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FOREWORD

Alhamdulillah, praised to Allah, Journal *Qanun Medika: Fakultas Kedokteran Universitas Muhammadiyah Surabaya* vol 06 no 01 has been published. It consists of 15 articles including 3 literature reviews, 3 case reports and 9 research articles in the medical field. We would like to thanks our reviewers and editorial board members who helped us in this publication. In order to be internationalized, we only published articles written in English since July 2019. We hope that these articles can be read widely both by domestic and foreign readers.

Thank you,
Yelvi Levani, MD.,M.Sc
Editor in Chief

Address
Faculty of Medicine
Muhammadiyah University of Surabaya
Jl.Sutorejo 59 Surabaya 60113
Telp.031-3811966 fax.031-3813096
Email: qanunmedika@um-surabaya.ac.id

Bank account
Qanun Medika
Bank Jatim cabang Dr.Soetomo
Bank account number 0323055441

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Literature Review

Amplification genetic engineering strategy by Crispr-Cas 13 Enzymes for detection and treatment COVID-19 mediated with gold nanoparticle (AUNP)

Salsabila Farah Rafidah[1] Ilham Rahmanto[2], Ardellia Bertha Pratiska[2]

1) Faculty of Public Health, Airlangga University, Indonesia
2) Faculty of Medicine, Airlangga University, Indonesia

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Correspondence:

ns.firman92@gmail.com

ABSTRACT

WHO declared the disease outbreak due to the COVID-19 coronavirus a global pandemic. Indonesian government's efforts to eradicate the pandemic through mass screening have not been effective due to the limitations of the three main modalities used to detect COVID-19, including Rapid Test Diagnostic (RTD) antibodies, RTD antigens, and Reverse Transcriptase-Polymerase Chain Reaction (RT-RTD PCR), In addition, other detection tools are sometimes used, such as Enzyme-Linked Immunosorbent Assay (ELISA) and rapid molecular tests. To eradicate this pandemic, the government needs COVID-19 detection tools that are effective, cheap, fast, and accessible. To determine the application of the genetic engineering strategy of amplification by the CRISPR-cas13 enzyme for detecting and treating COVID-19 mediated by gold nanoparticles (AuNP). This research uses a qualitative literature study with content analysis, observation development, and literature study; an alternative solution to this problem is CRISPR-Cas13, achieved by the SHERLOCK method. This method designs and screens a targeted group of CRISPR RNAs based on the identification of functional crRNAs of SARS-CoV-2. Amplification of CRISPR-Cas13 by SHERLOCK and PAC-MAN enzymes has the potential to be the latest detection and treatment method for gold nanoparticle-mediated COVID-19 (AuNP) in Indonesia.

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INTRODUCTION

On March 11, 2020, WHO (World Health Organization) declared the disease outbreak due to the COVID-19 coronavirus a global pandemic. The virus is a contagious disease caused by *SARS-CoV-2*, one of the newly discovered types of coronavirus. In its development, the COVID-19 disease outbreak, which first occurred in Wuhan, China, from December 2019 to April 2020, has spread to 210 countries and reached 2.7 million positive cases (Worldometers 2020). With the characteristics of its very rapid spread between humans, coupled with very high human mobility and across national borders, this virus becomes even more dangerous. Based on data from Satgas Covid (2021) at covid19.go.id, the total positive COVID-19 in Indonesia on the last update on May 3, 2021, was 1.682.004 people, and the mortality case was 1.535.491. Detection of COVID-19 can be carried out by anamnesis, physical examination, and supporting examinations. Clinical symptoms can vary depending on the degree of disease. Therefore, a significant step is needed for massive, effective, comprehensive, and sensitive diagnostics and treatment to eradicate the COVID-19 pandemic (Handayani et al, 2002).

The Indonesian government's efforts to eradicate the pandemic through mass screening have not been effective due to the limitation of the three main modalities used to detect COVID-19, including antibody Rapid Test Diagnostic (RTD), Antigen RTD, and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) (Yanti, Ismida, and Sarah 2020). Therefore, other detection tools, such as Enzyme-linked Immunosorbent Assay (ELISA) and rapid molecular test, are sometimes used. These modalities have their respective advantages and disadvantages. Although RT-PCR is the gold standard, this modality has several limitations, such as being time-consuming, requiring a very sophisticated thermolysis machine, and skilled laboratory assistants (Mustafa and Makhawi., 2021). On the other hand, the urgency for rapid detection is very high. However, antibody RTD and antigen RTD are less effective to use because there are still high false positive and false negative rates, so they must be confirmed using RT-PCR (Wahjudi., 2020). To eradicate this pandemic, the government needs a COVID-19 detection tool that is effective, cheap, fast, and easy to use (does not require special skills).

Therefore, no evidence recommends an effective anti-COVID-19 drug. The pharmacological management of COVID-19 as of April 2020 in Indonesia uses chloroquine, hydroxychloroquine, favipiravir, and remdesivir (Instiaty et al., 2020). Clinical studies limited to these four drugs demonstrated some efficacy of COVID-19 treatment with tolerable side effects. Potential serious side effects occur with chloroquine and hydroxychloroquine in the form of cardiac arrhythmias. Based on a clinical pharmacological review, the decision to use these drugs should consider the potential benefits and the risks to the patient (Instiaty et al., 2020). Other considerations in using these drugs include effectiveness, safety, availability, and accessibility (relatively cheap); until now, researchers are still looking for new drug candidates that can treat COVID-19 effectively and comprehensively.

The use of vaccines launched by the government to control this pandemic is only designed for disease prevention, and their effectiveness is still uncertain (Ophinni et al., 2020). Based on their content, several COVID-19 vaccine models exist, including mRNA vaccine models, inactivated viruses, virus vectors, and protein subunits. The Indonesian government chose Coronavac, made by a Chinese company, Sinovac, an inactive virus containing the protein S (Spike) antigen from *SARS-CoV-2* (Ophinni et al., 2020). This vaccine has been

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tested on at least 30.000 participants in several countries, such as Indonesia, Turkey, Brazil, and Chile, to assess its effectiveness. However, vaccination in Indonesia needs to reach at least 67% of the country's population to achieve herd immunity to stop the pandemic. This will take a long time, considering that Indonesia is the fourth most populous country in the world. In addition, vaccines can only prevent disease manifestations by creating antibodies and not curing the disease (Ophinni et al., 2020).

