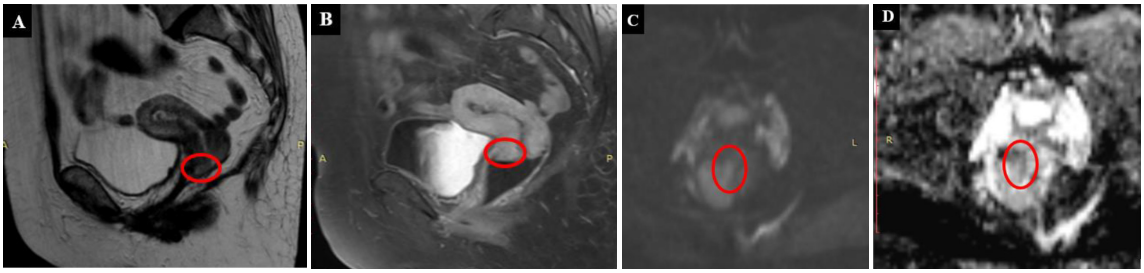

Figure 5 Pelvic MRI Examination of Case 5

The patient showed stage IB1 cervical cancer based on the FIGO 2018. (**A**, **B**) On sagittal T2WI and T1 post-contrast images showed a small lesion that gave a hyperintense signal, measuring 1.36 cm in the cervical region. In contrast administration, minimal enhancement was seen. (**C**, **D**) DWI and ADC sequences showed a restricted area in the cervical region

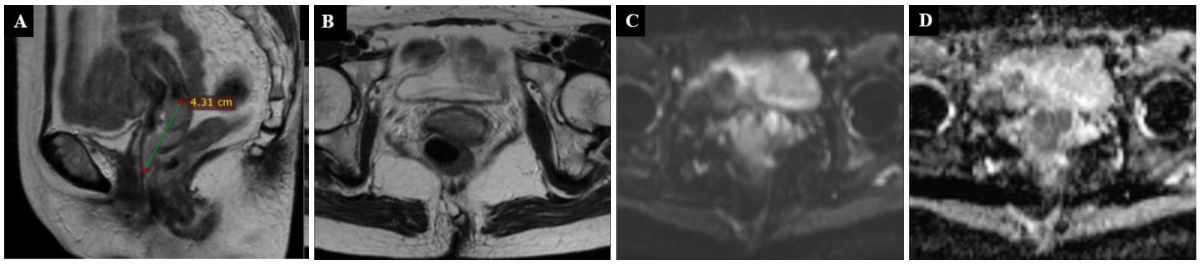

Figure 6 Pelvic MRI Examination of Case 6

The patient showed stage IIIA cervical cancer based on FIGO 2018. (**A**, **B**) Sagittal and axial T2WI showed a 4.31 cm hyperintense lesion in the cervical region that infiltrated the uterine corpus and inferior ⅓ of the vagina. The parametrium appears intact. (**C**, **D**) DWI and ADC sequences showed a restricted area in the cervical region

menopause at 50 years old. The patient had never received a cervical cancer vaccination (Figure 6).

Case 7. A 39-year-old woman came with chief complaints of vaginal discharge for four months, yellowish-white in color. Complaints are accompanied by pain in the lower abdominal area. The patient had menarche at 16 years old and had a history of being married twice, at 23 and 33 years old. The patient was not menopausal and used injectable contraception. The patient had never received a cervical cancer vaccination (Figure 7).

Discussion

Cervical cancer is the fourth most common cancer in women worldwide.[1] However, in developing countries like Indonesia, cervical cancer is the

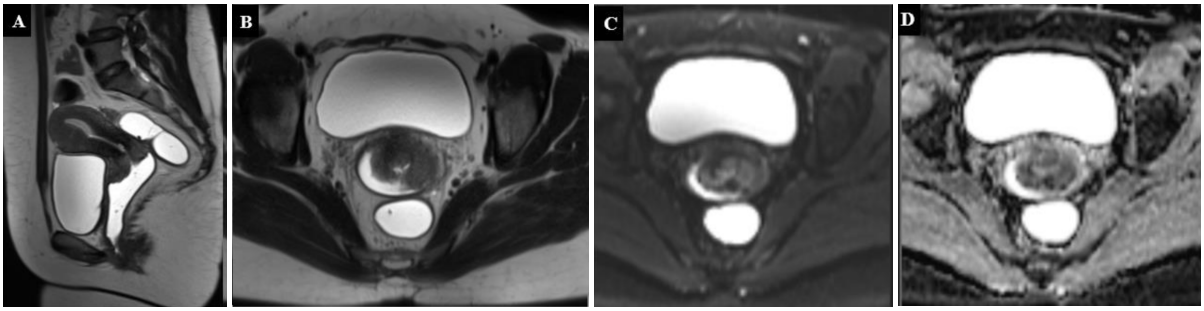

Figure 7 Pelvic MRI Examination of Case 7
The patient showed stage IIB cervical cancer based on the FIGO 2018. (**A**, **B**) Sagittal and axial T2WI showed hyperintense lesions in the cervical region that infiltrated the uterine corpus, the superior part of the vagina, and the left lateral parametrium. (**C**, **D**) DWI and ADC sequences showed the restricted area in the cervical region

most common malignancy.[1] It is the leading cause of death due to malignancy in women. Cervical cancer is a malignancy in the cervical tissue, the most inferior part of the uterus, and is associated with the vagina. Human papillomavirus (HPV) infection is a factor that initiates cell dysplasia and carcinogenesis in cervical cancer.[11–16]

Cervical cancer at an early stage is usually asymptomatic and can only be detected by cytological examination. The initial complaint is usually bleeding after intercourse, outside the menstrual period, and after menopause. At an advanced stage, pelvic pain and symptoms related to micturition and defecation may occur due to the involvement of the bladder and rectum.[3,4,11–13,17]

In October 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised its cervical cancer criteria.[4] Based on this revised classification, cross-sectional imaging, especially magnetic resonance imaging (MRI), has a crucial role in determining cervical cancer staging.[3,4,6,17–19] MRI can determine the origin of the mass, the size of the masses more accurately, invasion of the parametrium, pelvic wall, vagina, bladder, ureter, and rectum, and see the presence of lymph node involvement.[5,17,18] In our study, we highlight the importance of T2WI and DWI-ADC sequences in cervical cancer. In T2WI, we can determine if there is tissue edema or necrosis due to cervical cancer. DWI can be used to see the presence of cervical cancer lesions and to evaluate quantitatively the diffusion properties based on the value of ADC.[20–23]

In our study, the lesion in all seven patients can be seen in T2WI MR sequences and confirmed by the appearance of the restricted area in DWI-ADC. In T2WI, the lesion appeared hyperintense due to water content, either et causa inflammation due to infiltration of a cancer cell or necrosis of the tissue. There was a restricted area in DWI-ADC sequences that gave a hyperintense signal in DWI and hypointense in the ADC map.[24] In our study, contrast agent administration did not play an essential role in diagnosing cervical cancer. In Case 5, contrast enhancement is minimal in a small lesion, and the DWI-ADC had a more vital role in confirming that this was a malignant lesion. Contrast administration was essential in seeing a complication such as endometritis due to cervical stenosis due to mass compression, as seen in Case 3.

Conclusions

In this study, we confirm that T2WI and DWI MR sequences have a significant role and are sufficient for diagnosing cervical cancer. We hope these findings can be implemented in developing countries where the resources are limited to maximize the radiologist's role in diagnosing and staging cervical cancer and improve our services to cervical cancer patients.

Conflict of Interest

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

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RESEARCH ARTICLE

Knowledge Level of Midwives before and after an Online Training Participation

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Abstract

Fetal growth restriction is a prevalent pregnancy issue linked to numerous unfavorable postnatal outcomes. Suboptimal uterine-placental perfusion and inadequate fetal feeding are the vital pathophysiologic causes. Midwives play a crucial role in informing pregnant women about vitamin D inadequacy. This paper aims to determine the difference between midwives' prior and post-webinar knowledge levels. It was a cross-sectional study of individuals who participated in a webinar on November 21, 2021. Subjects were selected using a total population sampling approach from all midwives who participated in the webinar and completed pre-and post-tests. The difference between knowledge levels was evaluated using the difference between the pre-test and post-test scores in the general category. There was an increase in the number of participants who successfully answered the five-question component, a decrease in the number of participants who correctly answered the two-question section, and no change in the number of subjects who correctly answered question number one. The average score on the post-test was higher (67.28) than the pre-test (63.10), while the median score was the same at both time points. After attending a webinar, there was an increase in the proportion of subjects with a high level of knowledge (11.4% to 24%) and a drop in the proportion of subjects with a poor level of knowledge (32.3% to 27.1%). In conclusion, there was an improvement in the knowledge level of midwives before and after the webinar participation.

Keywords: Fetal growth restriction, knowledge, midwives, vitamin D deficiency, webinar

Introduction

Fetal growth restriction is a prevalent pregnancy issue that harms postnatal outcomes.[1] Placental insufficiency accounts for five to ten times the lifetime mortality and morbidity of fetal growth restriction, a common pregnancy-related illness.[1] These increase the likelihood that the fetus has metabolic disorders, polycythemia, pulmonary disease, intraventricular hemorrhage, cognitive impairment, and cerebral palsy. All can affect both full-term and premature infants.[2,3]

Maternal, fetal, and placental factors constitute the pathogenesis of fetal growth restriction.[2–4] Nutrition is one of the elements in maternal etiology. There was a correlation between small-for-gestational-age (SGA) baby size and maternal nutrition.[4–6] Previous studies discovered that a deficit in vitamin D was related to SGA in mothers and that moms with higher serum 25(OH)D levels may also be at a moderately increased risk.[7–9]

The occurrence of vitamin D insufficiency in pregnant women is a significant public health concern.[10–14] Vitamin D deficiency increases the risk of preeclampsia, gestational diabetes, preterm labor, and delivery of SGA infants.[10–14] It also increases the inadequate fetal immune system, wheezing and eczema, asthma, rickets in infants, decreased bone density, schizophrenia, and the risk of respiratory infections in infants.[10–15]

Knowledge of vitamin D deficiency is unquestionably essential for prenatal care providers. As the first line of antenatal care for pregnant women in Indonesia, midwives ensure that patients do not suffer from vitamin D deficiency throughout pregnancy. Due to the widespread COVID-19 pandemic in 2020, educational institutions and hospitals rely on e-learning to deliver continuing medical education. E-learning, often known as online learning, is the acquisition of pertinent knowledge and skills through the Internet and other information technologies. Currently,

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medical schools, teaching hospitals, and other health organizations are rapidly expanding their use of e-learning as a learning method.[16–19]

Webinars are e-learning utilized frequently in continuous learning for health workers.[20] The Merriam-Webster Dictionary describes a webinar as "a live online instructional session during which viewers may submit questions or comments."[21] Webinars are a type of online learning intervention backed by audiovisual software that connects students with the instructor. In addition, the synchronized nature of webinars enables individuals in different regions to exchange questions, suggestions, and comments.[20] Webinars are delivered live, as well as being recorded and saved for later review, reducing barriers to participating in professional development events.[22] This study aims to determine the difference between midwives' prior and post-webinar knowledge levels.

Methods

A cross-sectional study was conducted on November 21, 2021. Subjects were selected using a total sample approach from all midwives who participated in the webinar and submitted complete pre-and post-test data. There were 370 participants, but only 350 completed pre-test and post-test data. The Health Research Ethic Committee of Dr. Hasan Sadikin General Hospital granted LB.02.01/X.6.5.76/2022.

During a webinar and before administering the pre-and post-tests, informed consent to participate in the study was explained verbally. The webinar participants who participated in this study were to make decisions independently and without interference from any side.

The pre-test and post-test questions consist of eight true-false questions from relevant sources. Each accurate response received a score of 12.5, while each incorrect answer received a score of 0. The comparative analysis of knowledge levels was based on pre-and post-test scores. For example, with scores of 56, 76, and 76, the degrees of knowledge were classified as low, moderate, and high, respectively. A statistical test also evaluated the average and median pre-and post-test scores.

The information was analyzed using IBM SPSS version 21. (IBM Corp, Armonk, USA). A descriptive statistic was used to illustrate the average pre-and post-test scores.

Results

Table 1 showed the pre-test and post-test answers to each question component. There was an increasing number of participants who answered correctly in the 5 questions component (question number 2, 3, 4, 6, and 7). Meanwhile, a reduced number of participants who answered correctly in 2 questions (question number 5 and 8) and a same number of subjects who answered question number 1 correctly were obtained.

The subjects' pre-test and post-test scores were compared in Table 2 and Table 3. Before attending the training, a range of replies to each question suggested that more than one-third of participants had a poor level of knowledge regarding vitamin D deficiency in pregnant women. In contrast, slightly more than ten percent of participants had a high level of knowledge. After attending the webinar, there was a rise in the proportion of subjects with a high level of knowledge and a decrease in the proportion of subjects with a low level of knowledge. In addition, the average score on the post-test was more significant than the score on the pre-test, while the median score was identical.

Discussion

The goal of this study was to evaluate the pre- and post-webinar knowledge levels of webinar attendees. The study indicated that the webinar was successful in enhancing midwives' knowledge. Overall, the average post-test score went up, which shows that people now know more about how a lack of vitamin D can cause fetal growth restriction.

Due to poor maternal and fetal outcomes, low vitamin D levels, as measured by 25-hydroxyvitamin D [25(OH)D], continue to be an epidemic during pregnancy. Vitamin D deficiency during pregnancy is also connected with many major placental insufficiency-related problems, including fetal growth restriction. On the other hand, it has been demonstrated that enough vitamin D intake during pregnancy reduces the risk of issues and positively influences the baby's weight. On the other hand, the biological effects of vitamin D on prenatal outcomes have yet to be agreed upon.[23]

The placenta is responsible for most vitamin D metabolism during pregnancy, and adequate placental growth is essential for a healthy

Table 1 Pre-test and Post-test Answers of Each Question Component

Number	Questions	Correct Pre-test Answers n=350 (%)	Correct Post-test Answers n=350 (%)
1	Vitamin D has an important role for fetal growth	349 (99.7)	349 (99.7)
2	Impaired fetal growth in utero without congenital defects could not be prevented	285 (81.4)	290 (82.9)
3	Melanin will increase D3 levels in the blood	69 (19.7)	105 (30.0)
4	Fruits are one of the sources of vitamin D	139 (39.7)	164 (46.9)
5	Vitamin D level measurement in pregnant women is necessary	294 (84)	281 (80.3)
6	Vitamin D could only be added through daily vitamin D intake	183 (52.3)	199 (56.9)
7	Antenatal care visits based on the 2020 MCH handbook were at least five times in 1 pregnancy period	143 (40.9)	208 (56.8)
8	The risk of preeclampsia screening in the MCH handbook were not necessary to be filled in by the midwives	305 (87.1)	291 (83.1)

Table 2 Comparison of Pre-test and a Post-test Scores of Subjects

Knowledge Level	Pre-test n=350 (%)	Post-test n=350 (%)
Low	113 (32.3)	95 (27.1)
Moderate	197 (56.3)	171 (48.9)
High	40 (11.4)	84 (24.0)

pregnancy. Cytotrophoblast cells are the predominant placental cells that play a significant role during pregnancy.[23]

Increased knowledge of health workers after attending webinars was found in several studies that have been previously conducted.[23–25] The improvement of midwives' knowledge in this study was consistent with another study conducted in Australia that assessed midwives' knowledge at three-time points with the total knowledge score statistically difference in pre to immediate questionnaires and immediate to 6–8 weeks post-workshop/webinar.[24]

As stated in Table 1, question number one, "vitamin D has an important role for fetal growth," there is no improvement after intervention since the score is already high (99.7%). Question two, "impaired fetal growth in utero without congenital defects could not be prevented," show relatively low improvement from 81.4% to 82.9% after intervention because the midwives already had good knowledge before intervention. Question number three, "melanin will increase D3 levels in the blood," showed a relatively high increased score after the intervention, from 19.7% to 30%. Question number four, "fruits are one of the sources of vitamin D," only showed a relatively low increased score from 39.7% to 46.9%. Interestingly, there are decreased scores on question number five about "vitamin D level measurement in pregnant women is necessary," from 84% to 80.3%". The question number six "vitamin D could only be added through daily vitamin D intake," only showed a relatively low

Table 3 Difference in Knowledge Levels before and after Webinar Participation based on Pre-test and Post-test Total Scores using Descriptive Analysis

Variables	Median (Min–Max)	Mean±SD
Pre-test score (n=350)	62.5 (25.0–100.0)	63.10±15.31
Post-test score (n=350)	62.5 (25.0–100.0)	67.28±18.67

increased score from 52.3% to 56.9%. Question seven, "antenatal care visits based on the 2020 MCH handbook were at least five times in 1 pregnancy period," showed a relatively high increased score after intervention from 40.9% to 56.8%. There is also a decrease in score in question eight about "the risk of preeclampsia screening in the MCH handbook were not necessary to be filled in by the midwives" from 87.1% to 83.1%.

The webinar also had been studied in comparison with another method of professional development in terms of effectiveness. Compared to group discussion, a webinar was more effective as a training method.[26]

Before the pandemic, the webinar-based educational method was less common than during the pandemic. A study in 2017 from McKinney[27] demonstrated that webinars and similar web-based learning materials in public health were considered firm educational strategy tools. The downside of this method, including initial investment in hardware and software, specific technical support, and technical challenges, may be outweighed for many by greater efficiency and flexibility in scheduling, accessibility of resources, efficiency in costs and time spent on travel, and the support for online learning community development.[21]

A webinar format can be used for education during a pandemic when conventional training is impossible. It may fill the gap created by the suspension of traditional training, especially during the COVID-19 pandemic.[28] Although webinars are not considered a replacement but only a complement to conventional methods.[29]

The lack of a matching technique between the pre-test and post-test groups is a limitation of this study, as it prevents an analytical comparison between the two groups. Further study needs to be done with a control group to increase the study's accuracy. It is intended that midwives' more significant understanding of the association between vitamin D insufficiency and fetal growth restriction will strengthen their role in reducing the incidence of fetal growth restriction by educating pregnant mothers.

Conclusions

There was an increase in the proportion of subjects with a high level of knowledge after attending the training using the online approach. Therefore, health policymakers and educational institutions should consider increasing online activity to improve the effectiveness of health workers, especially during the COVID-19 outbreak.

Conflict of Interest

The authors declare that they have no conflict of interest exists in this study.