On the other side, genetic and nano-based diagnosis and treatment are widely developed by health analysis; one of the most accurate is CRISPR-Cas13. The implementation of this technology in the form of SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing), which integrates with Cas13 to detect single-molecule RNA (Gootenberg et al. 2017) by quantitative and accurate input measurement up to 1uL (2 aM), 3.5 times more precise signal sensitivity, multiplex, portable, fast, visual nucleic acid detection platform, and can distinguish different inputs by single nucleotides at low concentrations (Myhrvold et al., 2018).

PAC-MAN (CRISPR Antiviral Prophylaxis in human cells). This method performs viral inhibition that can effectively degrade the *SARS-CoV-2* sequence in human lung epithelial cells by antivirus modification which will divide up more than 90%. Gold nanoparticles (AuNPs) are also used as a lipid inhalation CRISPR RNA (crRNA) to target lung cells precisely. AuNP has stable properties, high sensitivity, and good bio capability to facilitate PAC-MAN placement to pulmonary epithelial cells. The purpose of this literature review is to analyze the potential of CRISPR-Cas 13 and gold nanoparticles as methods of detection and treatment of Covid-19 and as an effort to inform readers about the latest methods based on eradication technology in the form of detection and treatment for *SARS-CoV-2* (Abbott et al., 2020).

LITERATURE REVIEW

Genetic engineering CRISPR-Cas13 has the potential to become the latest technology in detecting and treating COVID-19. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) are defense mechanisms owned by bacteria to cleavage foreign genetic material such as from plasmids and viruses by creating specific RNA guides. Meanwhile, CRISPR-associated 13 (Cas13) isolated from the *Leptotrichia wades* bacteria plays a role in cutting off the foreign genetics (Mustafa and Makhawi 2021; Shihong Gao, Zhu, and Lu 2021). Several studies have proven that Cas13 can be used as a new diagnostic tool for COVID-19 that is no less sensitive and specific than RT-PCR called SHERLOCK (Patchsung et al., 2020). Therefore, researchers are developing PAC-MAN, which utilizes Cas13 so that it can be used as a new step in the treatment of COVID-19 in the form of aerosol drugs (Lotfi and Rezaei., 2020). As the transporters, SHERLOCK and PAC-MAN are combined with gold nanoparticles (AuNPs) which have stable properties for diagnostics and treatment of COVID-19 (Draz and Shafiee., 2018). It is predicted that this genetic engineering technique can be used to eradicate this prolonged pandemic in Indonesia.

The Mechanism of SHERLOCK for Detecting COVID-19

For detecting COVID-19, Cas13 in SHERLOCK is very specific and sensitive in detecting single-stranded RNA (ssRNA), such as in the *SARS-CoV-2* virus, compared to DNA. When the target viral RNA is detected, CRISPR RNA (crRNA) will immediately recognize and guide Cas13 to a suitable spacer and the base pair with the complementary sequence in the target viral RNA. Then, Cas13 will cleavage the distal part to the target RNA sequence paired with a spacer (Shihong Gao

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et al., 2021). Cas13 will also collaterally cleavage the RNA sensor to relieve the fluorescence color, indicating the virus's presence in the sample **(Figure 1)** (Shihong Gao et al., 2021). During its development, the SHERLOCK modality is divided into two forms: fluorescence assay readout and lateral flow strip readout. Compared to the fluorescence assay readout, lateral flow strip readout has several advantages because it uses visual colorimetric readout in commercial lateral flow, does not require special tools without purifying and isolating nucleic acid, and is highly sensitive for multiplex signal detection on lateral flow strips, making it more effective to use as a candidate for the latest COVID-19 detection tool in Indonesia (Mustafa & Makhawi., 2021).

The Mechanism of Lateral Flow Strip Readout and Gold Nanoparticles for Detecting COVID-19

The commercial lateral flow strip as a mediator for Cas13 can be used for single target detection. Simply put, the detection reaction in SHERLOCK is applied to a portable strip using a fluorescein (FAM)-biotin RNA sensor (Shihong Gao et al., 2021). The full-length RNA sensor will accumulate in the first streptavidin line (first band) if a negative result is obtained. A band is visualized because anti-FAM gold nanoparticle-conjugated antibodies were added for the detection reaction. Meanwhile, a positive test result indicates that the sensor RNA has been cleavage. The FAM antibodies can flow down the strip to bind to the second band and provide visualization **(Figure 2)** (Shihong Gao et al., 2021). In other words, the results of this test are as accessible and straightforward as a pregnancy test. AuNPs were chosen due to their stability, biocompatible, and unique optical properties, as well as their ability to produce colorimetric signals that can be seen in the test line (Patchsung et al., 2020).

Research Evidence of SHERLOCK as A New Method for Detecting COVID-19

The use of SHERLOCK CRISPR-Cas13 has been approved by the food and drug administration (FDA). It effectively detects the S (Spike) gene in the *SARS-CoV-2* virus (Lotfi and Rezaei, 2020; Patchsung et al., 2020). Research conducted by (Patchsung et al. 2020) using a lateral flow strip readout on nasopharyngeal and throat swab samples collected in 154 patients in Thailand showed a specificity of 100% and a sensitivity of 88% compared to RT-PCR. More than that, the limit of detection (LOD) reached 100% specificity and 97% sensitivity with the lateral flow readout. They also developed a lateral flow strip that can detect foreign agent contamination using AuNPs. Research by (Myhrvold et al., 2018) showed that SHERLOCK is also proven to be effective in detecting *Zika Virus* (ZIKV) and *Dengue Virus* (DENV). Therefore, researchers have also created SHERLOCKv2, which offers a sensitivity of up to 3.5 times with the addition of Csm6 (supporting type III CRISPR effector nuclease) (Mustafa and Makhawi., 2021). This method can also detect a single mutation in the virus and provide detection results in about one hour. This evidence shows that this method can be a breakthrough in virus detection tools, especially the *SARS-CoV-2* virus (Lotfi and Rezaei, 2020; Wang et al., 2021).

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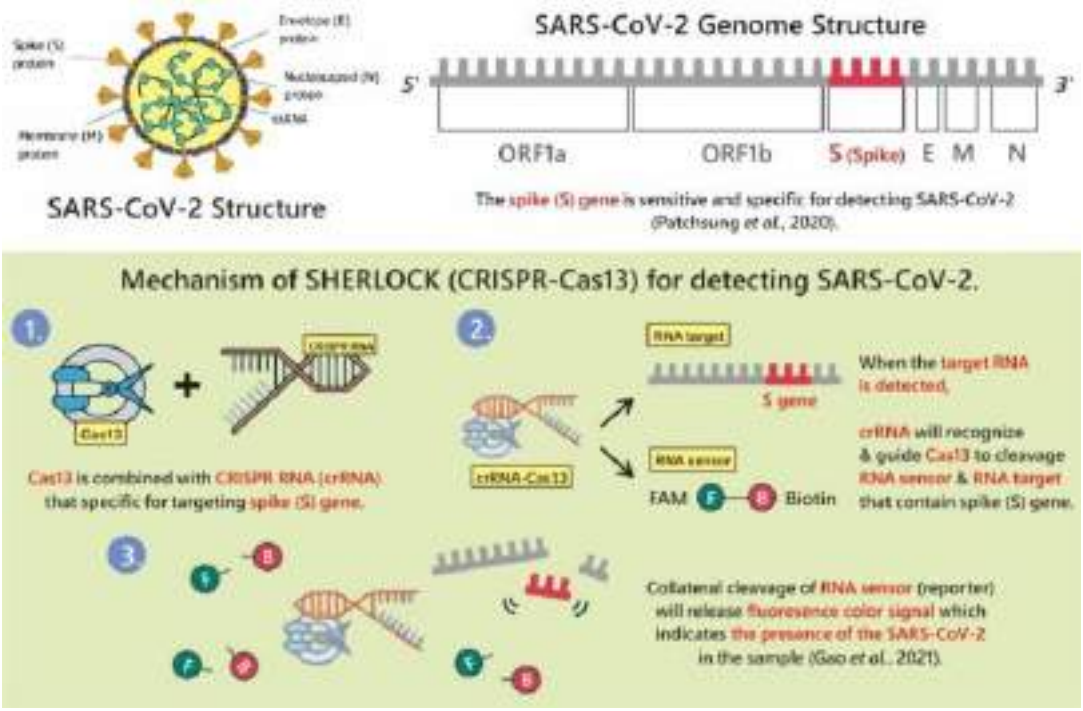

Figure 1. The *SARS-CoV-2* Structure & Genome Structure, and The Mechanism of SHERLOCK (CRISPR-Cas13) for Detecting *SARS-CoV-2*. (Author's Illustration, 2021)

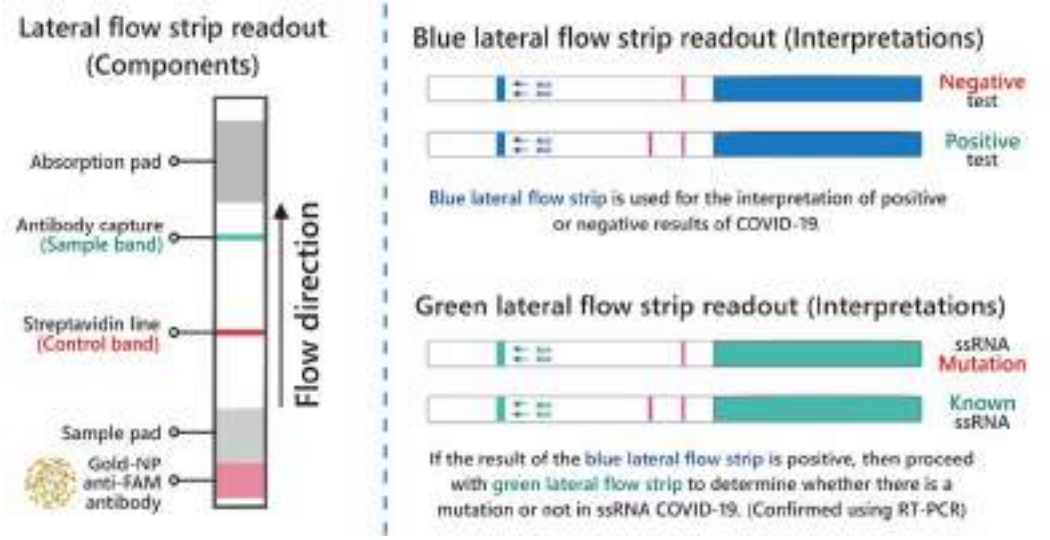

Figure 2. The Interpretations of Blue & Green Lateral Flow Strip Readouts (Patchsung et al., 2020).