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RESEARCH ARTICLE

Histopathology of Nephrotoxicity Associated with Administered Water Extract Purple Sweet Potato (*Ipomoea batatas*) in Mice (*Mus musculus*) in Stratified Phases of Dose

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Abstract

The main aim of the registered purple sweet potato (*Ipomoea batatas*) is to provide minimize the adverse chemical drugs, in addition to its anti-inflammatory, antioxidant, and antimicrobial effects. Potentially adverse effects may be observed in laboratory animals in particular, the extent to which this administration can cause toxicity. This study aimed to examine the histopathology of nephrotoxicity associated with administered water extracts of purple sweet potato in mice with stratified doses. The study was conducted at the Biomedical Laboratory, Faculty of Medicine, Universitas Islam Bandung on September 2019. Female mice (*Mus musculus*) strain Swiss Webster, aged between 6–8 weeks weighing 25 to 30 g, were obtained from Biopharma Laboratory, Bandung. The animal was acclimatized for seven days before being administered water extract purple sweet potato: eleven mice, one control group, and ten treatment groups underwent toxicity doses of purple sweet potato water extract administration. Purple sweet potato variant of Ayamurasaki prepared in various oral doses. The results show in the control group there were no histopathological changes, but in the group administered water extract purple sweet potato from the first phase seems in a mild grade of macrophage accumulation, mild vacuolization of tubular epithelial cells, mild vascular dilatation, and mild hydrophilic degeneration. In the second phase, macrophage accumulation was visible in moderate grades. The LD50 of purple sweet potato extract is greater than 5,000 mg/kgBW. The findings of this study indicate that registration of purple sweet potato extract in confirmatory doses is safe to administer and did not exhibit any mortality. The toxicity test of purple sweet potato water extracts in the kidney exhibits minimal chemical effects.

Keywords: Extract purple sweet potato, histopathology of kidney, nephrotoxicity

Introduction

The kidneys are responsible for maintaining the body's internal environment's homeostasis, which includes water, electrolyte, nitrogen, and acid-base balances. The kidney is commonly involved in the negative consequences of exogenous chemicals, such as medications. The use of drugs in therapy has the potential to induce direct toxicity. Despite this, drug-induced nephrotoxicity has been linked to substantial side effects, with antimicrobials accounting for one-third of the cases.[1] Proving the role of causation in drug-induced kidney disease is complex because it necessitates an understanding of the drug's biological relevance, mechanism of injury, duration, and evaluation of competing risk factors. These phenotypes provide a standardized framework for doctors, researchers, industry, and regulatory authorities to evaluate medication nephrotoxicity in a variety of situations.[2] To eliminate the side effects of utilizing medications, natural components, or medicinal plants can be used to decrease negative responses that can lead to kidney disorder. Medicinal plants are often better tolerated than synthetic drugs, according to a review of clinical data on adverse effects. However, major adverse effects, such as herbal-drug combinations, should be taken into account.[3]

Medicinal plants have been used in various countries for years and have contributed significantly to the treatment system,[4] particularly in Indonesia. Plants with medicinal characteristics are useful in herbal therapies and can be used to treat a variety of disorders

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due to phytoconstituents. Phytochemicals are natural chemical components found in variable concentrations in plant sections (leaves, trunks, and roots) that act as disease defense mechanisms. Purple sweet potatoes, scientifically known as *Ipomoea batatas* L., were one of the first plants utilized by traditional healers to treat a range of diseases.[5]

Ipomoea batatas L., contain a high concentration of carbs, fiber, vitamins, and minerals, also flavonoid and phenolic compound.[6,7] Four anthocyanins derived from peonidin and three anthocyanins derived from cyanidin were found to contribute significantly to antioxidant activity.[8] Biological activities of ipomoea consist of anticancer, anti-diabetic, anti-inflammatory, antibacterial, and hepatoprotective abilities.[9]

In the evolution of the existing therapeutic system, the perspective of ethnopharmacological research, and drug development from natural sources have played a significant role. Medicinal plant ethnopharmacology needs to be studied more thoroughly before it can be used as a treatment. The majority of natural sources with active chemicals employed today have ethnomedical applications. Ethnopharmacology expertise can be valuable to discover and create new ideas, safe, and economical medications.[10]

The ability to identify these effects early on is critical for allowing novel, safe medications to enter the market. Acute toxicity is defined as an unwanted consequence that occurs immediately or within a certain period after single or multiple doses of the chemical within 24 hours. Toxicity tests, on the other hand, are required to determine the efficacy of natural treatments. This study was to evaluate the histopathology of nephrotoxicity-associated administered water extracts of purple sweet potato in mice with stratified doses.

Methods

The purple sweet potato (*Ipomoea batatas*) variant of Ayamurasaki has gone through a plant determination process at the Herbarium Laboratory of a School of Life Science and Technology, Institut Teknologi Bandung last 2018 (2839/II.CO2.2/PL/2018). Purple sweet potato water extraction using cold maceration method in aqua dest for 48 hours, filtered and evaporated. This aqueous extract is then prepared in various oral doses.[11,12]

Female mice (*Mus musculus*) strain Swiss Webster, aged between 6–8 weeks weighing 25 to 30 g, were obtained from Biopharma Laboratory, Bandung. The study was conducted at the Biomedical Laboratory, Faculty of Medicine, Universitas Islam Bandung on September 2019. The animal was acclimatized for seven days before being administered water extract sweet potato: eleven mice, one control group, and ten treatment groups that underwent toxicity dose of purple sweet potato water extract administration. This method was following the used by Chinedu et al.[13] Animal models were separated into three phases and one confirmation phase, with the results of each phase determining the next step to be taken (i.e., whether to end the process or move on to the next step). The first stage consists of four mice, which are separated into four groups of one animal each. In stage two, three mice are divided into three groups of one animal each. Stage three also involves three mice, which must be divided into three groups of one animal each. Each group in each step gave varying doses of the test material to the various animals. The animals should be evaluated for 1 hour after administration, Then, for the next 24 hours, 10 minutes every 2 hours. Toxicity-related behavioral signs and mortality should be recorded. If no mortality is detected at this phase, research testing should proceed to the next. The final stage is the confirmatory stage, in which if mortality was observed at a given dose in any of the previous stages, To ensure that the substrate material was the cause of such deaths, a confirmatory test should be undertaken.

The doses of each group of phases are documented in Table 1. Histopathological assessments by kidney biopsy were previously anesthetized using 10 mg/kg body weight of ketamine given intramuscularly. The paraffin-embedded fixed kidney tissue was dehydrated in successive grades of ethanol. Hematoxylin-eosin (HE) staining was used on kidney tissue blocks cut into 4-µm sections. Macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration were graded as follows: no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%).[14] The histopathological analyses were performed by a pathologist. The data were analyzed using Microsoft 365.

To minimize animal suffering, all experimental procedures involving animals were carried out by

Table 1 Doses of Each Group of Stages in This Study

Phase	Dose (mg/kgBW)			
	Group 1	Group 2	Group 3	Group 4
1	50	200	400	800
2	1,000	1,500	2,000	
3	3,000	4,000	5,000	

Note: LD50=maximum dose of no mortality+minimum dose of mortality/2

the ARRIVE guidelines 2.0 for the care and use of laboratory animals.[15] This study was approved by the Health Research Ethics Committee of the Universitas Islam Bandung with Ethical Approval Number: 110/KEPK-Unisba/XI/2020.

Results

In the control group there were differences in macrophage accumulation, tubular epithelial cell vacuolization, vascular dilatation, and hydrophilic degeneration with the treatment group at the start of the first phase (Table 2). However, at the start of the second phase, macrophage accumulation was visible in moderate grades (Table 3). These indicates whether or not there is acute kidney injury. The histological examination revealed no differences in tissue damage between the right and left kidneys (Table 2, Table 3, and Table 4).

Kidney histopathology shown in the control group showed normal renal cortex, relatively healthy glomerulus, no accumulation of macrophages, dilated blood vessels, epithelial vacuolization, and degeneration. The treatment group showed histologic changes. Changes in kidney structure in the form of accumulation of macrophages range from mild to moderate grades. Macrophage accumulation with a positive value of 2/moderate was found starting at the beginning of the second phase of the treatment group (Figure). Necrotic conditions were not found in all control and treatment groups.

Discussion

This preclinical study provides continued evidence that nephrotoxicity is caused by the high dose of water extract purple sweet potato (*Ipomoea batatas*). Importantly in our model, in the confirmatory phase, 5,000 mg/kg body

Table 2 Histopathological Grade Change in the First Phase

Histopathological Changes	C S/D	50 S/D	200 S/D	400 S/D	800 S/D
Macrophage accumulation	−/−	+/+	+/+	+/+	+/+
Vacuolization of tubular epithelial cells	−/−	+/+	+/+	+/+	+/+
Vascular dilatation	−/−	+/+	+/+	+/+	+/+
Hydrophilic degeneration	−/−	+/+	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

Table 3 Histopathological Grade Change in the Second Phase

Histopathological Changes	1,000 S/D	1,500 S/D	2,000 S/D
Macrophage accumulation	++/++	++/++	++/++
Vacuolization of tubular epithelial cells	+/+	+/+	+/+
Vascular dilatation	+/+	+/+	+/+
Hydrophilic degeneration	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

Table 4 Histopathological Grade Change in the Third Phase

Histopathological Changes	3,000 S/D	4,000 S/D	5,000 S/D
Macrophage accumulation	++/++	++/++	++/++
Vacuolization of tubular epithelial cells	+/++	+/+	+/+
Vascular dilatation	+/+	+/+	+/+
Hydrophilic degeneration	+/+	+/+	+/+

Note: S: sinistra; D: dextra; no damage (– or 0), mild (± or 1, unicellular, patchy isolated damage), moderate (+ or 2, damage <25%), severe (++ or 3, damage 25% to 50%), and very severe (+++ or 4, damage >50%). severe (++ or 3, damage between 25 and 50%), and very severe (+++ or 4, damage >50%)

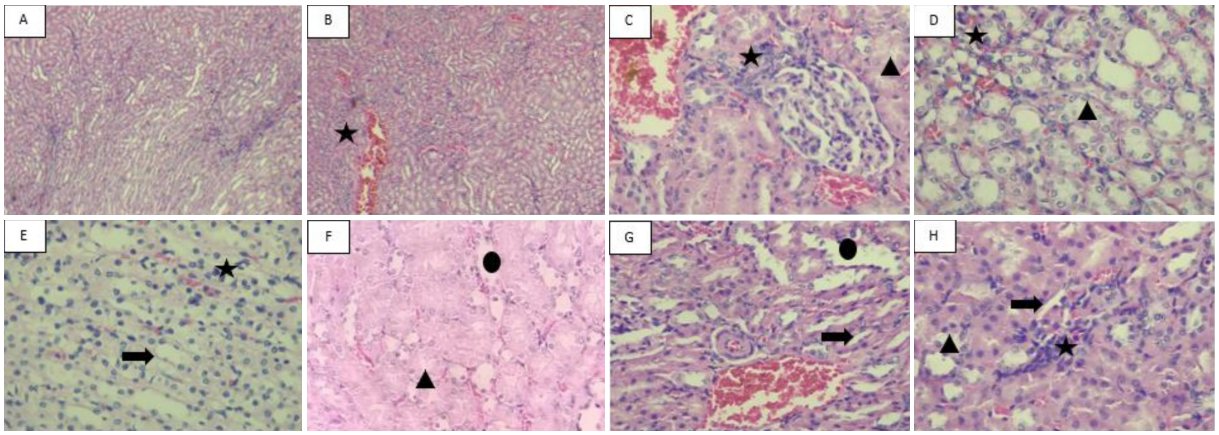

Figure Histopathology of Kidney

Light micrographs of the kidney sections based on histopathological changes among a group with HE staining. (**A**) Control group (100×). (**B**) The initial first phase (100×). (**C**) The last first phase (400×). (**D**, **E**) The second phase (400×). (**F**, **G**) The initial third phase (400×); (**H**) The last third phase (400×). The star (★) macrophage accumulation, the triangle (▲) vacuolization of tubular epithelial cells, the arrow (➡) vascular dilatation, and the circle (●) hydrophilic degeneration

weight no mortality occurs. Purple sweet potato has a high anthocyanin content compared to other sweet potato variants. Purple sweet potato contains several phytochemical substances such as saponins, alkaloids, flavonoids, tannins, triterpenoids, and quinones which are proven to have various benefits and are widely used. However, its absorption into the systemic circulation may cause toxicity. The toxicity of purple sweet potato is generally indicated by an increase in the accumulation of macrophages to necrosis.

The results of the study and histopathological observations of mice's kidneys after being given purple sweet potato with 3 phases dose of toxicity test showed that there was an accumulation of macrophage in mild to moderate in all treatment groups. Giving a dose of 50 started to cause mild macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration. This occurs due to toxic doses of purple sweet potato that accumulate in the kidneys, causing tubular epithelial cells and capillary endothelial cells to undergo oxidative injury from excessive reactive oxygen species (ROS) formation so that tubular epithelial cells are damaged and become inflamed. Histopathological changes involve complex interactions between Kidney hemodynamics, tubular and endothelial cell damage, and the inflammatory process are all factors to consider. There is increasing evidence supporting the role of impaired kidney vascular function, especially at the microvascular level, in the initiation and progression of early tubular damage. Cell injury and vascular endothelial cell dysfunction play important roles in this phase of the toxicity test. Endothelial cells lose their ability to

control systemic vascular resistance, perfusion, permeability, inflammation, and adhesion. The loss of this regulating function has a negative impact on kidney function.[16,17]

Research conducted by Kim et al.[18] looked at the effect of giving povidone-iodine which is widely used as an antiseptic on toxicity which was seen in the microscopic picture of the kidney showing tubular atrophy, various casts (erythrocytes, leukocytes, and epithelial cell casts) in the distal tubule, and inflammatory cell infiltration in the interstitium. The administration of purple sweet potato supplementation in Wistar rats induced by gentamicin showed more regeneration of kidney tubular epithelial cells than Wistar rats without purple sweet potato extract supplementation.

Purple sweet potato is good to be consumed as an alternative therapy because it has many beneficial phytopharmaceuticals from the safe dosage. Anthocyanin purple sweet potato (APSP) contains antioxidant and anti-apoptotic properties, as well as the ability to regulate the c-Jun N-terminal kinase (JNK) signaling pathway, making it a potential treatment for reducing lead (Pb)-caused reproductive damage.[19] *Ipomoea batatas* have been shown to protect the liver from alcohol-induced hepatotoxicity and fatty liver disease.[20] Sweet potato root extracts contain anthocyanins and flavonoids, which have anticancer potential against breast cancer cell lines.[21] Research on the consumption of sweet potatoes has been done quite a lot and the results are good. In rats fed a high-cholesterol diet, a combination of purple sweet potato tuber water extract and honey can keep lipid profiles and MDA in the normal range.[22] Medicinal plants can induce kidney injury by causing mild interstitial inflammation with vascular congestion, moderate inflammation, vascular congestion, and severe inflammation and vascular congestion.[23] Deoxycorticosterone acetate (DOCA-salt) was combined with purple sweet potato extract ethanol (EP) to repair kidney injury, decrease smooth muscle cell proliferation, and reduce aorta wall thickening.[24]

In this study, giving a dose of 5,000 mg/kgBW can lead to nephrotoxicity or mild acute kidney injury (AKI, based on the histopathological description, it is not moderate or severe. Because the condition of the battery is heavy and medium. According to several studies, animals model with moderate and severe AKI experience transitory unilateral ischemia, which results in histologic alterations and kidney destruction within both the mild and severe AKI groups that received four weeks of treatment. After severe ischemia, acute tubular damage with casts and loss of brush boundaries of the tubular epithelium was substantially more evident than after moderate ischemia, with the corticomedullary junction being the most conspicuous. The cortex showed early shrinkage of single nephrons, as well as perivascular and interstitial inflammatory cell infiltration.[25]

Induction of purple sweet potato caused histopathological changes, starting from the accumulation of macrophage, vacuolization of tubular epithelial cells vascular dilatation hydrophilic degeneration even at a dose of 5,000 mg/kgBW, the changes that occur are mild, even at the beginning of the administration of a light dose, the changes are considered non-existent.

The administration of *Ipomoea batatas* can induce mild AKI, and it may become moderate or even severe with doses of more than 5,000 mg/kgBW. This is in line with research conducted by Won et al.[26] on the administration of cisplatin. After a single cisplatin treatment, the kidney showed morphological alterations, including significant inflammation and degradation in the proximal and distal tubules. The morphological alterations, on the other hand, were typically thought to be minor or non-existent. On day 3, cisplatin-induced kidney impairment was more severe, with tubular cell death, tubular vacuolization, and cytoplasm shrinkage in the proximal tubule. Tubular degradation and severe necrosis were observed in some tubule parts on day 5. There were karyorrhectic tubular cells present, but there were no apparent alterations in the glomeruli. There were no kidney lesions in either the vehicle control or the CCl4-treated groups.

AKI is described as a sudden rise in serum creatinine, a reduction in urine production, or both. Besides that, AKI can be seen from the histopathological description, and in this study, which can induce the occurrence of early AKI, occurs macrophage accumulation vacuolization of tubular epithelial cells vascular dilatation hydrophilic degeneration. Similar to other research in AKI, certain studies, that use surfactant proteins A and D play a function in sepsis-induced acute kidney injury. Kidney histology in septic but not sham mice

demonstrates vacuolar degeneration of tubular cells, flattened tubular cells with tubular lumen dilatation, and a lack of brush border. The kidney injury score in septic mice is higher than in wild-type (WT) mice.[27]

This finding along with studies of the nephroprotective activity of *Zizyphus lotus* L. (ZLF) aqueous extract. The rats intoxicated with gentamicin (GM) had fewer glomeruli cells, lost tubular cell components, and experienced vascular congestion, culminating in epithelial cell atrophy. Furthermore, when compared to the healthy rats, the vulnerable foe had such a deformation of the Bowman's space as well as deformities in the epithelial membrane of the Bowman's capsule, whereas the healthy rats had a normal histoarchitecture kidney. The histoarchitecture of the kidneys is improved in animals treated with the ZLF extract and injected with GM when compared to the hazardous group. Furthermore, this histoarchitecture improvement is comparable to that of the control group.[28]

Administering water extract purple sweet potato can be used as an alternative treatment by paying attention to the appropriate dose. Further research needs to be done by increasing the dose of use that can cause mortality.

Conclusions

Overall, the results obtained in the present study have shown that the toxicity test of purple sweet potato water extracts (*Ipomoea batatas*) in the kidney exhibits minimal chemical effects, other than the expected effects as anti-inflammatory, antioxidant, and antimicrobial effects. The histopathological appearance of macrophage accumulation, vacuolization of tubular epithelial cells, vascular dilatation, and hydrophilic degeneration indicate lead to injury, but not shown mortality.