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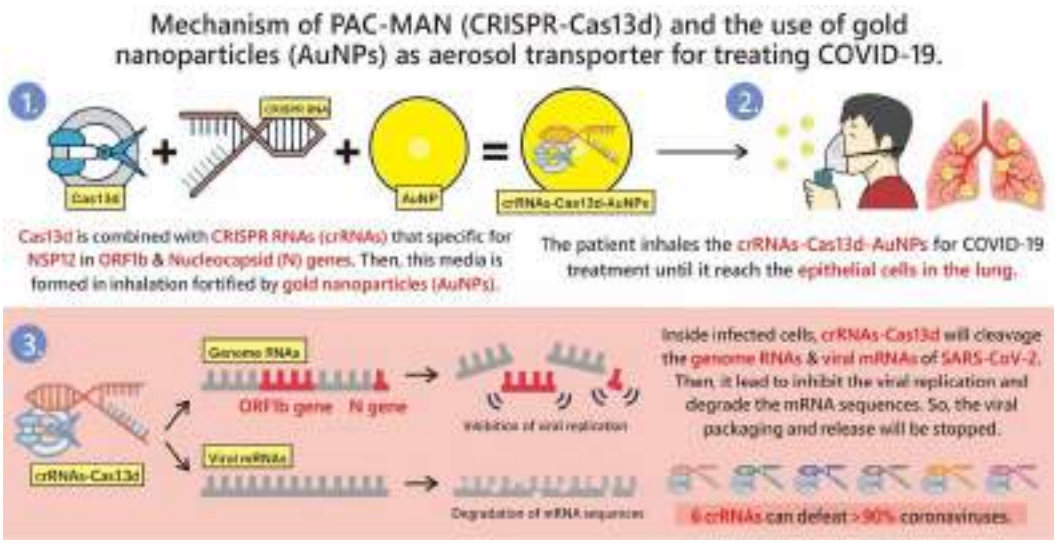

Figure 3. The Mechanism of PAC-MAN (CRISPR-Cas13d) and The Use of Gold Nanoparticles (AuNPs) as Aerosol Transporter for Treating COVID-19 (Author's Illustration, 2021).

Mechanism of CRISPR-Cas13 in the Treatment of COVID-19 (PAC-MAN) and The Use of Gold Nanoparticles for Aerosol Transporter

PAC-MAN (CRISPR Antiviral Prophylaxis in huMAN cells) performs viral inhibition by degrading the *SARS-CoV-2* sequence in human lung epithelial cells. This method designs and screens a group of targeted CRISPR RNA (crRNA) based on the identification results of the *SARS-CoV-2* cleavage functional crRNA (Abbott et al., 2020). This potential PAC-MAN approach was developed through the Cas13 enzyme in the form of collateral RNase activity and targeting viral nuclease in the following sequence.

The mechanism of PAC-MAN starts from the preparation of tools and materials, such as Cas13d (the smallest protein similar to Cas13 but has a strong target cleavage activity). Furthermore, these mechanisms are shown in **Figure 3**. The cells were transfected with gold nanoparticles (AuNP) until they reached the lung epithelial cells as the target cell. Integration with gold nanoparticles as an inhalation nanocarrier for local treatment is promising. Therefore, it has been widely regarded as candidate material.

Research Evidence of PAC-MAN as a New Method for Treating COVID-19

Based on a study of Scnn1b transgenic (Tg) mice treated with this treatment for 2 hours, inhaled AuNP rapidly binds to the alveolar epithelium. Therefore, epithelial targeting is required. It can be concluded that this is a further improvement, i.e., the PACMAN method corresponding to the defined crRNA and that this strategy for therapeutic targeting of epithelial cells is very successful. This method has been investigated and analyzed in various studies (Geiser et al., 2013; Yan et al., 2018). Geiser and Yan found that cas13d had the best strength in the cleavage process and was small in size, continued by Abbott et al. (2020) that the entire *SARS-CoV-2* genome of patients was sequenced based on the level of conservation found in RNA-dependent RNA polymerase (RdRP) and nucleocapsid (N) genes, (Metsky et al., 2020) also added in the results. The research recommends that the simpler approach is only one crRNA sequence

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instead of 2, especially in targeting *SARS-CoV-2* RNA.

Research Evidence of Gold Nanoparticles (AuNPs) as Transporter of CRISPR-Cas13 for Detecting and Treating COVID-19

Gold nanoparticles (AuNPs) have advantages over many other nanoparticles in chemicals. AuNP can form stable chemical bonds with groups containing S and N. This allows AuNP to attach to various organic ligands or polymers with specific functions. AuNP has a large role in eradicating a disease, especially diseases of the lungs. AuNP material in aerosol form has significant potential as a drug delivery system to treat COVID-19 due to its high stability, carrying capacity, and ability to provide water-soluble and insoluble drugs (Gelperina et al., in Anderson et al., 2020). Direct administration to the lung tissue also has the advantage of requiring a lower dose, minimizing side effects, and requiring less administration, which can result in better patient adherence (Rojanarat et al., 2012).

The Advantages of CRISPR-Cas13 as a New Method for Detecting and Treating COVID-19

SHERLOCK on the lateral flow strip readout provides convenience in terms of the detection of COVID-19 (Mustafa and Makhawi, 2021). This method is no less specific and sensitive than RT-PCR as the gold standard. Following WHO criteria regarding a good detection tool, lateral flow strips have several advantages: rapid, specific, sensitive, instrument-free, and cost-effective. PAC-MAN CRISPR-Cas13 offers advantages such as being easy to use, more cost-effective, sensitive, and specific than other therapeutic methods (Lotfi and Rezaei., 2020). This modality has minimal off-target effects on the host transcriptome in mammalian cells, thereby preventing unwanted and unpredicted mutations. The combination of PAC-MAN with transporter AuNP by aerosol (as nebulizer) can be a solution to the latest COVID-19 management in Indonesia. In other words, developing the SHERLOCK lateral flow strip readout and the PAC-MAN nebulizer can be a step forward for Indonesia in eradicating the COVID-19 pandemic.

CONCLUSION

The alternative solution to Covid-19 problem is CRISPR-Cas13, achieved by the SHERLOCK method, a proven detection method for detecting viruses. Next is PAC-MAN, which performs viral inhibition by degrading, integrated with gold nanoparticles (AuNPs) located at the tip of the biotin fluorescein (FAM) RNA reporter as a conductor and stabilizing reagent for the SARS-CoV-2 sequence in human lung epithelial cells. This method designs and screens a targeted group of CRISPR RNAs based on the identification of functional crRNAs of SARS-CoV-2 cleavage. As a result, the amplification of CRISPR-Cas13 by SHERLOCK and PAC-MAN enzymes has the potential to become the latest detection and treatment method for gold nanoparticle-mediated COVID-19 (AuNP) in Indonesia.

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Literature Review

Comparison of functional outcome after early and delayed anterior cruciate ligament reconstruction: A systematic review

I Putu Dharma Kresna[1], Kukuh Dwiputra Hernugrahanto[2], Rr. Indrayuni Lukitra Wardhani[3], Dwikora Novembri Utomo[4*]

1) Faculty of Medicine, Airlangga University, Surabaya, Indonesia.
2) Department of Orthopedics and Traumatology, Faculty of Medicine, Airlangga University, Soetomo General Hospital, Surabaya, Indonesia.
3) Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Airlangga University, Soetomo General Hospital, Surabaya, Indonesia.
4) Department of Orthopedics and Traumatology, Faculty of Medicine, Airlangga University, Soetomo General Hospital, Surabaya, Indonesia.

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Correspondence:

dwikora_utomo@yahoo.com

ABSTRACT

This study aims to find the optimal timing for Anterior Cruciate Ligament (ACL) reconstruction by comparing the outcome of early versus delayed ACL reconstruction, meniscus, and chondral damage. A systematic literature search was performed from February to March 2021 from 4 databases. Inclusion criteria were English language Randomized Control Trial (RCT) and observational studies published in 2000-2020, 20-50 years old patients with an isolated ACL tear with/without meniscal injury underwent ACL reconstruction. Early ACL reconstruction was estimated at less than six weeks post-injury, and delayed ACL reconstruction was estimated at more than six weeks. Tegner and Lysholm were the functional outcomes to compare early and delayed ACL reconstruction with a meniscus tear and chondral damage. The search yielded 3094 studies. After removing duplicates, titles and abstracts were screened, leaving 154 potential studies. The studies were selected, and eight studies were eligible. No statistically significant difference between early and delayed ACL reconstruction in Lysholm and Tegner score ($p>0,05$) was found. Both scores were similar regarding whether the patient performs early/delayed ACL reconstruction. Therefore, early ACL reconstruction could be an optimal timing for the patient who will undergo ACL reconstruction.

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INTRODUCTION

The anterior cruciate ligament (ACL) is the most common knee injury besides meniscus and, in most cases, needs surgical intervention. Therefore, in Orthopaedic Surgery, ACL reconstruction is the most common knee surgery as the ACL is injured more than any other structure in the knee (Gupton et al., 2021). It is estimated that 1 in 3000 people endures ACL injury in the United States of America, as 70% of these injuries result from sports activity. The injury of the ACL can be from contact or non-contact injury. 70% of the torn ACL cases occurred non-contact, without a direct blow to the knee joint, resulting from jumping landing and lateral cut maneuvers(S. Kim et al., 2011). These maneuvers usually occur in a sports activity with high movement frequency and high loadings of the knee, such as basketball, handball, soccer, and volleyball (Nessler et al., 2017). The mechanism of injury of the ACL can be multiple knee loadings. The ACL may be overloaded when quadriceps muscle forces are combined with the frontal plane and or transverse plane with insufficient hamstring muscle contraction especially when the knee is in the position of extension (Wetters et al., 2016). Other structures may also be injured, such as the meniscus, the chondral bone, PCL, and collateral ligament (Domnick et al., 2016).

ACL rupture is a common injury in active individuals. It can cause instability of the knee joint. This instability can make functional changes and other structural damage in the knee joint (Monk et al., 2016). If the tear of the ACL is not appropriately treated, it can lead to poor outcomes such as a higher rate of meniscus lesion and chondral damage (Friel & Chu, 2013).

In the treatment of the torn ACL, there are operative and non-operative treatments. The non-operative treatment has been an alternative; however, it can produce poor functional outcomes. In young adults with high demand for activity, the ACL reconstruction with grafting is the gold standard of treatment, replacing the damaged ACL with a new ligament using a harvesting graft. The ACL reconstruction with grafting regarding the results and the outcomes of the patient with high compliance shows good-long term outcomes and return-to-sport (Salmon et al., 2018). Each type of method of graft has its advantage and disadvantage; therefore, the surgeon needs to adapt the selection of the graft individually for each patient. The timing of reconstruction and rehabilitation also has an important role in obtaining an excellent outcome (Paschos & Howell, 2016).

Despite many studies of ACL anatomy and the development of surgical techniques for ACL reconstruction, the literature still debates the optimal timing for ACL reconstruction that deliver excellent outcome (Hetsroni & Marx, 2017). Many studies showed different terms for timing ACLR, which are acute or subacute instead of early, chronic instead of delayed ACL reconstruction. There is no clear term regarding the definition of acute because some authors use the terms early and acute interchangeably. Furthermore, there are no clear definitions regarding the cut of point in the timing of ACL reconstruction and the outcome of ACL reconstruction. According to Noyes et al., the average acute interval was six weeks, and the chronic operative period was three months after damage. (Noyes & Barber-Westin, 1997). Meanwhile, Chen et al. defined the acute ACL reconstruction as three to seven weeks, while the delayed ACL reconstruction lasted 6-11 months from injury to surgery. Manandhar et al. defined early ACL reconstruction as less than three weeks from injury to surgery, while delayed ACL reconstruction is defined as 42 until 60 days from injury to surgery (Chen et al., 2015; Manandhar et al., 2018).

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Some previous studies recommended early ACL reconstruction because delayed ACL reconstruction could increase the probability of chondral and meniscus injuries (Hetsroni & Marx, 2017). Moreover, inactive patients, due to surgical delaying, could cause a loss of muscle strength (Paschos & Howell, 2016). It was reported that there was a significantly higher incidence of involvement of other structure (meniscal/chondral) damage in the delayed surgery after three months (Ferguson et al., 2019). Another study showed a significantly higher incidence of meniscal tear when ACL reconstruction was performed eight weeks after injury than before eight weeks (Ghodadra et al., 2013).