Conflict of Interest

All authors state that they have no conflicts of interest.

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RESEARCH ARTICLE

Prevalence of Hepatitis B in Healthy Population in Kupang City, East Nusa Tenggara, Indonesia

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Abstract

Hepatitis B virus (HBV) infection has remained a global health problem. Around 2 billion people worldwide are infected, and more than 257 million are categorized as chronic patients with a risk of developing progressive liver diseases, such as cirrhosis, liver failure, and hepatocellular carcinoma. In 2013, East Nusa Tenggara province had the most hepatitis B cases in Indonesia. Several factors cause a lack of information on HBV prevalence in the general population. First, they are inadequate disease surveillance systems with a high possibility of some acute and chronic infections being unreported. Second, geographical barriers to achieving suitable and sufficient data collection, considering the total population of 250 million people distributed in more than 17,000 islands. Third, the limited testing facilities for detecting chronic HBV resulted in many people being undiagnosed. This study was conducted to discover the prevalence of hepatitis B in healthy populations. It was a cross-sectional study with a random sampling method from April 2016 to March 2020 in Kupang city, East Nusa Tenggara. Subjects are prison inmates, pregnant women, primary school students, high school students, health workers, orphanage children, and families who live under the same roof with hepatitis B patients. We screened 11,152 subjects for HBsAg positivity using the ELISA and rapid detection tests. We found that 1,490 subjects (13.4%) were reactive to HBsAg. This HBsAg-positive prevalence stood far above the national rate of 7.1% in 2013, meaning that Kupang city is a region with high hepatitis B endemicity. Therefore, the local government should develop prevention strategies, diagnosis, post-infection management, and effective treatment, including mass vaccination programs for at-risk groups.

Keywords: Healthy population, hepatitis B, prevalence

Introduction

Hepatitis B virus (HBV) infection remains one of the most critical health issues in the world, with approximately 257 million people worldwide having been chronically infected.[1,2] Chronic HBV infection can develop into severe liver complications like liver cirrhosis and hepatocellular carcinoma, causing around 887,000 deaths annually.[3,4] In high HBV endemic areas, hepatitis B is transmitted from mother to child at birth or through horizontal transmission via exposure to infected blood.[5,6] Around 90% of less-than-a-year-old children who are infected will develop chronic HBV infections, while in people who are infected as adults, only 5% will develop chronic infections.[5] HBV diagnosis is based on detecting the hepatitis B surface antigen (HBsAg), with chronic HBV infection characterized as HBsAg persistence in the blood for more than six months.[5]

Indonesia, with a population of more than 250 million people, had an HBsAg prevalence of 9.4% in 2007,[7] which dropped to 7.1% in 2013, suggesting a shift from a high HBV endemic country to moderate endemicity.[3,7,8] As with other countries in Southeast Asia, Indonesia experiences a double burden of HBV transmission, perinatal and horizontal transmissions.[9,10] Efforts to prevent and control HBV transmission in Indonesia have been taken, although some challenges remain. The infant hepatitis B vaccination program has been implemented since 1997 and has reduced cases of HBV infection, yet HBsAg was still detected in 5% of children under the age of 5 years old.[1] It may be caused by the uneven coverage of birth-dose vaccination, commonly lower in several provinces with low socioeconomic levels.[11]

Further, high HBsAg prevalence in pregnant

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women may contribute to significant HBV transmission to children in the perinatal period.[1] As such, the government implemented a triple elimination program for HIV, syphilis, and HBV infections in 2015 through mandatory screening for those three infections in pregnant women. Similar to the vaccination coverage, the coverage of hepatitis B early detection in pregnant women is still uneven, with several provinces' coverage lower than the nation's average of 69.95%.[11]

East Nusa Tenggara (Nusa Tenggara Timur, NTT) was one of the island provinces in the eastern part of Indonesia. NTT has a high level of HBV infection, especially in the East Sumba and West Sumba regions, where most HBV cases in 2013 were found.[12] In 2017, HBV and hepatitis C virus (HCV) prevalence among blood donors in NTT were 3.5% and 0.5%, respectively.[11,13] NTT reported the national highest HBsAg prevalence of 5.53% in pregnant women (national average of 1.8%), based on the hepatitis B early detection screening in 2018.[11] It indicated a high rate of mother-to-child HBV transmission in NTT, which may be exacerbated by the still low coverage of infant vaccination of 51.72% (national average of 90.61%).[11] HBV horizontal transmissions also occurred in NTT. A 2016 study on 89 people with household contacts with 11 hepatitis B cases in Kupang, NTT, showed that 18/89 (20.2%) were positive for HBsAg.[14] A similar study in Alak subdistrict, Kupang, in 2019 showed five out of 33 (15.2%) household contacts of 12 hepatitis B index patients were found positive for HBsAg.[15] A recent study reported a high prevalence of HBsAg (13.2%), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc), 13.2%, 39.8%, and 28.7%, respectively, in a population of 341 high school students from Kupang (age 13–22).[16] A similar study in six orphanages in Kupang reported 15 HBsAg-positive children out of 310 subjects.[6]

Considering the high HBV transmissions in NTT, HBV prevalence data on healthy populations and high-risk populations in NTT are required to identify the proportion of HBV carriers in the people that can potentially transmit HBV infections to others. This data can also be used as baseline data to improve hepatitis B prevention, management, and treatment programs in NTT. To date, there is no public hepatitis B screening program available. Therefore, this study aimed to determine the HBsAg prevalence in healthy-looking and high-risk populations in Kupang, NTT.

Methods

A cross-sectional study with a random sampling method was conducted from April 2016 to March 2020 in Kupang, East Nusa Tenggara. A total of 11,152 subjects were recruited, consisting of seven subject groups: (1) 328 elementary school students: mean age 8.3±1.95 years (5–12 years), 152 males; (2) 346 high school students: mean age 18.4±1.65 years (15–21 years), 123 males; (3) 321 prison inmates: mean age 32.9±4.4 years (19–45 years), 151 males; (4) 325 healthcare workers, mean age 32.5±1.6 years (20–57 years), 177 males; (5) 359 orphanage residents: mean age 14.5±6.8 years (6–27 years), 189 males; (6) 531 household contacts with 66 index cases with hepatitis B: mean age 39.5±7.8 years (5–64 years), 236 males; and (7) 8,942 pregnant women: mean age 33.5±2.3 years (19–46 years). All subjects were healthy individuals with no liver disease-related clinical symptoms. HBV vaccination history for each subject is not available.

Approximately five mL of venous blood samples were collected from April 2016 to March 2020 from the six subject groups. They are (1) elementary schools: SD Inpress RSS Oesapa, SD GMIT No. 7 Oebufu, SDN 3 Oeba, SDN Inpres 2 Oeba, SDN 1 Liliba, SD Noelbaki, and SDN Naikoten 2; (2) high schools: SMAN 1, SMAN 2, SMAN 3, SMAN 4, and SMAN 9; (3) prisons: Lapas Kelas IIA Kupang, Lapas Kelas III Wanita Kupang, Rutan Kelas IIB Kupang, Lapas Kelas IIA Anak Kupang; (4) healthcare facilities: RSUD Prof. Dr. W.Z. Johannes Kupang, RSUD S.K. Lerik Kupang, RSD Naibonat, Puskesmas Pasir Panjang, Puskesmas Alak, Puskesmas Manutapen, Puskesmas Sikumana, Puskesmas Oebobo, Puskesmas Kota Atambua, Puskesmas Camplong, Puskesmas Tarus, Puskesmas Bakunase, Puskesmas Tarus, dan Puskesmas Kupang Kota; (5) orphanages: Panti Asuhan At-Tiin, Panti Asuhan Asyiyah, Panti Asuhan Nurusaadah, Panti Asuhan Sonaf Maneka, Panti Asuhan Kasih Agape, dan Panti Asuhan Syalom; and (6) 85 households. All samples were taken to the Laboratory of Immunology and Serology, Health Analyst Study Program, Poltekkes Kemenkes Kupang, and stored in a −20°C freezer until use. In addition, HBsAg data from the pregnant women group were taken from the hepatitis B screening results in 2017–2019 conducted at several public health centers (*puskesmas*) and hospitals in Kupang, NTT, including Puskesmas Pasir Panjang, Puskesmas

Oebobo, Puskesmas Manutapen, Puskesmas Alak, RSUD Prof. Dr. W.Z. Johannes Kupang, RSUD S.K. Lerik Kupang, and RSUD Naibonat. HBsAg tests were performed using Hepanostika HBsAg Ultra (Batch B1V10P01; Biomerieux, Paris, France) immunoassay kit according to the manufacturer's instructions. HBsAg screening on pregnant women at *puskesmas* and hospitals was conducted using (Mono Test®, Raseny Safety®, Nova Test®, and Egens®) HBsAg rapid diagnostic test.

Statistical analyses were performed using Statistical Package for Social Sciences v.26 (SPSS Inc., Chicago, IL, USA). To assess the relationship between variables using the chi-square test. Odd ratio (OR) value to determine the size of risk factors with disease incidence; calculated from the incidence of disease in the risk group compared to the incidence of illness in the non-risk group. The contingency coefficient (Cc) shows the correlation percentage between independent and dependent variables. The Cc value is used when statistical results do not find an OR value.

The nature of the study was explained to all the participants and all of them signed the informed consent form by the principles of the Revised Declaration of Helsinki. The protocol of the study was approved by the Health Research Ethics Committee of the Peltekkes Kemenkes Kupang, NTT (Approval No. LB.02.03/1/0045/2019).

Results

From a total of 11,152 subjects, 1,490 subjects (13.4%) were detected with positive HBsAg, comprising 18.9% (62/328) elementary school students, 19% (66/346) high school students, 16.5% (53/321) prison inmates, 16.9% (55/325) healthcare workers, 20.8% (75/359) orphanage residents, 14.7% (78/531) household contacts, and 12.3% (1,101/8,942) pregnant women. HBsAg-positive prevalence was higher in the younger population group (<19 years old) of orphanage residents (20.8%), high school students (19%), and elementary school students (18.9%), compared to the older subjects' groups. HBsAg-positive subjects in the school students (both elementary and high) and inmates' groups were primarily male, while the other three groups were mainly female. HBsAg positivity in the older subjects' groups (>19 years old) was detected in all levels of education, regardless of gender. The high-risk populations: prison inmates, household contacts of hepatitis B patients, and healthcare workers all have a higher HBsAg prevalence than 13.4%. A higher percentage of positive HBsAg in the healthcare workers group was found in midwives (5.5%) and nurses (4.3%). Older pregnant women (>29 years old) have a higher percentage of HBsAg positivity (>30%).Detailed demographic characteristics of the subjects are described in Table 1.

The association between the characteristics of subjects and HBsAg positivity was described in Table 2. Males were associated with positive HBsAg status in elementary school students (p=0.000, OR=2.978 [1.658–5.350]), high school students (p=0.003, OR=2.280 [1.323–3.930]), and healthcare workers (p=0.008, OR=0.451 [0.249–0.818]) groups. Male students had a 2.978 and 2.280 times higher risk of being infected with HBV than females in elementary and high school, respectively. Male orphanage residents, prison inmates, and household contacts were 0.645, 1.206, and 0.960 times likelier to be infected with HBV than females. In contrast, male healthcare workers had a 0.451 lower risk for HBV infection than females.

Association between age and HBsAg positive status was found in elementary school students (p=0.000, OR=0.227 [0.122–0.422]), prison inmates (p=0.000), orphanage residents (p=0.009), and household contacts (p=0.001) groups. Stratified by age, elementary school students aged 0–9 years old had 0.227 times lower risk of HBV infection, while the 10–19 years old high school students had 1.060 higher risk for HBV infection. Orphanage residents aged 10–19 also had a 9.395 times higher risk of being infected with HBV than those aged 0–9 and 20–29 years old. The correlation between age and HBV infection in inmates was 42%, suggesting a 42% higher possibility of HBsAg negativity as they grew older. In household contacts and healthcare workers' groups, the correlation between age and HBV infection was 17% and 26%, respectively. Finally, the correlation between age and HBV infection in pregnant women was 70%, indicating a 70% chance of avoiding HBV infection as they grew older.

Educational levels were associated with HBsAg-positive in orphanage residents (p=0.021), prison inmates (p=0.000, OR=3.692 [1.975–6.901]), healthcare workers (p=0.002), household contacts (p=0.000) and pregnant

Table 1 Demographic Characteristics of Study Subjects

Subject Groups Characteristics	Total n	HBsAg	
		Positive n (%)	Negative n (%)
Elementary school students			
Gender			
Male	152	42 (12.8)	110 (33.5)
Female	176	20 (6.1)	156 (53.7)
Age (years)			
0–9	225	20 (6.1)	205 (62.5)
10–19	103	31 (9.5)	72 (22.0)
Total	328	62 (18.9)	266 (81.1)
High school students			
Gender			
Male	123	34 (9.8)	89 (25.7)
Female	223	32 (9.2)	191 (55.2)
Age (years)			
10–19	246	49 (74.2)	197 (70.4)
20–29	100	19 (28.8)	81 (28.9)
Total	346	66 (19.1)	280 (80.9)
Prison inmates			
Gender			
Male	151	27 (8.4)	124 (38.6)
Female	170	26 (8.1)	144 (44.9)
Age (years)			
10–19	51	3 (5.7)	48 (17.9)
20–29	90	10 (18.9)	80 (29.9)
30–39	152	20 (37.7)	132 (49.3)
40–49	28	20 (37.7)	8 (3.0)
Education level			
Elementary school	121	21 (6.5)	100 (31.2)
Junior high school	97	22 (6.9)	75 (23.4)
High school	82	10 (3.1)	72 (22.4)
University	21	0 (0)	21 (6.5)
Total	321	53 (16.5)	268 (83.5)
Healthcare workers			
Gender			
Male	177	21 (6.5)	156 (48.0)
Female	148	34 (10.5)	114 (35.1)
Occupation			
Midwife	153	18 (5.5)	135 (41.5)
Doctor	20	2 (0.6)	18 (5.5)
Pharmacist	43	9 (2.8)	34 (10.5)
Nurse	53	14 (4.3)	39 (12.0)
Lab technician	56	12 (3.7)	44 (13.5)
Age (years)			
10–19	10	0 (0)	10 (3.1)
20–29	46	8 (2.5)	38 (11.7)
30–39	146	26 (8.0)	120 (36.9)
40–49	123	21 (6.5)	102 (31.4)
Education level			
High school	67	23 (7.0)	44 (13.5)
University	258	32 (9.0)	226 (69.5)
Total	325	55 (16.5)	270 (83.1)
Orphanage residents			
Gender			
Male	189	33 (9.2)	156 (43.5)
Female	170	42 (11.7)	128 (35.7)
Age (years)			
0–9	78	10 (13.3	68 (18.9)
10–19	192	37 (49.3)	155 (43.2)
20–29	89	28 (37.3)	61 (17.0)
Education level			
Elementary school	136	21 (5.8)	115 (32.0)
Junior high school	105	23 (6.4)	82 (22.8)
High school	95	21 (5.8)	74 (20.6)
University	23	10 (2.8)	13 (3.6)
Total	359	75 (20.9)	284 (79.1)
Household contacts			
Gender			
Male	236	34 (6.4)	202 (38.0)
Female	295	44(8.3)	251 (47.3)
Age (years)			
0–9	24	1 (0.2)	23 (4.3)
10–19	76	11 (2.1)	65 (12.2)
20–29	131	6 (1.1)	125 (23.5)
30–39	146	32 (6.0)	114 (21.5)
40–49	150	27 (5.1)	123 (23.2)
50–59	4	1 (0.2)	3 (0.6)
Education level			
Elementary school	98	23 (4.4)	75 (14.2)
Junior high school	148	21 (4.0)	127 (24.1)
High school	138	21 (4.0)	117 (22.2)
University	147	10 (1.9)	137 (25.8)
Total	531	78 (14.7)	453 (85.3)
Pregnant women			
Age (years)			
10–19	1,021	148 (13.4)	873 (11.1)
20–29	1,721	164 (14.9)	1,557 (19.9)
30–39	3,214	390 (35.4)	2,,824 (36.0)
40–49	2,986	399 (36.2)	2587 (33.0)
Education level			
Elementary school	2,632	326 (3.6)	2,306 (25.8)
Junior high school	2,321	245 (2.7)	2,076 (23.2)
High school	2,507	289 (3.2)	2,218 (24.8)
University	1,482	241 (2.7)	1,241 (13.9)
Total	8,942	1101 (12.3)	7,841 (87.7)
Total	**11,152**	**1,490 (13.4)**	**9,662 (86.6)**

women (p=0.000) groups. Orphanage residents with higher educational levels had a 9.694 times lower risk of being infected with HBV than those with lower academic levels. Inmates with a high school educational level showed a 3.692 times higher risk for HBV infection. The correlation between educational levels and HBV infection in household contacts and healthcare

Table 2 Association between Subject Characteristics and Positive HBsAg

Subject Groups	Characteristics	p	OR (Cc)
Elementary school students	Gender	0.000*	2.978 (1.658–5.350)
	Age	0.000*	0.227 (0.122–0.422)
High school students	Gender	0.003*	2.280 (1.323–3.930)
	Age	0.845	1.060 (0.588–1.912)
Prison inmates	Gender	0.533	1.206 (0.669–2.175)
	Age	0.000*	Cc=42%
	Education level	0.000*	3.692 (1.975–6.901)
Health workers	Gender	0.008*	0.451 (0.249–0.818)
	Occupation	0.082	Cc=15%
	Age	0.000*	Cc=26%
	Education level	0.002*	Cc=70%
Orphanage residents	Gender	0.092	0.645 (0.386–1.076)
	Age	0.009*	Cc=16%
	Education level	0.021*	Cc=16%
Household contacts	Gender	0.869	0.960 (0.592–1.558)
	Age	0.001*	Cc=17%
	Education level	0.000*	Cc=15%
Pregnant women	Age	0.000*	Cc=2%
	Education level	0.000*	Cc=5%

Note: *p<0.05 significant

workers' groups was 66.6% and 70%, suggesting percentages of people with lower HBV risks due to their higher educational levels. The correlation between the academic level and HBsAg positivity in pregnant women was 5%, indicating a 5% chance of higher educational levels in reducing HBV infection in pregnant women.