Conversely, other studies reported that early ACL reconstruction resulted in stiffness, and arthrofibrosis and reduced the rate of return to work. Another reason for delaying reconstruction is to give the opportunity for the patient to regain normal knee function with non-operative treatment. Gage et al., advised that ACL reconstruction should be delayed until full passive extension with an average time of 18 days to achieve extension after an ACL injury to avoid arthrofibrosis post-operatively (Gage et al., 2019). Shelbourne recommended waiting at least three weeks to perform ACL reconstruction to avoid the risk of arthrofibrosis, which decreased when ACL reconstruction was delayed for 21 days, subsequently expanding rehabilitation time (Shelbourne et al., 1991). Conversely, Bottony et al., in their study, concluded that early ACL reconstruction did not develop in loss of motion or suboptimal clinical results when rehabilitation protocol pointed out in extension and early range of motion (Bottoni et al., 2008). Some studies reported no significant differences between early and delayed ACL reconstruction. Frobell et al. reported that a rehabilitation strategy plus early ACL reconstruction performed within ten weeks after an injury did not give a significant difference in results compared to rehabilitation plus optional delayed ACL reconstruction performed between 6.5 - 20 months after injury (Frobell et al., 2010). There is a lack of consensus regarding the timing of ACL reconstruction and its result that supports getting to work early.

This study aims to know whether early ACL reconstruction is more optimal for patients than delayed ACL reconstruction.

METHODS

The research was conducted using a systematic review consisting of three stages: data retrieval, data collection, and data interpretation. Before taking data, the right first step was to determine the PICO (Patient, Intervention, Comparison, Objective). The participant was a patient who had undergone ACL reconstruction. The intervention of the review was an ACL reconstruction, a surgery to reconstruct the injured ligament with a new ligament either by autograft or allograft. The comparison of the review was the timing of ACL reconstruction. Early ACL reconstruction was defined as less than six weeks after injury, while delayed ACL reconstruction was more than six weeks. The optimal timing for patients who undergo ACL reconstruction is still debatable. Still, most studies showed that ACL reconstruction should be performed within six weeks after injury with a well-planned rehabilitation program, such as quadriceps exercise. Conversely, above six weeks or delaying more than six weeks after injury could increase the risk of meniscus and cartilage damage to patients (Chen et al., 2015; Cipolla et al., 1995; Ferguson et al., 2019; Noyes & Barber-Westin, 1997; von Essen et al., 2020).

The outcome of the review was Tegner and/or Lysholm score. Tegner and/or Lysholm knee rating scores were applied to assess the functional outcome. The combination of Tegner and/or Lysholm scores is intended for

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a patient with ACL injury/ post-op of the ACL (Collins et al., 2011). The main benefit of the activity scale is that it can be used to monitor progress in activity level in the same person over time rather than comparing different patients. The pre-injury level and the current and desired activity levels can be determined using this scale. The Tegner score is a sports score that describes a typical daily activity of a patient; it consists of 10 distinct levels (1-10) of physical activity with 0 as a result from injury, 1-5 representing levels of work-related to activity and/or recreational sport, 6-9 representing a competitive/organized sport and 10 which represent the most elite athletes. The Lysholm score is widely and commonly used to assess the knee ligament injury and surgical outcomes; that consists of eight item scores that are proportional and scored up to 100 points on scales. The Lysholm score is described in some range of an interval and value such as 95 – 100 as excellent; 84 - 94 as good; 65 – 83 as fair; and <64 as poor (Lysholm & Tegner, 2007).

After determining the PICO, the authors (D.H, D.W, L.H) looked for screening in PROSPERO or the database whether there had been a systematic review with a similar title, and the results were not available. If similar title/results were found, then the differences in cut-off timing of reconstruction could be searched to distinguish among the reviews, so this research was continued. Data collection began with selecting keywords first. In this research, the keywords were as follows: ‘‘anterior cruciate ligament reconstruction’’ AND ‘‘surgery’’ AND ‘‘timing’’ OR “early” OR ‘‘delay’’.

From these keywords, the search results were summed from all search databases. Four databases were used in the study, namely Pubmed/MEDLINE, Science Direct, Scopus, and Google Scholar. The initial search was carried out, then the installation of automation tools could be started to focus the data obtained. Once the search results have been obtained, recording was performed, and duplication was removed because some studies might appear in more than one database. Duplication could be removed with the help of Mendeley. Furthermore, the data were selected according to the inclusion and exclusion criteria.

Selection was carried out in two stages by three authors (DK, DH, LW); the first stage was selection based on title and abstract. Excluded titles and abstracts were inappropriate with keywords or PICO that have been set at the beginning. In addition to the title and abstracts being screened for selection, full-text availability was also screened. The second stage of the selection was reading the full-text article to select studies that meet the inclusion and exclusion criteria requirements. The inclusion population of the journals was active people ranging 20-50 years old with an isolated tear of the ACL who underwent ACL reconstruction. The age criteria were chosen because surgery management which was ACL reconstruction, was usually a preferable treatment for younger athletes, those who have an occupation that requires a good physique or those who wish to return to their pre-injury sporting activities (Frobell et al., 2013; Smith et al., 2010) The diagnosis of the ACL injury can be through history taking, physical examination with Lachman or Anterior Drawer test, MRI scanning or diagnostic arthroscopy. Randomized control trials and observational studies were included in the selection of studies and were published from 2000-2020. The range of year was used in the studies because there were minimum studies that were published in the last 5-10 years; therefore, the study expanded the range of years from 2000 to 2020. Early ACL reconstruction was estimated less than six weeks after injury, while delayed ACL reconstruction was estimated more than six weeks post-injury to minimize the bias of

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journal selection and studies. Studies that met the criteria were called eligible. After obtaining eligible studies, the articles were assessed with Risk of Bias 2 (RoB2) for the RCT studies and Newcastle – Ottawa Quality Assessment Scale. RoB2 has been frequently used as a tool to assess the risk of bias for RCT studies. It was shown that RoB2 has been proven to be the appropriate tool to check the risk of bias tools as it is comprehensive and was approved by Cochrane (Sterne et al., 2019). Assessment consisted of 5 domains: randomization process (D1), deviations from the intended treatments (D2), missing the outcome data (D3), measurement of the outcome data (D4), and selection of the reported outcomes (D5). The end results from RoB2 were low quality, some concerns and high-quality study. For the observational studies, Newcastle – Ottawa Quality Assessment Scale was used to assess the quality of the observational studies which is one of the assessment tools that was approved by Cochrane. The observational studies were assessed with Newcastle – Ottawa Quality Assessment Scale by following the guidelines from 3 domains: selection of the participants, comparability, and outcomes (Wells et al., 2011). After the study assessment, articles could be read and extracted for each data in the study.

The first extracted data was the identity of the study, which was the author's name and time of writing. Furthermore, the data analyzed were types of studies. After that, it was done to be more specific, namely the data characteristics of the study sample. It consisted of the type of study, the country that had taken place in the study, number of patients in included studies and follow-up, injury to surgery time in either early or delayed ACL reconstruction, mean age of the patient, type of graft, each study's follow-up time, and surgical technique. The next was related to study variables: the Tegner score and/or Lysholm score and secondary data such as meniscus tears and chondral damage incidences. If there are data which are Tegner and/or Lysholm score that was presented in the form of the median, the methods from Hozo et al., were used to convert it to mean if possible (Hozo et al., 2005). The extracted data would be interpreted for retrieval conclusion. Should there be any disputes between authors, the fourth, the more senior author (DN) would aid in making the decision.

RESULTS

Figure 1 explains the collection and data selection which produced eight articles that fulfilled the eligibility criteria of the systematic review. The PRISMA chart started with collecting data using an electronic device from February to March 2021 from the database: Google Scholar, PubMed, Scopus, and ScienceDirect. From these databases, 3094 studies were obtained. Sometimes, articles were published in more than one database, so duplication selection was needed using Mendeley's application. Five hundred fifty-five studies obtained were duplicates which were then eliminated and ended with 2539 studies. Our first selection was based on the title, abstract, and full access to the article. The screening criteria used three points as in the plot: records excluded based on title, abstract, and full text of the studies. After eliminating the studies, there were 154 potential studies.

The Second Selection was based on the study's eligibility criteria, all English language articles of randomized control trial studies, and observational studies published from 2000 until 2020 that researched active people ranging from 20-50 years old who underwent ACL reconstruction. Early ACL reconstruction was defined as performing ACL reconstruction within six weeks post-injury, while delayed ACL reconstruction was more than six weeks post-injury. Early ACL reconstruction was performed within a few weeks of the injury

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to allow any joint effusion to subside, and a rehabilitation regimen focusing on quadriceps muscle and range of motion exercises was immediately implemented. In comparison, delayed ACL reconstruction was defined as an elective surgery with a pre-rehabilitation program such as quadriceps exercise, bracing, and others. From the 154 studies, only eight eligible studies fulfilled the criteria further analyzed for the risk of bias with RoB2 and