Discussion

Robust epidemiological data on HBV infection is needed to develop effective and efficient strategies for hepatitis B prevention and management. There was a lack of HBV prevalence in the general population of Indonesia due to inadequate surveillance systems, geographical barriers, and limited testing facilities for HBV detection.[13] Therefore, many people in Indonesia are unaware of their HBV infection status. Thus, there is a need for HBV screening in the general population and in high-risk populations such as dialysis patients, people in prisons, people who inject drugs, people with multiple sex partners, household contacts of hepatitis B patients, and healthcare workers.[5] HBsAg prevalence in high-risk populations is higher than in the general healthy populations. For example, HBsAg prevalence in young adults in Indonesia was 15.7% (mostly male).[3] In South Korea, HBsAg positivity was highest in men and women in their 40s and 50s (5.7% and 4.7%, respectively).[10] In Burkina Faso, HBsAg positivity in pregnant women (11.11%), blood donors (11.73%), and HIV-positive people (12.61%) were higher than in the general populations (9.41%).[17] Positive HBsAg was found in 9.2% of pregnant women in Gambia,[18] while 1.04% of blood donors in Burundi were reportedly HBsAg positive.[19] In Europe, the highest HBsAg prevalence was found in people in prisons (0.3–25.2%), drug users (0.5–6.1%), and men who had sex with men (0–1.4%).[20] In the USA, 11% of mentally disordered people were infected with HBV,[21] and 20.2% of male prisoners were HBsAg-positive.[22] Meanwhile, 8% of prison inmates in the UK have positive anti-HBc antibodies.[23]

HBV prevalence data is required, both at the country and sub-national levels, to estimate the hepatitis B disease burden and to direct the appropriate health policies and prevention programs (vaccination) regarding hepatitis B.[24] NTT is one of the HBV-endemic provinces in Indonesia.[12] The risks for HBV transmission in NTT are high, either vertically or horizontally, with low coverage of hepatitis B universal vaccination and pregnant women screening compared to the nation's average.[11,12] There are no data on HBV

prevalence in general populations and high-risk populations in NTT. However, the prevalence of HBsAg positivity in a specific population may indicate the level of HBV endemicity in that region.[1] This study was conducted from 2016 to 2020 to determine HBsAg prevalence in the general healthy-looking populations, including several high-risk people in Kupang, NTT.

This study revealed HBsAg positivity in 1,490 subjects (13.4%) from a total of 11,152 healthy-looking subjects in Kupang, NTT. This HBsAg prevalence was significantly higher than the national average of 7.1%, confirming NTT as HBV endemic province in Indonesia. High-risk populations, such as prison inmates, household contacts of hepatitis B patients, and healthcare workers, all have higher HBsAg prevalence than the general populations. Higher percentages of HBsAg positivity in the younger population (<19 years old) might indicate the increased risks of horizontal HBV transmission among peer groups in Kupang. In addition, high HBsAg-positive prevalence in pregnant women groups in Kupang indicates the high incidence of mother-to-child transmission in Kupang. According to the subject groups, the orphanage residents have the highest HBsAg prevalence of 20.9% compared to the other subject groups.

HBsAg positivity in this study was found proportionally similar between gender in the first six groups of elementary school and high school students, orphanage residents, prison inmates, healthcare workers, and household contacts (males: 49.1% vs females: 50.9%). Separated per subject group, males were significantly associated with HBsAg positivity ($p<0.01$) in elementary school students, high school students, and healthcare workers' groups. Males were also associated with a higher risk for HBV infection, except in the healthcare workers' groups. The association between the male gender and HBsAg positivity has been shown previously.[25] This association might reflect the HBV pathogenesis-related mechanisms involving the sex hormones or related to the different lifestyles between males and females, including smoking, drinking, personal hygiene, and sexual activity.[25]

This study's younger subjects (<19 years old) have an average higher HBsAg than the older subjects' groups. All the younger subjects in this study were born after implementing the mandatory national hepatitis B immunization program in 1997 and were expected to have lower HBsAg prevalence. This result may be caused by the possibility of hepatitis B vaccination failure and the high rate of vertical HBV transmission.[9,26] Hepatitis B vaccination in children resulted in immunity to HBV in the form of antibodies against HBsAg (anti-HBs),[1,26] and this protection against HBV infection may last lifelong. However, those who received incomplete vaccination doses may not produce protective anti-HBs levels,[5] and as reported, NTT has low coverage of hepatitis B universal vaccination.[12] Failure to pay protective anti-HBs levels may also be caused by the appearance of vaccine-escape mutants, where amino acid substitutions in HBsAg cause its escape from antibody detection and neutralization, leading to reinfection with HBV.[27] However, the cause of high HBsAg positivity in these subjects cannot be confirmed due to unavailable HBV vaccination records and no additional measurement of anti-HBs levels.[16]

The highest HBsAg-positive prevalence (20.8%) was found in orphanage residents, which their living situation may cause. Orphanage residents are not usually categorized as high-risk populations. Still, considering their similar living situation to prison inmates, they should also be regarded as high-risk populations for horizontal HBV transmission. The orphans mostly live in one large room, shared between an average of 10–20 people, allowing for frequent close contact between the residents.[6] They also commonly share personal hygiene products like toothbrushes, nail clippers, razors, towels, and soaps, increasing the possibility of HBV transmission among them.[6,28]

The HBsAg prevalence in the prison inmates group, as one of the high-risk groups for HBV transmission, was 16.5%, higher than the average HBsAg prevalence of 13.4% in the general population. The prevalence rate of chronic hepatitis B infection among prison inmates was generally higher (1.0–3.7%) in comparison with the general population. It is caused by their high-risk behaviors, including injection drug use and unsafe sex practice, and their living conditions, where they commonly share personal items.[22,23]

Household contact with hepatitis B patients was also considered a high-risk population as they frequently share household items like razors, plates, cutlery, glassware, face towels, and toothbrushes.[15,29] Previous studies in several Asian countries have shown that the potential of HBV transmission from hepatitis B patients to those living in the same household is high. Especially

for parents, siblings, or other household residents who were in close contact, share household items, have poor personal hygiene habits, and have previous blood transfusion history.[30,31] In this study, HBsAg positivity in household contacts was 14.7%, confirming previous studies' results of high HBsAg prevalence in household contacts in Kupang.[15]

The percentage of positive HBsAg in healthcare workers in Kupang was significantly high at 16.9%. As one of the high-risk population groups for HBV transmission, there is still no mandatory hepatitis B immunization program for healthcare workers in Indonesia. Direct contact with hepatitis B patients and patient samples of patients may increase healthcare workers' risks of contracting HBV(8). Accordingly, higher HBsAg-positive prevalence was observed in those with direct contact with patients and patients' samples, midwives (5.5%), nurses (4.3%), and laboratory assistants (3.7%) compared to pharmacists (2.8%). Female healthcare workers have higher HBsAg positivity than male healthcare workers (10.5% vs 6.5%), most likely because most midwives and nurses were females. These findings confirmed previous study results in healthcare workers in Makassar, South Sulawesi, where HBsAg prevalence was higher in midwives and laboratory staff.[8]

Vertical HBV transmission from mother to child is the primary source of HBV transmission in endemic areas1. HBsAg prevalence in pregnant women in this study was 12.3%, higher than previously reported in other regions in Indonesia.[32] It confirms the previous 2018 report of the national highest HBsAg prevalence in pregnant women in NTT.[11] Maternal age and educational level significantly affect HBsAg positivity, with higher percentages of HBsAg positivity in older pregnant women (>29 years old) and lower percentages of HBsAg positivity in those with higher educational levels. Association of HBV infection with the mother's age and academic levels have been reported previously. Younger women are more likely to have higher HBV DNA viral load, and positive hepatitis B e antigen (HBeAg) compare to older women.[32] Meanwhile, lower educational levels are associated with a higher risk of HBV infection and preterm labor.[33] Academic levels were also negatively associated with HBsAg positivity in other subject groups of orphanage residents, prison inmates, healthcare workers, and household contacts. Higher educational levels may reduce the risk of HBV infection. In addition, higher academic levels may cause behavioral changes that increase HBV testing, vaccination, and treatment rates.[34]

The high rates of HBV infection in the healthy population in Kupang, NTT, warrants improved HBV prevention and management programs to minimize future HBV-related disease burden in NTT. Hepatitis B vaccination is a proven method to stop both HBV vertical and horizontal transmission in the population. It is effective for hepatitis B prevention and HBV-related liver cirrhosis and hepatocellular carcinoma.[29–31] The hepatitis B vaccine may prevent perinatal HBV transmission in highly endemic countries if the initial dose is given immediately after delivery (>12 hours).[35] All infants, unvaccinated children, and young adults aged <19 years old living in HBV-endemic countries should also be vaccinated to reduce their risks of contracting HBV infection.[2,32,35] Additional hepatitis B vaccination programs for high-risk populations can be performed to prevent specific HBV pre-exposure and minimize horizontal HBV transmission in the population.[35] The populations were hemodialysis patients, injecting drug users, people having household contact with positive HBsAg patients, healthcare and public safety workers, people with HIV infection, and people who are imprisoned can be performed to prevent specific HBV pre-exposure and minimize horizontal HBV transmission in the population.[35]

Improving the low coverage of infant vaccination and hepatitis B early detection screening in pregnant women in NTT is crucial in managing HBV infection in the province. One of the essential things to do is to raise people's awareness and understanding of hepatitis B. Topics, especially its risks of transmission and ways of prevention, and available screening, care, and treatment options.[34,36] Hopefully, people will be more aware of doing HBV testing and actively seeking hepatitis B vaccination if they have high risks for HBV infection. Several comprehensive strategies to reduce the risk of HBV transmission in NTT are (1) mandatory HBsAg testing in pregnant women and prophylactic administration for babies born to HBsAg-positive mothers; (2) universal hepatitis B vaccination in newborns; (3) additional vaccination/booster for children and adolescents who were not previously vaccinated; (4) vaccination in adults with high risks of HBV infection, especially the healthcare workers and

hepatitis B patients' household contacts.[6-10,21–26,37]

Early hepatitis B screening in pregnant women should also be complemented by administering hepatitis B vaccination and antiviral therapy during pregnancy to reduce the risk of perinatal HBV transmission.[35–37] Regular hepatitis B screening in high-risk population groups will help identify those infected with the virus and minimize the risk of horizontal transmission by advocating for good personal hygiene habits and discouraging personal sharing items. Additionally, providing complete personal protective equipment for healthcare workers and frequent personnel rotation in public health facilities may help minimize the risk of horizontal HBV transmission.

Our study showed a high HBsAg-positive rate of 13.4% in the general healthy-looking population in Kupang, NTT. This study included many subjects, allowing for the determination of HBsAg prevalence in different subpopulations and the association between age, gender, and educational levels and HBV infection. The limitation of the study was only HBsAg was screened, and no other HBV markers were detected, which may limit HBV infection profile interpretation in the subjects. The high HBV prevalence in the general population calls for more effective HBV prevention and control programs in NTT. So far, the hepatitis B program is not the main priority of the local health officials, as NTT also has high rates of maternal and neonatal mortality,[15,38,39] child stunting,[40,41] malaria,[42,43] and tuberculosis[44] infections. Because hepatitis B is a chronic silent disease, HBV-related morbidity and mortality are likely underestimated.[36] They will only get higher if no effective HBV prevention and control steps are taken. Increasing public education and awareness of the risks of hepatitis B transmission should be done, as well as increasing universal infant vaccination coverage in NTT. Increasing access to HBV testing facilities might also encourage people to test for HBsAg and reduce the risks of HBV transmission in the population. An effective hepatitis B prevention and control program needs robust epidemiological data on HBV prevalence in the population. Thus, additional studies on the prevalence of HBsAg and other HBV markers in the people of the other regencies in NTT will provide complete HBV epidemiological data in the province. Further studies on anti-HBs protective levels and HBV DNA analysis in vaccinated adolescents and young adults will provide the molecular background on the high rate of HBsAg in these subpopulations.

Conclusions

A high prevalence of hepatitis B was found in healthy populations in Kupang, NTT based on HBsAg detection. Therefore, this HBV prevalence data can be used by the regional government of NTT as primary data for hepatitis B prevention and management programs to reduce HBV transmission and disease burden in the population.

Conflict of Interest

The authors declare no competing interests.

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RESEARCH ARTICLE

Effects of Proteasome Inhibitor on Catalase Expression and Intima-media Thickness in the Aorta of Atherosclerotic Rats

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Abstract

Various studies have been carried out to obtain proper management for atherosclerosis. Proteasome, a subcellular enzyme complex, is a potential therapeutic target for atherosclerosis. However, the effect of proteasome inhibitors on atherosclerosis still needs to be explored. It was an experimental study with a post-test-only control group design conducted at the Faculty of Medicine, Universitas Riau in Juni–November 2021. This study aimed to analyze the effects of proteasome inhibitors on catalase expression and intima-media thickness (IMT) in the thoracic aorta of atherosclerotic rats. Fifteen male Wistar rats were randomly divided into three groups (five rats per group), namely rats given standard feed (control, group I), rats induced atherosclerosis (group II), and rats induced atherosclerosis and given proteasome inhibitor (group III). The proteasome inhibitor, bortezomib, 50 μg/kgBW/day was given intraperitoneally on days one and three. After 4 days, rats were terminated, and the thoracic aorta was taken for the IMT analysis and catalase expression assessment using immunohistochemistry. Catalase expression was carried out quantitatively using Adobe Photoshop software. Analysis of variance test was used to compare the expression of catalase and IMT. A p value<0.05 was considered statistically significant. The results showed a significant decrease in IMT in group III compared to group II and an increase in catalase expression in group III compared to group II but not statistically significant. This study concludes that administration of bortezomib 50 μg/kgBW in atherosclerotic rats could inhibit thickening tunica intima-media in the thoracic aorta, although not significantly increasing the catalase expression.

Keywords: Atherosclerosis, bortezomib, catalase, intima-media thickness, proteasome inhibitor

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed and developing countries.[1] In 2019, according to the World Health Organization, CVD became the first cause of death in the world, and 17.9 million people have died from coronary heart disease (CHD). About 32% of all global deaths are caused by CHD.[2,3] Coronary heart disease occurs due to the atherosclerosis process.[4] Atherosclerosis is a chronic inflammatory process that causes plaque buildup on the artery walls.[5] This atherosclerosis process occurs gradually over a long time, based on the stages (initiation, progression, and complication stages).[6] Atherosclerosis process can be evaluated from the thickness of blood vessel walls, namely the thickness of tunica intima and tunica media.[7]

Studies have been carried out to obtain appropriate management of atherosclerosis.[4] Proteasome, a subcellular enzyme complex, is a potential therapeutic target for atherosclerosis.[8] The previous research by Ismawati et al.[9] revealed an increase in proteasome expression in blood vessels at every stage of atherosclerosis, and the highest growth occurs at the progression stage. The effects and mechanisms of proteasome inhibitors' action that inhibits proteasome are essential and interesting to be analyzed in atherosclerosis.[8] Bortezomib, the first developed proteasome inhibitor, has been used for cancer therapy since 2003.[10] The bortezomib dose of 50 μg/kgBW for six weeks in low-density lipoprotein (LDL) receptor (LDLR−/−) deficient mice suppresses the formation of the early atherosclerotic lesion.[11] Different results are obtained in advanced atherosclerosis studies using the same dose and experimental animals but do not show therapeutic effects.[12]

Several studies have shown the antioxidative effect of low-dose proteasome inhibitors in

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inhibiting atherosclerosis, but none are based explicitly on the stages of atherosclerosis. For example, Ludwig et al.[13] suggested that the administration of low doses of a proteasome inhibitor in rats induced by hypertension could reduce the levels of superoxide and malondialdehyde (MDA). Similarly, the study by Li et al.[14] also showed that proteasome inhibitors could protect vascular cells against oxidative stress by increasing the expressions of antioxidants such as superoxide dismutase (SOD) and catalase. Catalase, a cellular antioxidant that plays a vital role in overcoming oxidative stress, catalyzes the conversion of hydrogen peroxide to oxygen and water ($2H_2O_2 \rightarrow 2H_2O+O_2$).[15] Mammals, including humans and mice, express catalase in every tissue, and the highest concentrations of catalase are found in the liver, kidneys, and erythrocytes.[16] However, the protective role of catalase in atherosclerosis still requires further research.

This study aimed to analyze the effects of proteasome inhibitors on catalase expression and intima-media thickness (IMT) in the thoracic aorta of atherosclerotic rats. It is essential to conduct this study since it will serve as a basis for developing proteasome inhibitors for atherosclerosis therapy.

Methods

It was an experimental study with a post-test-only control group design conducted at the Faculty of Medicine, Universitas Riau, in Juni–November 2021. This study used 15 male Wistar rats from the Sekolah Tinggi Ilmu Farmasi Riau in Pekanbaru, Indonesia. Some requirements were given to rats to make them homogeneous. They are 10–12 weeks old and weigh ±200 grams. They also have no macroscopic abnormalities.

Rats were placed in cages in rooms with proper ventilation, humidity, and temperature between 20–26°C. All rats were fed with standard feed for one week to be adapted to the environment. Rats were divided randomly into three groups (five rats per group). Group, I was a group of rats given only standard feed, group II was a group of rats induced with vitamin D3 and given an atherogenic diet, and group III was a group of rats also given bortezomib in addition to an atherogenic diet and induced with vitamin D3. The treatment of experimental animals in this research was consistent with the Helsinki Convention. All procedures were approved by the Medical and Health Research Ethics Unit, Faculty of Medicine, Riau University, with letter number B/046/UN19.5.1.1.8/UEPKK/2021.

Atherosclerosis induction was carried out using an atherogenic diet (5% goat fat, 2% cholesterol, 0.2% cholic acid) for four days and a high vitamin D3 (700,000 IU/kg) through gastric intubation on day one.[9] Bortezomib was administered intraperitoneally at 50 μg/kgBW/day.[13]

Thoracic aortic samplings were performed after the rats were anesthetized using ether. The thoracic aorta was then fixed using a formalin buffer. The IMT assessment was performed on hematoxylin-eosin (HE) slides. All slides were observed under a light microscope at 100× magnification. The examination was carried out using an application on the microscope (Leica) at five points, and then the mean value was taken.[17]

Expression of catalase in the aorta was assessed by an immunohistochemical technique based on the procedure (ABclonal, MA, USA). The primary antibody was the catalase monoclonal antibody (A11220, ABclonal, MA, USA). Phosphate-buffered saline (PBS) was used as a negative control. Seven 2D images at 400× magnification were taken on each preparation using a microscope camera (Leica). Adobe Photoshop CS3 software was used to evaluate the percentage of area and intensity. The percentage area showed the breadth of expression, and the intensity showed the concentration.[18]

Statistical analyses for the intensity and percentage of catalase area and IMT were done using the ANOVA test. For IMT, it was followed by post hoc analysis using LSD. The p value below 0.05 is statistically significant.

Results

IMT measurement results show that the highest IMT was in the atherosclerosis group (II), while the lowest was in the control group (I). Administration of bortezomib 50 μg/kgBW/day in rats induced by atherosclerosis can inhibit the thickening tunica intima-media, which was statistically significant (Table 1).

Microscopic examination in the atherosclerosis group (II) showed thickening tunica intima-media, but the atherosclerosis group given bortezomib (III) almost had the same thickness of tunica intima-media as the control group (I). In addition, the atherosclerosis-induced group

Table 1 Intima-Media Thickness (IMT) in Groups at the End of the Study

Replication	IMT of Groups (mm)			p*
	I	II	III	
1	0.0700	0.1070	0.0820	0.001
2	0.0762	0.0950	0.0790	
3	0.0670	0.0920	0.0640	
4	0.0818	0.1070	0.0799	
5	0.0768	0.0910	0.0640	
Mean±SD	0.0744±0.003	0.0984±0.004[a]	0.0737±0.004[b]	

Note: I: control group; II: atherosclerosis-induced group; III: atherosclerosis-induced group and given bortezomib; *ANOVA test, values are presented as mean±SD; [a]p<0.05 compared to group I; [b]p<0.05 compared to group II

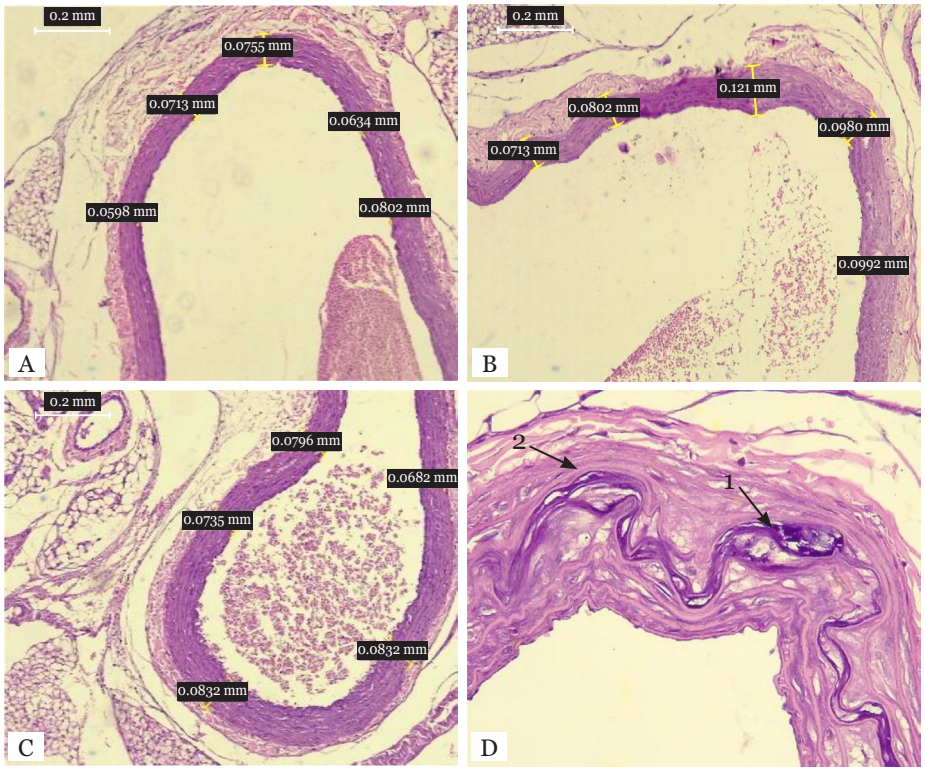

Figure 1 Histopathology of Thoracic Aorta

(**A**) Control group (I); HE, 100× magnification. (**B**) Atherosclerosis group (II); HE, 100×. (**C**) Atherosclerosis+ bortezomib group (III); HE, 100×. (**D**) Atherosclerotic lesions; HE, 400×. 1: calcification. 2: smooth muscle proliferation

revealed vascular smooth muscle cells (VCMC) proliferation and calcification as characteristics of the progression stage.[9] The atherosclerosis group given bortezomib showed milder atherosclerotic lesions (Figure 1).

Catalase expression was seen in all groups in the tunica intima, media, and adventitia. However, there was a difference in the distribution of catalase expression between the control and atherosclerosis groups. The catalase expression in the control group was more concentrated in the tunica adventitia. In contrast, it was more evident in the tunica intima and media in the atherosclerosis group. The distribution of catalase expression in the atherosclerosis group treated with bortezomib was similar to that in the atherosclerosis group (Figure 2).

In this study, catalase expression in the atherosclerosis group was lower than in the control group. This decrease can be seen from

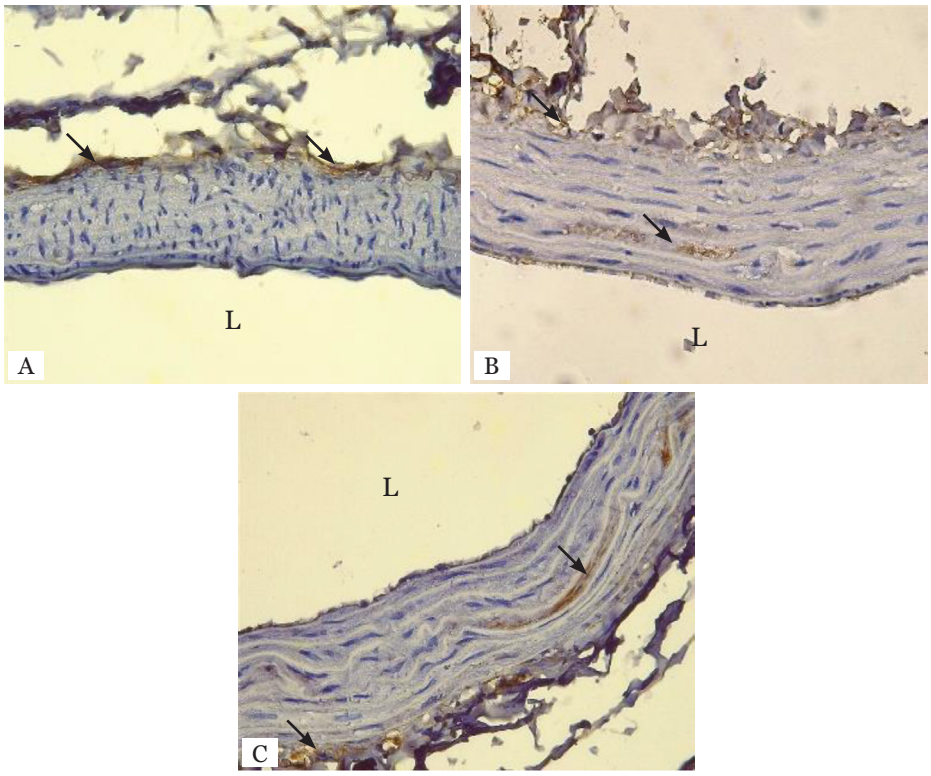

Figure 2 Catalase Expression in the Aorta by Immunohistochemical Examination (Arrow)
HE, 100× magnification. (**A**) Control group (I). (**B**) Atherosclerosis group (II). (**C**) Atherosclerosis+bortezomib group (III). L: lumen side

Table 2 Frequency of Foods Containing Vitamin D that Most Consumed by Respondents

Characteristics	Groups			p*
	I	II	III	
Percentage area (%)	3.09±0.75	1.63±0.32	2.43±0.0.58	0.577
Intensity	86.23±6.31	86.21±11.48	92.26±3.53	0.425
Mean±SD	0.0744±0.003	0.0984±0.004a	0.0737±0.004b	

Note: I: control group; II: atherosclerosis-induced group; III: atherosclerosis-induced group and given bortezomib; *ANOVA test; [a]p<0.05 compared to group I; [b]p<0.05 compared to group II

the difference in the percentage of area in the atherosclerosis group compared to the control group, although the intensity is not different. On the other hand, catalase expression in the atherosclerosis+bortezomib group was higher than in the atherosclerosis group, but this increase was not statistically significant (Table 2).

Discussion

Atherosclerosis induction in this study succeeded in obtaining atherosclerotic lesions at the progression stage with macrophages, foam cells, smooth muscle proliferation, and calcifications. vitamin D3 administration contributes to increasing vascular calcification and stimulating the proliferation of vascular smooth muscle. In addition, the administration of an atherogenic diet, which contains cholesterol and goat fat, increases LDL, and hypercholesterolemia occurs. Further, cholic acid gives a more atherogenic lipoprotein picture by increasing LDL levels and reducing HDL, causing endothelial damage.

The decrease in IMT in the atherosclerosis group given the bortezomib indicated the potential anti-atherosclerosis effect of the proteasome inhibitor. The IMT reflects the atherosclerotic process and predicts cardiovascular events.[7]

This decreasing IMT was also confirmed by histopathological examination that showed a decrease in lesions formed in the atherosclerosis group given bortezomib. A study by Wilck et al.[11] in administering bortezomib 50 µg/kgBW for six weeks in LDLR−/− mice also obtained similar results, suppressing the formation of early atherosclerosis lesions.

Atherosclerosis is initiated by the entry of low-density lipoprotein (LDL) into the artery wall, then this LDL is oxidized and turns into oxidized LDL (oxLDL). The oxidized lipoprotein components induce a local inflammatory response. Further, oxidative stress occurs as the effect of oxLDL on endothelial cells, characterized by increasing pro-oxidant enzymes (NADPH oxidase, xanthine oxidase) and decreasing antioxidant system (superoxide dismutase, catalase, glutathione peroxidase).[19]

As a result, significant differences did not occur in catalase expression in atherosclerotic rats compared to the control group. This result is different from an in vitro study, which obtained an increase in catalase expression in cells exposed to oxLDL.[20] This difference is probably because, in an in vitro study, it occurred at the initiation of atherosclerosis, whereas in this study, atherosclerosis was in the stage of atherosclerosis progression. Research on transgenic mice showed increased expression of catalase associated with reduced cardiac pathology, reduced oxidative stress, and increased life expectancy.[21] Oxidative stress and damage in advanced stages of atherosclerosis are some of the causes of antioxidant failure. Research on CHD patients showed a decrease in the concentration of the antioxidant glutathione (GSH).[22]

Only a few studies are analyzing the antioxidant effect of proteasome inhibitors, especially bortezomib.[23] In this study, the administration of proteasome inhibitors to atherosclerosis-induced rats increased catalase expression, although it was not statistically significant. It is different from a survey by Dreger et al.[23] that in vitro administration of proteasome inhibitor MG132 to myocytes significantly increased catalase expression.This difference may be due to differences in type, method of administration of proteasome inhibitors (in vitro vs in vivo), and the stage of atherosclerosis. In addition, the measurement of catalase expression in this study also has limitations in assessing the function of catalase as an enzyme to assess its activity. Measurement of enzyme expression or concentration will also measure the inactive enzymes.[15]

The difference in catalase expression in this study is not statistically significant. However, the difference in the distribution of catalase expression in the atherosclerosis group, the atherosclerotic group was given bortezomib, and the control group indicates a possible role of catalase in overcoming oxidative stress. In addition, this study found that in the control group, catalase expression was dominant in the tunica adventitia. In contrast, catalase expressions were prevalent in the tunica intima and tunica media in the other two groups.

The anti-atherosclerosis effect of a proteasome inhibitor in this study might not go through the antioxidative pathway but through the anti-inflammatory course. A survey by Wilck et al.[11] showed that bortezomib had a decreasing effect on plasma MCP-1 and IL-6 through an anti-inflammatory mechanism, namely a decreasing VCAM-1 expression in mice in the early stages of atherosclerosis.[12] Another possibility is the effect of bortezomib on increasing catalase or other antioxidants in other tissues, which also plays a role in overcoming oxidative stress at this stage of atherosclerosis. The highest concentrations of catalase are found in the liver, kidneys, and erythrocytes.[16]

Conclusions

In short, administering bortezomib 50 µg/kgBW for four days in rats induced by atherosclerosis could inhibit the thickness of the tunica intima-media. However, no change was in catalase expression. Therefore, further research is needed to analyze the expression of antioxidant catalase in other organs, such as the liver and kidneys.

Conflict of Interest

We have no conflict of interest.

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RESEARCH ARTICLE

Electrocardiogram Characteristics of Chronic Obstructive Pulmonary Disease Patients are Associated with Severity and Disease Duration

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitations associated with an increase in chronic inflammatory responses to the airways and lungs. COPD patients are more likely to be hospitalized and die from cardiovascular disease. This study aims to determine the factors associated with the incidence of electrocardiogram (ECG) abnormalities in COPD patients. This a cross-sectional study with an analytical observational design. From October 30 to December 5, 2019, data was collected on 42 COPD patients, inpatients, and outpatients at Muhammadiyah Palembang Hospital who met the inclusion and exclusion criteria. A questionnaire was used to collect data, and spirometry and an electrocardiogram test were used to measure pulmonary function and detect ECG abnormalities. Research variables included age, sex, smoking habits, severity, and duration of COPD. Data analysis using the chi-square test and followed by a logistic regression test found a significant relationship between severe to very severe COPD and ≥5 years of suffering from COPD with the incidence of ECG abnormality ($p<0.05$). The severity and the length of time of suffering from COPD are significantly related to the incidence of ECG abnormalities in outpatients and inpatients.

Keywords: COPD, electrocardiogram (ECG), smoking

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitations, generally progressive and associated with an increased chronic inflammatory response to the airways and lungs due to harmful particles or gases.[1] Heart disease is one of the comorbid factors of COPD; patients with COPD have a high chance of developing heart disease.[2] The coexistence of two conditions can not be separated from the linkage of the function of the lungs and heart. It most likely can be caused by having the same risk factors: smoking, age, unhealthy lifestyle, and low socioeconomic factors.[3,4] COPD patients are more likely to be hospitalized and die from cardiovascular disease,[5] which impacts the management of patients.[6] Changes in the electrocardiogram (ECG) image are associated with the risk of acute exacerbation and an increased risk of death in patients who do not have a previous heart history.[7–9]

ECG images are often found in COPD patients, such as right axis deviation (RAD), right bundle branch block (RBBB), P-pulmonary/right atrial hypertrophy (RAH), and right ventricle hypertrophy (RVH). This ECG change in COPD patients is highly related to the severity of the disease.[9–11]

Changes in ECG characteristics in COPD patients are related to the severity of the disease and affect the patient's prognosis. We know the aspects related to the incidence of ECG abnormalities in COPD patients and expect to raise awareness of the onset of cardiovascular impact in patients who do not have a comorbid history of cardiovascular disease, both inpatients and outpatients. This study aims to determine the factors associated with the incidence of ECG abnormalities in COPD patients.

Methods

This type of research is observational analytical research with a cross-sectional approach. The population and sample in the study were patients who had been diagnosed with COPD. This study used purposive sampling strategies to collect samples from inpatients and outpatients at Muhammadiyah Palembang Hospital from October 30 to December 5, 2019.

The inclusion criteria in this study were

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patients with age ≥21 years, patients diagnosed with COPD in the internal ward and polyclinic, and were willing to sign informed consent. In contrast, the exclusion criteria in this study were patients with tuberculosis, patients with non-pulmonary disorders causing cardiac abnormalities, and patients who could not be performed the ECG installation (injury to thoracic region, mammae carcinoma). In addition, these COPD patients were experiencing symptoms of exacerbation.

A questionnaire was used to collect data, and a spirometry examination was used to assess lung function. The patient was asked to blow into the spirometer, and then the FEV_1 was measured. Degrees of lung function are divided into mild to moderate degrees (FEV_1≥50% of the predicted value) and severe to very severe degrees (FEV_1<50% of the expected value). An electrocardiogram is performed to detect ECG abnormalities. Data collected were processed using SPSS version 24. The data were analyzed using chi-square tests in bivariate analysis and, afterward, logistic regression in multivariate analysis.

This study has received ethical clearance from the Bioethics, Humanities, and Islamic Medicine Committee of the Faculty of Medicine, Universitas Muhammadiyah Palembang (Approval No. 17/EC/KBHKI/FK-UMP/X/2019).

Results

This research was conducted at Muhammadiyah Palembang Hospital with 42 respondents who had met the criteria for inclusion and exclusion. The most commonly observed ECG abnormalities are cardiac conduction problems in the form of RBBB (54%) followed by ischemic images (T inversion, ST depression, pathological Q) by 28%, rhythm abnormalities in the form of tachycardia and atrial fibrillation (2.1%), P-pulmonary/RAH (1.9%), RVH (1%), and RAD (1%).

Table 1 shows the picture of the most ECG in COPD patients is an abnormal ECG of 31/42 patients. Most COPD patients were aged ≥60 years (27/42 patients), male (27/42 patients), had a history of smoking (27/42 patients), had a very severe degree (29.1%), and had COPD for <5 years (27/42 patients).

Table 2 reveals a significant association between the severity of COPD and the length of time COPD patients have been suffering from it, along with the abnormalities of the ECG image in COPD patients, with p<0.05.

Table 1 Baseline Characteristics of Respondents

Characteristics	n=42
Age (years)	
<60	15
≥60	27
Sex	
Male	27
Female	15
Smoking habits	
Yes	27
No	15
COPD severity stage	
Mild to moderate	13
Severe to very severe	29
Diseases duration	
<5 Years	27
≥5 Years	15
ECG	
Normal	11
Abnormal	31

Discussion

This study showed a significant association between the severity of COPD (p=0.001) and the length of suffering from COPD (p=0.014) with abnormalities of ECG in COPD patients. Furthermore, they remained significant following a logistic regression test, even though the patient's age, male sex, and smoking history had no significant correlation (p>0.05).

In this study, the results found that most degrees in people with COPD are severe to very severe, which is 29/42 patients. In addition, the ECG picture found in this study showed most patients had an abnormal ECG (31/42 patients). This study's results align with previous studies' results that the more severe the degree of COPD suffered by patients, the greater the risk of ECG abnormalities and arrhythmias.[12–14]

Another study said ECG abnormalities in patients with COPD are related to the severity and duration of the disease. Hence, ECG becomes one of the examinations that can be used to assess the severity of COPD.[16,17] The severity and duration of the disease are significantly related to the incidence of ECG abnormalities.

Table 2 Statistical Analysis Factors Associated with ECG Abnormality

Variable Independent	ECG Abnormality		p Value[1]	Adjusted p Value[2]
	Yes	No		
Age (≥60 years old)	16	11	0.636	0.77
Sex (male)	16	11	0.636	0.99
Smoking (yes)	17	10	0.850	0.98
COPD severity stage (severe to very severe)	23	6	0.001*	0.004*
Diseases duration (≥5 years)	13	2	0.014*	0.03*

Note: [1]Chi-square analysis; [2]Logistic regression analysis; *p<0.05, significant

In addition, in another study, ECG examination of COPD patients showed a relationship between the severity of COPD and changes in P waves and QRS complexes. The higher the severity of COPD, the more visible changes in P waves and QRS complexes.[14]

ECG abnormalities arise both due to the comorbidities of cardiovascular disease and the impact of COPD disease on the cardiovascular system. The mechanism of arrhythmia in COPD is thought to be related to hypercapnia. Hypercapnia is a condition of higher CO_2 levels in the blood than average. Known CO_2 is a substance with proarrhythmic properties[18] that increases the risk of arrhythmias in the heart.[15]

The presence of several related mechanisms, such as tachycardia, arterial stiffness, increased occurrence of thrombus, hypoxemia, infection, and the use of short-acting b2 agonists.[17,19] causes ischemic abnormalities in COPD, as also seen in this study. Increased pulmonary artery resistance in patients with higher degrees of COPD leads to increased water trapping and lung hyperinflation. In addition, the right ventricle is enlarged, and the movement of the heart's vertical axis is due to COPD. Then the heart will rotate clockwise, so that right ventricle hypertrophy is closely related to the onset of right axis deviation.[20]

The mechanism of conduction disorders in COPD patients is through an increase in afterload followed by changes in heart structure. These changes also cause the heart's electrical conduction system to undergo remodeling, so conduction disorders can occur, resulting in abnormalities of the ECG image. The most conduction is in the form of the RBBB, as revealed by this research. The increased risk of cardiovascular disorders, among others, is also due to systemic inflammation in COPD patients associated with an increased risk of trauma to the heart that increases cardiovascular complications.[21,22] The importance of conducting an ECG examination in performing cardiovascular disease management in COPD patients for a better patient prognosis.[23]

In this study, the age of most COPD sufferers was ≥60 years old. As we age, the body's ability to regenerate will decrease, so damaged body cells will be replaced by fibrosis tissue.[20] COPD patients tended to have abnormalities in ECGs compared to non-COPD patients in the patient population over the age of 65 years of age.[24] However, in this study, there was no significant association between age over 60 years and the incidence of ECG abnormalities. This is likely because 53% of the under-60 age group has a severe degree of disease severity that has an impact on ECG characteristics in that group of patient.

Increased age and gender are risk factors associated with increased severity of COPD[25] and are a risk factor for increased cardiovascular comorbid.[26] This study found that sex and smoking were not directly related to ECG abnormalities in COPD patients. Most subjects are male, which is in line with research conducted by Jatav et al.[16] that COPD patients are more men than women. The higher prevalence of men in COPD patients was also associated with smoking habits. Longer duration of exposure to cigarette smoke and recurrent respiratory infections will lead to a decrease in the quality of life of COPD patients. Factors related to specific ECG abnormality categories, such as ischemia images, arrhythmias, or structural abnormalities of the heart, need to be investigated further.

Conclusion

The severity and the length of time of suffering from COPD are significantly related to the incidence of ECG abnormalities in outpatients

and inpatients.

Conflict of Interest

There is no conflict of interest at all authors.

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RESEARCH ARTICLE

Occupational Safety and Health Hazards among Smoked Fish Workers in Demak

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Abstract

Smoked fish is an essential commodity in Central Java. Smoked fish workers must always ensure the availability of smoked fish products for the community. To work continuously, workers need to maintain their safety and health. Workers are constantly exposed to potential hazards from their work. This study aimed to describe the potential occupational hazards of smoked fish workers and identify efforts to control these hazards. This descriptive research involved smoked fish workers cleaning, cutting, washing, and smoking fishing in Demak city, Central Java, in March 2021. The job safety analysis (JSA) method was used to describe potential hazards in every work process. The results showed that the potential risks found in the working process of smoking fish were a wet and humid work environment, sharp work equipment, non-ergonomic work postures, and a hot work climate. It can be concluded that workers are exposed to various hazards in their work and work environment. Therefore, it is necessary to increase occupational safety and health (OSH) awareness and working environment conditions in the smoked fish industry so that workers will always be safe and healthy at work.

Keywords: Job safety analysis, occupational safety and health (OSH), OSH hazards, smoked fish worker, work environment

Introduction

Indonesia is famous for its diverse specialties. The food is the result of agriculture/plantation and marine products. One of the marine products is fish. Various kinds of food are processed from fish, one of which is smoked fish, an essential commodity in Central Java. The smoked fish center is one of the informal sector industries that is multiplying and supports the economy of fishing communities. Still, this sector has a reasonably high health risk because workers pay less attention to work safety rules.[1]

A study on fishermen in West Java showed that 7 out of 17 had health problems, with the highest number suffering from hypertension. All respondents had experienced work-related hazards and accidents. The most significant health hazard that fishermen complain about is the sting of a green jellyfish. Handling marine products can also increase the health and safety risks of fishermen. Increased knowledge about safety and health at work, as well as training on accident handling, needs to be carried out so that workers can prevent exposure to potential hazards at work.[2]

Smoking fish in Indonesia was initially done traditionally by using simple equipment and not paying attention to hygiene and sanitation aspects so that it can impact health and the environment. Short chimneys affect air pollution and health. In addition, non-ergonomic work postures cause many health problems for workers.[3]

The working process of smoking fish begins with cleaning the fish. Fish that have been cleaned are then cut into pieces according to the specified size. The pieces of fish are then washed and stabbed with bamboo. The fish then go into the smoking process. Health complaints found in previous studies were as follows: 87% of workers had MSDs complaints, 40% of workers complained of dermatitis, and 76% of workers had respiratory complaints.[4]

This study aims to analyze the potential occupational hazards of fish-smoking workers and identify efforts to control these hazards.

Methods

This research is a descriptive study conducted at a smoked fish center in Demak city, Central Java, in March 2021. The subjects of this study were smoked fish workers in cleaning, cutting, washing, stabbing, and smoking fish.

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Each work process was analyzed based on the job safety analysis (JSA) form. The JSA method was used to describe potential hazards in every work process.[5] Workers were observed from the start of work to completion to fill out the JSA form. In addition, researchers took pictures when workers were doing work with the workers' permission.

The research protocol has been approved and received an ethical clearance certificate number 200/EA/KEPK-FKM/2020.

Results

Based on the study's results, it was found that each work process was carried out successively in one day. Each fish that has been processed must be completed until the smoking process. The fish may be damaged or rot if smoking is done the next day.

The process of cleaning the fish can be seen in Figure 1. In this picture, it can be seen that workers are splitting and cleaning the entrails of the fish and cutting the fins of the fish. Workers sit in tiny chairs (*dingklik*) and use flip-flops for footwear.

Figure 1 shows that workers use pieces of wood as a work table as well as a cutting board. Around the workers, there are several buckets and fish to be cleaned. Fish droppings are also placed on the floor.

Figure 2 shows the process of cutting fish into smaller pieces with a predetermined size. Several buckets of fish containers were seen in front of the workers to separate the pieces of fish.

Figure 2 Fish Slaughter

The fish washing process shown in Figure 3 is carried out with water stored in a bucket. This process is repeated several times until the fish are clean. Figure 3 also shows that the worker was still sitting on a small/short chair and the body looked slightly bent to reach the bucket. In this washing process, workers were seen wearing cloth gloves.

The process of skewering pieces of fish with bamboo was carried out by workers who sat on

Figure 1 Fish Cleaning

Figure 3 Fish Wash

Figure 4 Fish Stabbing

Figure 5 Fish Smoking Process

short chairs and saw their bent backs. Workers wear flip-flops. Bamboo slats can be seen piled up on the floor.

The last process carried out in this work was smoking the fish (Figure 5). This process begins with preparing fuel for smoking fish. The fuel for this process was dried corn cobs. The method of smoking fish was carried out in a relatively narrow room so that workers would be exposed to heat and fumes from the smoking process.

Discussion

The process carried out in the work of smoking fish has potential hazards that can endanger the safety and health of workers. For example, potential hazards in the fish cleaning process include fish/ fish droppings that can trigger allergies and dirty and slippery floors because they are always wet, which can cause falls, scratched hands, or fish thorns. In addition, sitting for too long, especially with a low enough chair, can trigger complaints of aches and back pain.[6–8]

The smoked fish production process uses many repetitive activities with a continuous sitting position and grabbing, retrieving, and bending movements. Work activities like this will certainly cause injury to the muscles, joints, ligaments, and tendons. These disorders are usually referred to as musculoskeletal disorders (MSDs) complaints or complaints of the musculoskeletal system, which are conditions of discomfort or even pain.[9–11]

Cutting fish has various potential hazards, including dirty and slippery floors that can cause falling or slip and knives/sharp objects that can cause hands to be cut. In addition, an unergonomic and uncomfortable sitting position and sitting for too long can cause backache or pain.

Workers are exposed to several potential hazards during the fish-washing process. Floors that are always wet can cause slips and falls. Sitting positions that are not ergonomic and too long can cause backache or pain. Hands that are always in contact with water can cause workers' skin to become irritated. If not addressed immediately, these complaints can develop into skin diseases in workers.

Occupational skin diseases contribute to the majority of occupational diseases, especially in Asia, where most of the workforce is in the unorganized sector. A study was conducted on the number of reported disease incidences with patterns of occupational skin diseases reported in Asian countries and different types of occupational allergens. Some of the skin diseases seen in workers in Asian countries are similar to those in Western countries, including skin diseases caused by chromate in construction and electroplating workers, epoxy resins and chromate in painters, wood dust in workers in the furniture industry, dyes in textile workers, formaldehyde and chromate in those working in the leather and dyeing industry, skin diseases in

domestic workers, cooks and health care workers. Skin diseases in workers engaged in agriculture, carpet weaving, sanitation, coffee plantations, coal mines, and also fish processing workers.[12]

A study was conducted on hundred and eleven of 135 (82.2%) seafood workers at two food markets in Ningbo, East China. The prevalence of hand dermatitis was 50.5% (56/111) in seafood workers, which was significantly higher than the control group (7.43%, $p<0.001$). It was found that the incidence of superficial hand fungal infections in seafood workers was much higher than in the community (26.1% vs. 2.7%, $p<0.001$). Without waterproof gloves, longer working hours per day and a long history of work in the seafood sector increase the risk of hand dermatitis. Hand skin disease is prevalent in workers who handle seafood. And these public health problems must be addressed, especially in this working population.[13]

In the process of skewering fish, workers are exposed to the potential danger of sharp sticks that can cause sticks to prick their hands. In addition, slippery floor surfaces can cause slips and falls. Sitting positions that are not ergonomic and too long can cause backache or pain. Workers' hands in this process are also always wet because the pieces of fish to be pierced are submerged in a water-filled bucket. So that when it is about to be skewered, the fish must be taken piece by piece by the worker by dipping his hand in the bucket.

A study stated that jobs where there are activities of workers who have to immerse their hands in liquid for >2 hours per shift or wear waterproof (occlusive) gloves for a suitable time, or wash their hands >20 times per shift are commonly known as wet work. This study investigated wet work as a significant risk factor for developing irritant contact dermatitis on the hands. The study also provides a detailed description of exposure to wet work among certain occupational groups who deal extensively with water and other liquids in their work. In addition, the study also highlights the extent and importance of the health effects caused by exposure to wet work.[14]

The process of smoking fish exposes workers to smoke and hot steam, which can cause eye, skin, and respiratory irritation. Exposure to hot temperatures can cause workers to experience heat stress. The sitting position is not comfortable/not ergonomic, and sitting for too long can cause backache or pain.

A study investigating musculoskeletal symptoms in workers at a fish processing plant in Ghana found that workers' necks were stooped and experienced neck flexion. Workers also stand for long periods, elevate the shoulders, abduct the arms, repeatedly reach forward and deviate the wrists. It follows the questionnaire results where musculoskeletal symptoms most occur in the neck, shoulders, lower back, wrists/hands, and knee areas. There was no significant relationship ($p<0.05$) between musculoskeletal symptoms with age, working hours, and length of work. Even so, if this condition occurs continuously, the musculoskeletal complaints in workers will get worse. Therefore, in this study, it is suggested to redesign the task, change the workplace, and train workers to improve their quality of work and health.[15]

Results from one study showed that nearly 71% of women (aged 23.0±6.4 years) reported MSDs, especially in the upper back (54%), lower back (33%), knees (35%), and shoulders (27%). Pain severity was high among workers with high comorbidity (pain in two or more areas). One-third of workers consider the work environment to be the cause of their MSDs. Almost all psychosocial factors and job stress are associated with low back MSD. In addition, cold and humid environments, awkward standing work postures for long hours, high physical activity, poor task clarity, and high mental load are important risk factors for MSDs.[16]

A descriptive study conducted on 368 workers in the seafood industry in Myanmar showed a prevalence of MSDs of 45.1% occurring in the last seven days. Marital status, the number of dependents, other health problems, working hours, repetitive hand movements, awkward wrist posture, prolonged standing, and manual handling of heavy loads were found to be associated with MSDs. The research findings also indicate the need for adequate knowledge about ergonomics and awareness campaign programs focusing on preventing MSD, especially low back pain. Business owners are advised to detect MSD symptoms early in seafood processing workers.[17]

Research conducted in the salmon industry found that from a Nordic questionnaire, 80% of workers showed musculoskeletal symptoms in the right hand/wrist, followed by the shoulder in 60% of workers and arm/elbow in more than 50%. There was a statistically significant relationship between productivity and MSD risk ($p<0.05$).[18] A

study of the average annual claim rates on health-related workers found that claims on workers in the seafood processing industry were significantly higher than all industries in Alaska. The most common injuries/diseases were sprains/strains/tearing (n=993, 36%); by body part, upper limb (1212, 43%); and by event, contact with objects/equipment (1020, 37%) and overreaction/body (933, 34%). Frequent incidents include repetitive movements; fatigue when handling tools, fish, and buckets; and contact with fish, cookware, and machinery. Ergonomic and safety solutions should be implemented to prevent musculoskeletal injuries/diseases in seafood processing.[19]

New sources of exposure to this type of allergen continue to be reported. Through clinical databases and surveillance systems, the effects of the presence of a new allergen can be monitored. In the fish processing process, certain ingredients may be allergens for some workers. Maybe workers have not recognized it because early detection and screening have yet to be implemented. Primary prevention in the workplace Must be done. This process of identifying and assessing potential hazards must be carried out to reduce the impact of disease occurrence. Further research and efforts to improve the prevention of occupational skin diseases should continue.[20]

Hygienic and sanitary working conditions in fish processing facilities are most challenging to control and sometimes even very dangerous for workers. Various data literature on fish processing work still raises many questions regarding assessing working conditions concerning worker knowledge, evaluation of work risks, risk of occupational diseases, and working conditions in the working group.[21]

Hazard controls that can be carried out in this work per the hazard control hierarchy are as follows. The substitution step can replace the water to wash the fish from the reservoir with running water. Engineering can be done by replacing the appropriate work table and chairs (there were seat backs, cushions, and height according to the length of the legs), engineering/adding the installation of exhaust fans/making air ventilation. Administrative steps are used by stretching every 2 hours of work, doing work with the 5R concept (*ringkas*/concise, *rapi*/neat, *resik*/clean, *rawat*/treat, *rajin*/diligent), and cleaning the work area after. Additionally, arrange regular changes in washing water, conduct regular health checks on workers (at least once a month) by checking blood pressure, and diagnose the complaints felt by workers. This health check can be done by utilizing the available clinics at the fish smoking center.

The last control hierarchy was using personal protective equipment (PPE). Workers can use appropriate PPE such as gloves, masks, and boots/anti-slip shoes. PPE is adjusted to the potential hazards faced in each work process.

Conclusion

It can be concluded that potential hazards from the smoked fish process were fish droppings that can trigger allergies, accidents caused by knives or pricked by fish bones, non-ergonomic work conditions, and fumes.

Conflict of Interest

All authors convey that there is no conflict of interest between all parties.

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RESEARCH ARTICLE

Protective Effect of the T1212C Macrophage Mannose Receptor Gene Polymorphism on Pulmonary Tuberculosis

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Abstract

The interaction between the mannose receptor, which is encoded by the macrophage mannose receptor (MMR) gene, and the most virulent antigen (the mannose-capped lipoarabinomannan) cell wall of virulent strains of *Mycobacterium tuberculosis* trigger an innate and adaptive immune response. It also produces pro and anti-inflammatory cytokines, which play a role in the pathogenesis of tuberculosis (TB) infection. Therefore, MMR gene polymorphism is a risk factor associated with the prognosis for active pulmonary TB. This study aimed to determine the correlation between MMR gene polymorphism and active or latent pulmonary tuberculosis. In this phase, MMR gene polymorphism was analyzed using a case-control design consisting of 74 control group subjects (patients with latent TB) and 74 case groups (patients with active pulmonary TB). The subject's MMR gene DNA sequencing examination. The study was conducted at the Teaching Hospital, Faculty of Medicine, Universitas Padjadjaran Bandung, from February 2014 to January 2015. The statistical analysis used chi-square and odds ratio. The study's result has shown the MMR gene polymorphism factor that correlated to the incidence of active pulmonary TB was T1212C (OR=0.253; 95% CI=0.111–0.575; p=0.001). There was an MMR gene in one SNP in the control group (C1323T) only and five single nucleotide polymorphisms (SNPs) in both groups (C1303T, C1221, T1212C, G1186A, and G1195A). Therefore, it can be concluded that MMR gene polymorphism on the T1212C site correlated with the incidence of active pulmonary tuberculosis and was protective.

Keywords: Active pulmonary TB, latent TB, MMR gene, single nucleotide polymorphisms, T1212C

Introduction

Interaction between the host immune response and defense mechanism conducted by *Mycobacterium tuberculosis* (MTB) creates a balance of cytokine production and pro and anti-inflammation chemokine. It causes the pathogenesis of tuberculosis (TB) infection.[1–4] MTB's host immune response is started by recognizing microorganism antigen structures called pathogen-associated molecular patterns (PAMPs). Receptors specifically recognize PAMPs in a congenital immune system called pathogen recognition receptors (PRRs). PRRs are expressed on many effector cells such as macrophages, dendrites, and lymphocyte cells B.[1,4–6,8]

The basic pathogen-associated molecular patterns of TB infection are the lipid riched-MTB cell walls structure, such as mannose-capped lipoarabinomannan (Man-LAM), which has immunogenic effects as the most common important virulence factor of MTB. Some PRRS roles can recognize the interaction between PAMPs and MTB. They were the C-type lectins, toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) like receptors (NLRs), dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), and Dectin-1.[1,6]

C-type lectins are PRRS involved in recognizing pathogen's polysaccharide structure with one of the most important receptors, mannose receptor (MR), consisting of eight bond identifier domains with one cysteine-rich domain on one alveolar macrophage. MTB stimulation through MR creates a bridge between natural and congenital immunity that will be connected by setting the endosomal and phagosomal pathways and producing proinflammatory cytokines and

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chemokines. The most important of these is tumor necrosis factor α (TNF-α), a family of interleukin (IL)-1, namely (IL-1β, IL-18), IL-12, and INFg, as well as anti-inflammatory cytokines of which IL-10 and transforming growth factor-β (TGF-β).[1,4,6–8]

Based on the Qidwai et al.[9] study, it was estimated that about 275 single nucleotide polymorphisms (SNPs) located on 19 genes were involved in affecting protein structure and a person's vulnerability to being infected with TB. In addition, a study by Azad et al.[10] explained that more than 50 genes affect a person's susceptibility to TB disease.

The study in China found six single nucleotide polymorphisms (SNPs) MMR/MRC-1 encoding MR and located on chromosome 10p12 consisting of 30 exons. They are associated with the incidence of pulmonary tuberculosis (G1186A, G1195A, T1212C, C1221G, C1303T, and C1323T) in exon 7. The study used PCR and DNA sequencing methods on pulmonary TB patients and a control group of healthy people. Allelic G1186A frequency (rs34039386) of the MMR gene in the Chinese population was higher in pulmonary tuberculosis patients than in the healthy control group. There were significant differences between the frequency distribution of the two groups ($p=0.037$, OR=0.76, 95% CI=0.58–0.98). The genotypic analysis also showed that genotype AG in the Chinese population was significantly correlated with pulmonary tuberculosis ($p<0.01$, OR=0.57, 95% CI=0.37–0.87). This study first reported that the SNP in MMR genes might be associated with pulmonary tuberculosis in the Chinese population and reduce the risk.[11]

This study aimed to determine the picture of MMR gene mutations and polymorphism type in patients with active pulmonary TB and latent TB and to analyze the incidence of MMR gene polymorphism, a risk factor for active pulmonary tuberculosis. There has not yet been a study about the role of MMR gene SNPs in Indonesia, so it is expected that the study can be a basic addition mechanism of susceptibility to pulmonary TB disease in Indonesia.

Methods

This study used a case-control design with 148 subjects consisting of a control group (patients with latent TB) and a case group (patients with active pulmonary TB). Each group is 74 people. The study was conducted from February 2014 to January 2015 in the TB Research Clinic of the Teaching Hospital, Faculty of Medicine, Universitas Padjadjaran Bandung. Schematically, the flow of subject selection was in Figure 1.

The inclusion criteria for the case group were patients aged 15–55 years with clinical symptoms of pulmonary tuberculosis, sputum examination of positive acid-fast bacilli (AFB) with the Ziehl-Neelsen method by collecting samples during the early when at least two times positive and having positive smear culture. The inclusion criteria of the control group were latent TB patients aged 15–55 years who live together with people with TB but do not have any complaints and symptoms of TB, with the results of interferon-gamma release assay (IGRA) being positive. Exclusion criteria were subject to disease conditions that interfered with the immunological response, including diabetes mellitus, HIV/AIDS, or steroid treatment.

The first optimization of the research was to design the PCR primer for the MMR gene before sequencing the MMR gene DNA. The success of DNA sequencing is highly dependent on the success of the PCR process, and the success of the PCR process is highly dependent on the choice of primer design. The principle of PCR is to multiply exponentially specific nucleotide sequences in vitro. To identify the series to be duplicated, particular specific primers are needed. This area, known as a primer, will later be multiplied to thousands or millions of copies so that after electrophoresis, bands of the amplified DNA will be seen. The primer design was based on DNA sequences[11,12] with known protein-related sequences from the Genbank database.[13]

Based on previous research in China, a PCR primer for the MMR gene was found, later called primer I (20 bp length), as follows: forward primer 5'-TTG AGG CTG CAA TGA GAC AT-3' and reverse primer 5'-AGT GTA AGG TAG ACT GCT CT-3'. Then a new primer design was produced at the Biomolecular Clinical Pathology Laboratory, Dr. Hasan Sadikin General Hospital (hereinafter referred to as primer II) with a length of 20 bp, namely: forward primer 5'-CTA GTC AGT GGT GGC CGT AT-3' and reverse primer 5'-CAC ATT GTG GTC GCA TTT TCA GC-3'. Researchers took about 3 mL of venous blood from both groups to examine DNA isolation, PCR, and DNA sequencing.

DNA isolation used a DNA extraction kit (QIAamp DNA Blood Midi, Germany). Then, PCR primers (20 bp long) were used to detect

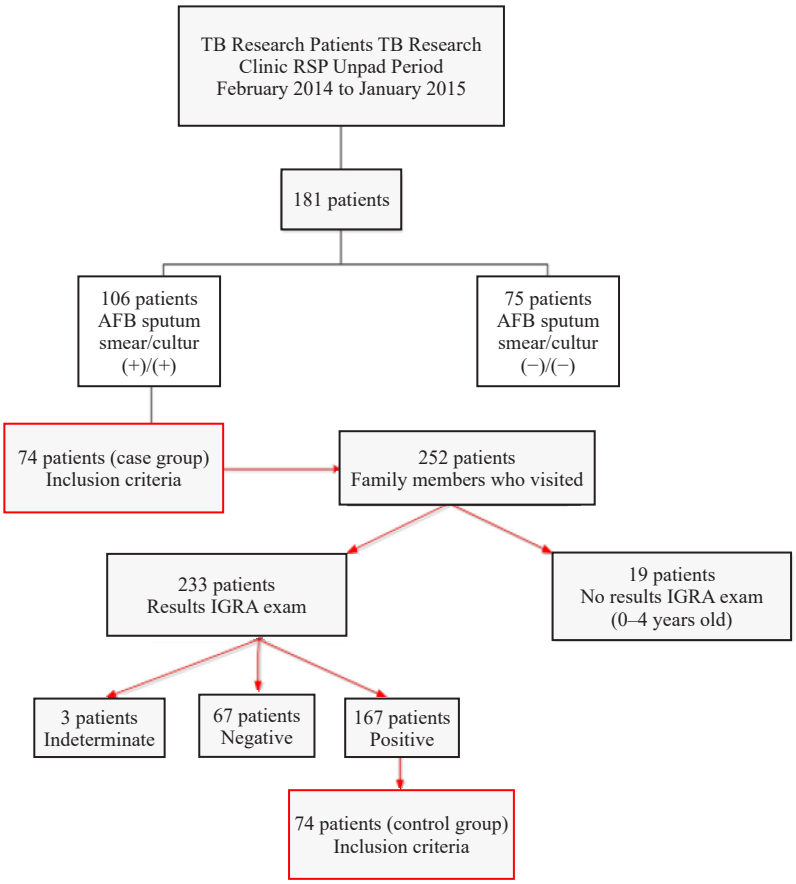

Figure 1 Flow of Subject Selection

the MMR gene DNA fragments using Primer3 software. Finally, confirmation was done using the NCBI Basic Local Alignment Search Tool (BLAST). We look at the possibility of primary mispriming with other areas on the MMR genes other than the region to be amplified.

MMR genes were detected using conventional PCR with DreamTaq master mix PCR reagent and gel-based PCR method. PCR products were then performed by PCR purification and clean-up kit (Geneaid), then DNA sequencing was completed with ABI 3130xl genetic analyzer tool. The exon 7 chromosome 10p MMR gene sequencing DNA examination was conducted at Eijkman Biomolecular Institute in Jakarta. Data of sequencing results were calculated in proportion to the type of mutation and analyzed by chi-square test to assess the odds ratio (OR) of each kind of mutation using R software.

The Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, approved the study with letter number 344/UN6. C2.1.2/KEPK/PN/2014.

Results

The number of cases was 74, with 74 control. Characteristics of research subjects based on age, sex, and body mass index can be seen in Table 1.

Results of DNA sequencing genes MMR exon 7 were analyzed using DNA baser software. It was found six site mutations, namely G1186A (rs34039386, Gly396Ser), G1195A (rs71497223, Gly396-Ser), T1212C (rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435 Phe), and C1323T (Asn441Asn) on both groups. The overview of MMR genes DNA sequencing in both groups, with baser DNA software as an example, can be seen in Figure 2.

The MMR gene mutations found MMR gene polymorphism confirmed in Asian populations using the genome browser HapMap software. On the G1186A site sequentially, the frequency of genotype A/A was 24% and 16%; the case group

Table 1 Characteristics of Research Subjects

Variables	Case Group n=74 (%)	Control Group n=74 (%)	Total n=148 (%)	p
Sex				
Male	34 (46)	33 (45)	67 (45)	0.869*
Female	40 (54)	41 (55)	81 (55)	
Age (year), median (JIK)	36 (17)	34 (19)	35 (19)	0.711#
Aged group (years)				
<20	5 (7)	8 (11)	13 (9)	0.775*
20–29	16 (22)	18 (24)	34 (23)	
30–39	22 (30)	17 (23)	39 (26)	
40–49	24 (32)	22 (30)	46 (31)	
50–59	7 (9)	9 (12)	16 (11)	
BMI (kg/m²), median (JIK)	17.83 (3.16)	23.73 (8.26)	19.46 (7.89)	<0.001#
BMI category (kg/m²)				
Underweight (<18.5)	47 (64)	11 (15)	58 (39)	<0.001*
Normal (18.5–24.99)	25 (34)	28 (38)	53 (36)	
Overweight (≥25)	2 (3)	35 (47)	37 (25)	

Note: *chi-square test; #Mann-Whitney test; JIK: interquartil space; BMI: body mass index

Table 2 Distribution of SNP Exon 7 Gene MMR Genotype Frequency

SNP Site	Genotype	Case Group n=74 (%)	Control Group n=74 (%)	p	OR (95% CI)
G1186A	GG	24 (32)	21 (28)	-	Reference
	AA	18 (24)	12 (16)	0.569	1.313 (0.515–3.347)
	GA	32 (43)	41 (55)	0.316	0.683 (0.324–1.440)
G1195A	GG	71 (96)	71 (96)	-	Reference
	AA	0 (0)	0 (0)	1.000	1 (0.019–51.091)
	GA	3 (4)	3 (4)	1.000	1 (0.219–4.560)
T1212C	TT	63 (85)	43 (58)	-	Reference
	CC	1 (1)	4 (5)	0.161	0.171 (0.018–1.580)
	TC	10 (14)	27 (37)	0.001	0.253 (0.111–0.575)
C1221G	CC	72 (97)	72 (97)	-	Reference
	GG	0 (0)	0 (0)	1.000	1 (0.019–51.081)
	GC	2 (3)	2 (3)	1.000	1 (0.168–5.948)
C1303T	CC	72 (97)	70 (95)	-	Reference
	TT	0 (0)	0 (0)	1.000	1.028 (0.020–52.541)
	CT	2 (3)	4 (5)	0.681	1.851 (0.381–8.991)
C1323T	CC	74 (100)	72 (97)	-	Reference
	TT	0 (0)	0 (0)	1.000	1.028 (0.020–52.481)
	CT	0 (0)	2 (3)	0.681	1.850 (0.381–8.975)

Note: analysis of genotype difference between the case and control groups used the chi-square test if the assumption was fulfilled and used Fisher's exact if the chi-square premise not met

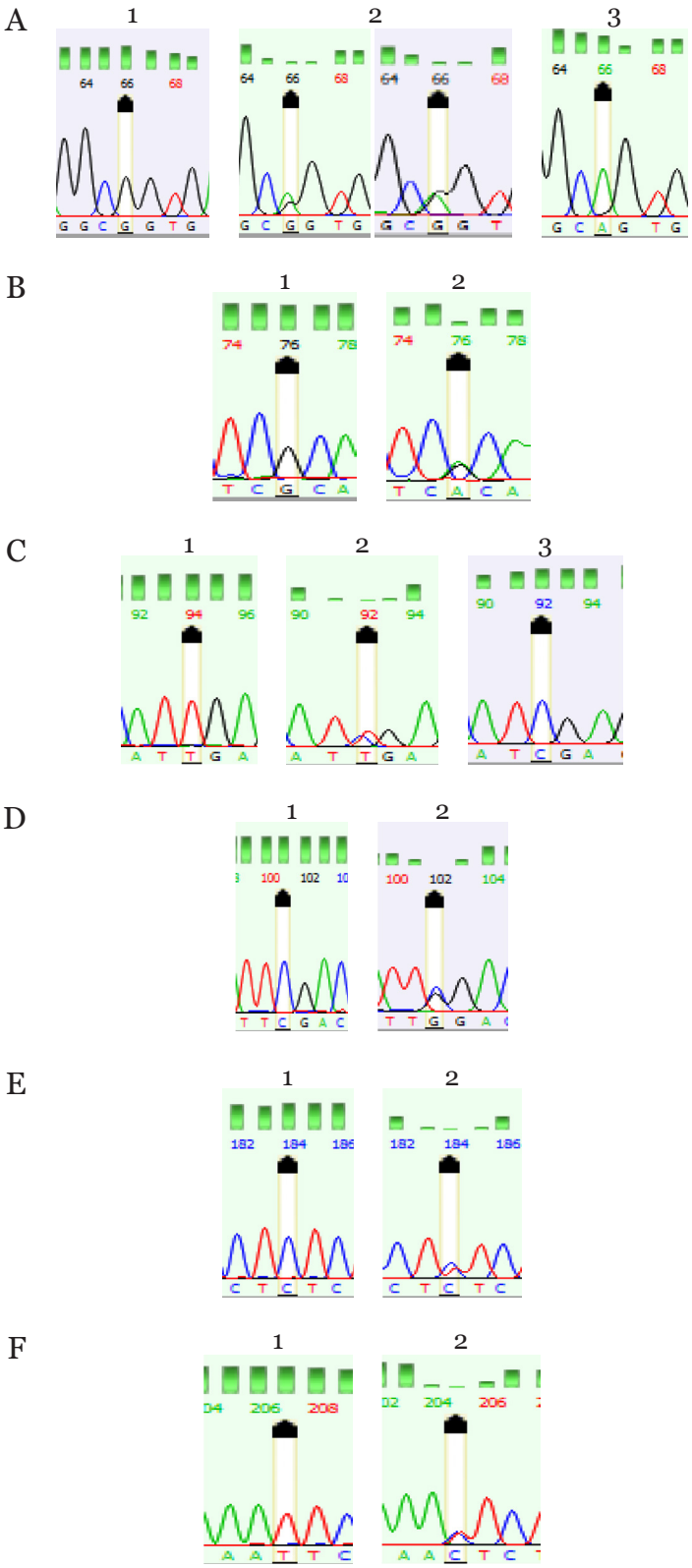

Figure 2 DNA Sequencing on Exon 7 MMR Gene

(A) G1186A; (**1**) Genotype G/G; (**2**) Genotype G/A; (**3**) Genotype A/A. **(B)** G1195A; (**1**) Genotype G/G; (**2**) Genotype G/A. **(C)** T1212C; (**1**) Genotype T/T; (**2**) Genotype T/C; (**3**) Genotype C/C. **(D)** C1221G; (**1**) Genotype C/C; (**2**) Genotype C/G. **(E)** C1303T; (**1**) Genotype C/C; (**2**) Genotype C/T. **(F)** T1323C; (**1**) Genotype T/T; (**2**) Genotype T/C

Table 3 Distribution of MMR Gene Exon 7 SNP Allele Frequency

SNP Site	Allele	Case Group		Control Group		p	OR (95% CI)
		n=148	Frequency	n=148	Frequency		
G1186A	G	80	0.541	83	0.561	-	1.00
	A	68	0.459	65	0.439	0.726	0.921 (0.583–1.457)
	HWE (p)	0.266		0.000			
G1195A	G	145	0.980	145	0.980	-	1.00
	A	3	0.020	3	0.020	1.000	1.00 (0.199–5.037)
	HWE (p)	0.859		1.000			
T1212C	T	136	0.919	113	0.764	-	1.00
	C	12	0.081	35	0.236	0.002	2.982 (1.484–5.993)
	HWE (p)	0.423		1.000			
C1221G	C	146	0.986	146	0.986	-	1.00
	G	2	0.014	2	0.014	1.000	1.00 (0.139–7.195)
	HWE (p)	0.906		1.000			
C1303T	C	146	0.986	144	0.973	-	1.00
	T	2	0.014	4	0.027	0.684	2.028 (0.366–11.244)
	HWE (p)	0.906		1.000			
C1323T	C	148	1.000	146	0.986	-	1.00
	T	0	0.000	2	0.014	0.498	5.068 (0.241–106.477)
	HWE (p)	0.000		1.000			

Note: all difference analysis between the case and control groups used the chi-square test if the assumption were met and used Fisher's exact if the chi-square hypothesis were not; HWE: Hardy-Weinberg equilibrium

was higher than the control group (OR=1.313, 95% CI=0.515–3.347, p=0.569). However, the frequency of genotype G/A was 43% and 55%; the case group was lower than the control group (OR=0.6833, 95% CI=0.324–1.440, p=0.316).

On T1212C sites sequentially, the C/C and T/C genotype frequency in the case group was lower than in the control group (OR=0.171, 95% CI=0.018–1.580, p=0.161 and OR=0.253, 95% CI=0.111–0.575, p=0.001). There was no significant difference in genotype frequency in both groups on G1195A, C1221G, C1303T, and C1323T sites (Table 2).

The frequency of the C allele at the T1212C site in the case group was lower than in the control group. The frequency was statistically significant (0.081 and 0.236) with OR=2.982, 95% CI=1.484–5.993, p=0.002). The frequency of alleles at the sites G1186A, G1195A, C1221G, C1303T, and C1323T were not significantly different between the two groups (Table 3).

Discussion

The characteristic of the study's subject in Table 1 from the case and the control group based on sex. There were 34 males (46%) in the case group and 33 males (45%) in the control group. While females were 40 (54%) in the case group and 41 females (55%) in the control group, this difference was not statistically significant. Suppose it was seen based on the age group. The median age was 36, with 19 interquartile distances in the case group. While in the control group, there was a median age of 34 with an interquartile distance of 19.

According to the body mass index (BMI) characteristic, the underweight condition was the most in the case group in 47 subjects (64%), while in the control group were 35 subjects (47%) that experience overweight BMI (≥25 kg/m^2). The results followed the previous study, which stated that BMI was related to nutrition status. One of the influential factors on host body resistance is defending against microorganisms attacking someone's body, such as TB. A low body mass index is one of the TB infection risk factors.[14–17] However, a good BMI did not guarantee someone was free of TB infection. It could see that most of the control group with IGRA(+) had good BMI status and were overweight.[11,18]

This study showed six SNPs in exon 7 of the MMR gene, G1186A (rs34039386, Gly396Ser), G1195A (rs71497223, Gly396Ser), T1212C

(rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435Phe), and C1323T (Asn441Asn). In addition, was found two mutations: transitions and transversions. Transitions are mutation changes of the same base couple pain to purine (A becomes G or G becomes A) or pyrimidine to pyrimidine (C becomes T or T becomes C). It occurred on two sites G1186A, G1195A, T1212C, C1303T, and C1323T. Only one site that experienced transversion was nitrogen base changes, which caused several changes. The changes were purine to pyrimidine (G become C, G become T, A become C, or A become T) or pyrimidine to purine (C become G, C become A, T become A, or T become G). It occurred on the T1221C site.

In this study, polymorphisms of a gene can change the protein produced by the gene to lower its function. There was also polymorphism which was influenced by ethnicity and geography. Following the previous study in China, MR played an important role in congenital and adaptive immunity. This receptor-activated immune response recognizes extracellular carbohydrates that bond glycan from pathogen microbe structure and could play an important role in causing TB infection. Six SNPs in exon 7 from the MRC1 gene were analyzed. That study showed that genotype frequency (p=0.037, OR=0.76, 95% CI=0.58–0.98) and allele (p<0.01, OR=0.57, 95% CI=0.37–0.87) were statistically significant. OR genotype and allele value for G1186A were less than 1. It indicated that MMR gene polymorphism affected pulmonary TB development and could reduce the risk of pulmonary TB.[11]

G1186A site of MMR gene was a non-identical mutation that could change Gly amino acid into Ser. This site mutation could change MR function, influencing the MR protein bind of polysaccharide structure on the MTB surface. Therefore, it gave a contribution to anti-inflammation factor secretion. Different from the previous study in China.[11] It indicated five other SNPs of the MMR gene G1195A (rs71497223, Gly396Ser), T1212C (rs71497224, Ile404Ile), C1221G (rs34284571, Leu407Phe), C1303T (Leu435Phe), and C1323T (Asn441Asn) did not show a significant relationship with pulmonary TB (p>0.05). The study also showed that the polymorphism site was unrelated to pulmonary TB susceptibility. However, it was found that there was a significant difference between the case and control groups. T1212C (rs71497224, Ile404Ile), respectively genotype frequency T/T, C/C, and T/C in the case group, 85%, 1%, and 14%, while in the control group 58%, 5%, and 36%. T/C genotype frequency in the case group was lower than in the control group (OR=0.253, 95% CI=1.111–0.575, p=0.001).

It indicated that AA dominant mutation occurred more in pulmonary TB patients than in latent TB. However, this incident was not meant to be significant because of p>0.05. This condition indicated that G1186A played an essential role in pulmonary TB, appropriate with the previous research in China.[11]

Both groups' dominant and recessive mutation models on G1195A, C1221G, C1303T, and C1323T sites were not different from the previous study. Alter et al.[19] found that the frequency of allele SNP G1186A exon 7 of the MMR gene had significant differences between the leprosy patients as the case group and healthy people as a control group in the Vietnamese population (p=0.036, OR=0.76, 95% CI=0.60–0.96). Because OR value was less than 1, the results showed that the site had a significant protective role for leprosy and could reduce the risk of infection. Similarly, this study found that G1186A SNP allele frequency on leprosy as a case group was different from healthy people as a control group in the population of Brazil (p=0.016, OR=1.34; 95% CI=1.06–1.70). Odd ratio value of more than 1 indicated that the polymorphism was associated with the susceptibility to leprosy. Hattori et al.[20] reported that the frequency of the G1186A SNP allele in exon 7 of the MMR gene was not significantly associated with asthma in the Japanese population. Other studies explain that the role of the MMR gene can determine the diagnosis, susceptibility, and prognosis of TB, a biomarker for the progression of lung interstitial damage, specific glioma, and inflammatory bowel syndrome.[21–29]

It suggested that differences in genetics are a key factor in an individual's susceptibility to disease and gene polymorphism. From the result of previous studies could be concluded that the MMR gene polymorphism G1186A SNP was associated with TB and may have a protective function.[11,12,28,29]

There is no association between SNPs exon 7 on G1195A, C1221G, C1303T, and C1323T MMR gene and the incidence of pulmonary tuberculosis. Therefore, more samples require further research to analyze SNPs on MMR genes. Nevertheless, the

relationship of MMR gene SNP with the incidence of pulmonary tuberculosis in both groups could be statistically significant. However, more practical methods other than DNA sequencing are still needed, such as the PCR TaqMan method or DNA sequencing using restriction fragment length polymorphism. In addition, it is also proposed to analyze proinflammatory and anti-inflammatory cytokine levels that are affected by the expression of mannose receptors on the whole subject of study to clarify further the mechanism of the effect of genetic variation on cytokine products on the incidence of pulmonary tuberculosis.

Conclusions

The study concluded that there was 5 SNPs MMR gene (G1186A, G1195A, T1212C, C1221G, and C1303T) in both groups. In addition, MMR gene polymorphism on the T1212C site was associated with pulmonary tuberculosis and was protective.

Conflict of Interest

None declared.

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RESEARCH ARTICLE

Effect of Psychosocial Factors in the Use of Telemedicine

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Abstract

Telemedicine is the impact of industrial revolution 4.0, which urges the development of health system technology to increase access to health services. This condition is contrary to the use of society, where consumers decide to stop using telemedicine services after several benefits. This study aims to identify the effect of psychosocial factors on consumer decisions in utilizing telemedicine services. This study was analytical observational research with a cross-sectional design. The population of this study was consumers aged 17–40 years who needed access to health services. Data collection was done in January–May 2021 by distributing online questionnaires tested for validity and reliability to 198 respondents in Surabaya. The data obtained were analyzed using logistic regression. The results showed that consumer psychological factors, including motivation, psychology, and learning, influenced decisions to use telemedicine services ($p<0.05$). Meanwhile, the social factors of the reference group did not have a significant effect ($p>0.05$). High motivation, positive perception, learning, and family encouragement influence consumer decisions to use telemedicine services, whereas the reference group does not. This research can be used as a consideration for healthcare technology developers and decision-makers in promoting the use of telemedicine so that it continues to be used in the long term.

Keywords: Consumer decisions, health services, health technology development, psychosocial factors, telemedicine

Introduction

Various countries in the world have now taken advantage of information and communication technology to improve the convenience of the community in accessing public services, including public health services.[1] Currently, with the industrial revolution 4.0, technological developments continue to rush and encourage technological evolution that urges various public sectors. Undeniably, the health sector has also faced the impact of this 4.0 industrial revolution through various health technology developments. One example of technology development in the health sector is telemedicine services.[2]

Telemedicine is a medical service practice for diagnosis, consultation, education, and transfer of medical data using information technology as a mode of communication.[3] The World Health Organization (WHO) also defines telemedicine as providing health services with distance as the main factor through information and communication technology.[4,5] This telemedicine service has many benefits for health workers and patients because it can save time and resources and increase the effectiveness of providing health services to patients.[3] This is because, through information and communication technology, interactions between health workers and patients will be carried out online through various platforms so that it can obtain many benefits.[6]

Since the COVID-19 pandemic in 2020, there has been a significant increase in the use of telemedicine due to various policies related to restrictions on community mobility.[7] Many people have started using telemedicine services to consult with doctors, get diagnoses, and purchase drugs online to take care of themselves and others. However, new problems began to arise regarding the allotment of telemedicine services due to increasing consumer demand since the COVID-19 pandemic. Based on research conducted in the United States on 934 users of telemedicine services, 427 respondents, or 45.7% of all, decided to stop using because of loss of interest and hidden costs.[8] This is undoubtedly a severe problem faced by the public telemedicine service development platform, so it is essential to identify what factors influence consumer decisions in utilizing telemedicine services.

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The rapid increase in telemedicine services during the COVID-19 pandemic shows that external or environmental factors significantly influence. However, other things related to external factors are also essential to identify, namely social factors and individual factors related to consumer psychology.[9] Basically, consumer behavior is influenced by personal, psychological, social, and cultural factors.[10] Several studies investigate consumer behavior related to problems security with or ethical use of tracking apps,[11] the use of health applications on smartphones,[12] as consumer adoption and acceptance behavior in digital health services[13] based on various technology acceptance theories.[7,9]

In telemedicine, trust or psychological between consumers and providers is very important because of virtual situations where they cannot communicate directly.[14] This indicates that consumer motivation, perception, social factors, or psychosocial consumers have an essential role in the consumer's decision-making to use telemedicine.[9] However, there are still few studies that identify the influence of consumer psychosocial factors in the use of telemedicine. Hence, this study aims to determine the effect of psychosocial factors on consumer decisions in telemedicine.

Methods

This study was analytical observational research with a cross-sectional study. The population in this study were all people aged 17–65 who actively use smartphones (smartphones). The inclusion criteria applied in this study were having internet access, knowing the existence of telemedicine services, requiring access to healthcare services during the research period, agreeing on informed consent, and being willing to become research subjects. This inclusion criterion aims to obtain a population relevant to the research objectives and reduces bias in the data collection process. Based on the calculation of the sample size according to Lemeshow, the minimum number of respondents in this study was 100 participants. This research was conducted regarding ethical clearance number 175/HRECC.FODM/IV/2021 from Airlangga University Faculty of Dental Medicine Health Research Ethical Clearance Commission.

Data collection was carried out from January to May 2021 through the distribution of questionnaires along with informed consent to the population in Surabaya. Surabaya is the capital city of East Java province, with an area of 326.36 km^2. The administrative area of the city of Surabaya consists of Central Surabaya, North Surabaya, East Surabaya, South Surabaya, and West Surabaya, which consists of 31 sub-districts and 153 urban villages. The largest age group in the city of Surabaya is in the range of 20–24 years.[15] The questionnaires were distributed to the population provided online through social media. Each question has been tested for validity and reliability outside the population group with an r=0.785. The score on each question consists of values from 1 to 4. The higher the score, the higher the value on that variable. After screening data, there 215 subjects were collected at the beginning, but 17 participants were excluded because they claimed they didn't require healthcare services during the research period, so a total of 198 respondents who met the inclusion criteria during the research period in this study were analyzed.

The data analysis process was carried out descriptively and analytically. Descriptive statistical analysis was conducted to describe the characteristics of the research respondents. The statistical test used is the logistic regression test to see the effect of psychosocial factors on the decision to use telemedicine services.

Results

The age group of respondents who are the research subjects is dominated by the age range of 17–25 years (83.8%). The most recent education level of respondents is high school graduates (71.2%). The respondent's occupation is dominated by a student (75.3%) with the highest income level in the range of fewer than one million rupiahs per month (65.7%). The majority of respondents have used telemedicine services, as many as 160 respondents, or 80.8% of the total research subjects (Table 1).

The results of the analysis of the respondents' psychological factors showed that motivation (p=0.007), perception (p=0.017), and learning (p=0.000) influenced their decision to use telemedicine services (Table 2). The social factors indicated that the family had a significant influence on consumer decisions in using telemedicine (p=0.003), while the reference group had no significant (p=0.193).

Table 1 Characteristics of Respondents

Variables	n=198 (%)
Age (years)	
17–25	166 (83.8)
26–35	22 (11.1)
36–40	10 (5.1)
Education	
Junior high school	3 (1.5)
High school	141 (71.2)
Diploma	8 (4.0)
Undergraduate degree (D4)	40 (20.2)
Graduate degree (S1)	6 (3.0)
Occupation	
Student	149 (75.3)
Private employees	20 (10.1)
Government employees	10 (5.1)
Entrepreneur	8 (4.0)
Unemployed	11 (5.6)
Income (million)	
<1	130 (65.7)
1–2.5	31 (15.7)
2.5–5	21 (10.6)
5–10	7 (3.5)
>10	9 (4.5)
Telemedicine use	
Yes	160 (80.8)
No	38 (19.2)

Discussion

Characteristics of respondents were reviewed based on age group, education level, occupation, and income earned. The majority of the age group respondents in this study were in the age group of 17-25 years (83.8%), followed by the age group of 26-35 years (11.1%). This age group is an age group that belongs to the millennial generation. The millennial generation is a young population born in 1981–2000 or at the age of 40 years.[16] The millennial age group tends to be highly interested in and accept technological developments. Other research also states that the millennial age group, with the support of knowledge or higher education, has a greater chance of receiving telemedicine services.[17]

The majority of respondents' education in this study was in the high category, namely high school graduates 71.2% and D4/S1 graduates 23.2%. Other research also shows that consumer groups dominate telemedicine users with higher education.[18] Someone with higher education will be more interested in taking advantage of the latest technological innovations than individuals with low levels of education. Respondents with a high level of education have more curiosity to try new things, especially in the technology field.[19]

Students dominate the type of work in this study, and private workers use individual consumption patterns in utilizing a service.[10] The advantage of telemedicine is that it facilitates access to health services anytime and anywhere, meeting to meet face to face. Research shows that telemedicine services are used by consumers who find it challenging to take time off from work and have difficulty leaving the house due to physical or mental limitations.[20] However, this cannot be considered because there was a pandemic during the research period, so all work was done from home. In addition, this telemedicine service can also be utilized by consumers of various income levels. Previous research has shown that consumers use telemedicine with lower-middle income[21] or high-income.[22]

In this study, consumer psychological factors, which include motivation, perception, and learning, significantly influence the decision to use telemedicine services (p=0.007). The results showed that cause motivation to fulfill their health needs and feel safe from disease transmission influenced their decision to use telemedicine. This is in line with previous research, which states that motivation can influence consumers to use telemedicine services, including hedonism (hedonic motivation).[23] Other studies also explain that encouraging consumers to use telemedicine services increases convenience, comfort, pleasure, and satisfaction in obtaining health services.[24] This shows that various internal and external factors can positively or negatively motivate consumers to use telemedicine services.[25]

Consumer perception in this study proved to have a significant influence on the decision to use telemedicine (p=0.017). Respondents' perceptions consist of respondents' views or assessments of ease of access, ease of use, quality of service, and affordability of service rates in digital health service applications. This is supported by previous research, which states that the intention to use telemedicine services is a function of perceived ease of use, trust, perceived risk, and resistance to technology.[26] Other studies also state that consumer perceptions of the tariff, quality, and value of telemedicine services have a positive effect on the decision to use.[27]

Table 2 Psychosocial Factors on Decisions to Use Telemedicine

Factors	Total Scores Categorization n=198 (%)				p	Exp (B)
	1	2	3	4		
Psychological						
Motivation	0 (0)	10 (5.1)	69 (34.8)	119 (60.1)	0.007*	2.662
Physiological drive to get access to health	1 (0.5)	14 (7.1)	108 (54.5)	75 (37.9)		
The urge to avoid queues or crowds	2 (1.0)	17 (8.6)	84 (42.4)	95 (48.0)		
Encouraging a sense of security from disease transmission	0 (0)	15 (7.6)	88 (44.4)	95 (48.0)		
Perception	0 (0)	18 (9.1)	100 (50.5)	80 (40.4)	0.017*	2.000
Ease of access	0 (0)	10 (5.1)	88 (44.4)	100 (50.5)		
Ease of use	0 (0)	12 (6.1)	97 (49.0)	89 (44.9)		
Quality service	0 (0)	15 (7.6)	117 (59.1)	66 (33.3)		
Fare affordability	5 (2.5)	36 (18.2)	106 (53.5)	51 (25.8)		
Learning	16 (8.1)	114 (57.6)	52 (26.3)	16 (8.1)	0.000*	11.385
Self-experience	42 (21.2)	110 (55.6)	30 (15.2)	16 (8.1)		
Other people's experiences	43 (21.7)	95 (48.0)	44 (22.2)	16 (8.1)		
Social						
Reference group	17 (8.6)	47 (23.7)	91 (46.0)	43 (21.7)	0.193	1.267
Role of friends or relatives	9 (4.5)	55 (27.8)	90 (45.5)	44 (22.2)		
Role of health influencers	13 (6.6)	66 (33.3)	86 (43.3)	33 (16.7)		
Family	13 (6.6)	36 (18.2)	39 (19.7)	110 (55.6)	0.003*	2.263
Parents role	22 (11.1)	62 (31.3)	71 (35.9)	43 (21.7)		
Siblings role	20 (10.1)	51 (25.8)	87 (43.9)	40 (20.2)		

Note: *p<0.05, significant; 1: very low; 2: common; 3: high; 4: very high

Psychological factors that influence respondents' decisions to use telemedicine are learning that does not only come from personal experiences or experiences of others. The results showed that learning influenced the decision to use telemedicine services (p=0.000). This is in line with previous research, which states that learning from experience can influence consumers to take advantage of technological developments in health; other studies also say that the experiences of individuals and others influence decisions and acceptance of telemedicine services.[28]

Family social factors have a significant influence on consumer decisions in using telemedicine services (p=0.003). Family members who have used telemedicine services substantially impact consumers' intentions to participate in using them in the future.[29] Family support also affects consumer acceptance of technological developments through decisions on telemedicine services,[30] while the reference group shows results that do not affect consumer decisions in telemedicine services (p=0.193). This is not in line with previous research, which stated that social groups or reference groups influenced consumers to use telemedicine services.[31] However, this could be because, during the research period, consumer interactions with reference groups due to social distance very analysis results analysis showed no influence on consumer decision-making. In this study, telemedicine or other health care technologies developers understand consumer purchasing decisions' behavioral characteristics. They can also direct the promotion of telemedicine services according to the aspect of consumers so that their use continues in the long term.

This research has some limitations in the process. First, this study is based on cross-sectional data collected from individual surveys. So it still requires further longitudinal field studies in the future to determine the decision

to use long-term telemedicine. Second, the limitation of this study is that it does not consider other psychosocial factors that may influence the decision to use telemedicine. Other psychosocial factors that can still be investigated are lifestyle, personality, and consumer attitudes. Third, because this study was conducted in a specific population, these needed to be more may not be generalizable to other people with healthcare health care policies and systems.

Conclusions

This study reveals that psychosocial factors such as motivation, perception, learning, and family influence individual decisions to use telemedicine services. Meanwhile, the reference group has no significant effect.

Conflict of Interest

There is no conflict of interest in this article.

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