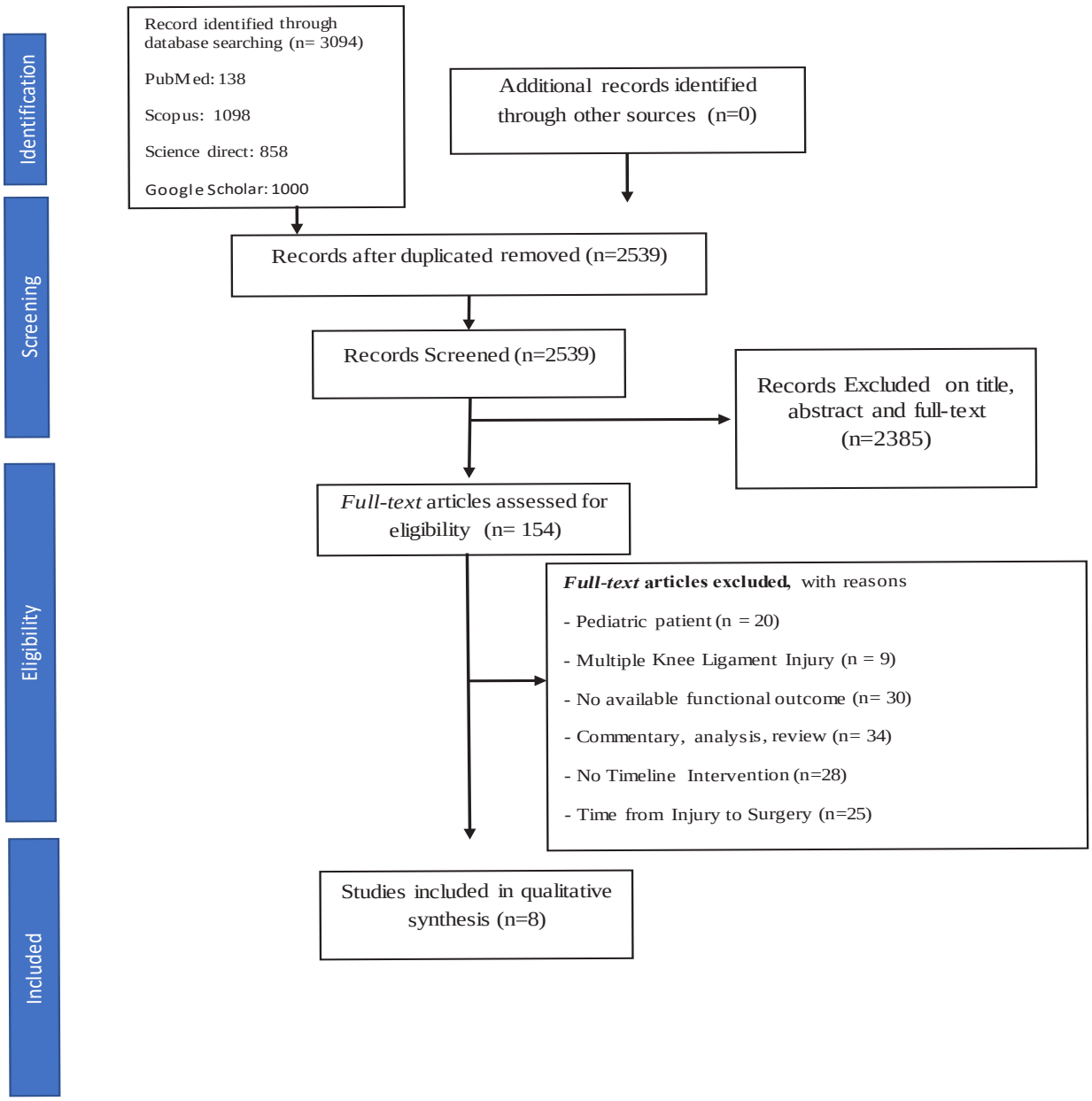

Figure 1

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Table 1 Risk of Bias 2 tools from 6 RCT studies.

Intention-to-treat	Unique ID	Study ID	D1	D2	D3	D4	D5	Overall
	1	(Meighan et al., 2003)	!	!	+	+	+	!
	2	(Bottoni et al., 2008)	!	+	+	!	!	!
	3	(Eriksson et al., 2018)	+	+	+	!	+	!
	4	(Manandhar et al., 2018)	!	+	+	!	+	!
	5	(Chen et al., 2015)	!	!	+	!	+	!
	6	(von Essen et al., 2020)	!	+	+	!	+	!

(Low Risk: + Some Concerns: !)

Table 2 . Risk of Bias 2 tools from 2 Observational studies.

No	Studies	Selection				Comparability	Exposure		
		Representatives of the exposed cased	Representatives of the non-exposed cased	Ascertainment of exposure	Selection of outcome parameters clearly specified in methods		Assessment of outcome?	Was observation period long enough for outcomes to occur?	Non-Response rate
1	(Hur et al., 2017)	*	*	*	*	*	*	*	*
2	(Herbst et al., 2017)	*	*	*	*	*	*	*	*

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Newcastle – Ottawa Quality Assessment Scale.

From table 1, six studies showed some concerns mainly because the process of randomization and allocation of the patient was unclear. There was also some unclear allocation as to whether the participant or the assessor knew what intervention the patient had. There were also some concerns regarding the outcome of some studies. There was also one study that had some concerns regarding the selection of reported results. From table 2, the two studies had a score of 8, which was good.

The study was conducted using a Systematic Review, and these were the results of data extraction from the eight following studies, which qualified the inclusion and exclusion criteria. There were nine tables, including the RoB2 table, Newcastle – Ottawa Quality Assessment Scale, demography table, Lysholm table, and Tegner table, meniscus tears tables, and chondral/cartilage damage tables.

Table 3 is the demography table of the eight following studies. The country of the studies was the place where the study had been conducted. Included studies were referred to all patients that underwent ACL reconstruction, and the follow-up was referred to all patients that underwent ACL reconstruction and could be followed up according to each outcome of the respective studies. There were patients who had lost contact during follow-up and could not be contacted. The injury to surgery time of the studies in early ACL reconstruction ranged from days to weeks, while the delay in ACL reconstruction ranged from weeks to a year. The mean interval of the age of the studies was 20-30 years old. The graft choices of the surgeon who did the surgery in the studies chose Hamstring as a graft, and only one study chose LARS. Follow-up times were varied, ranging from 2 weeks until five years. Two studies (Eriksson et al., 2018; von Essen et al., 2020) had the same initial patients but different follow-up times. One study (Herbst et al., 2017) differentiated between isolated ACL injury patients and ACL injury with the meniscal repair; they divided them into two groups. All studies used arthroscopy as their technical surgery.

Table 4 shows the Tegner and/or Lysholm score from 6 RCT and two observational studies. There were three RCT studies (Bottoni et al., 2008; Chen et al., 2015; Manandhar et al., 2018) and two observational studies (Herbst et al., 2017; Hur et al., 2017) reported the mean outcome of the Tegner score and five studies (Bottoni et al., 2008; Chen et al., 2015; Eriksson et al., 2018; Hur et al., 2017; von Essen et al., 2020) reported the mean outcome of the Lysholm score. Three studies (Eriksson et al., 2018; Meighan et al., 2003; von Essen et al., 2020) did not show the outcome of the mean Tegner score; they only showed the median Tegner score. There were also two studies (Manandhar et al., 2018; Meighan et al., 2003) that had no reference regarding the mean outcome of the Lysholm score. One Study (Herbst et al., 2017) did not explicitly state the mean Lysholm score. The study only revealed the chart follow-up of the score.

Meighan et al. defined early ACL reconstruction as less than two weeks from injury to surgery, while delayed ACL reconstruction is defined as eight until 12 weeks from injury to surgery. The delayed group had pre-operative physiotherapy from the intervention itself, while the early group did not have pre-operative physiotherapy. The differences in the pre-operative management could have different post-operative outcome, which could have a significant advantage on the functional outcome of the delayed group. However, after one year of follow-up, they concluded that whether the patient received early or delayed ACL reconstruction, both showed a reduced score in Tegner activity score

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Table 3 . Demography Table

No	Author	Type of Studies	Country	Number of Patients				Injury to Surgery Interval		Mean Age	Graft	Follow Up Time	Surgical Technique
				Included		Follow-up		Early	Delayed				
				Early	Delayed	Early	Delayed						
1	(Meighan et al., 2003)	Randomized Control Trial	Scotland	13	18	13	18	<2 weeks	8-12 weeks	21 (15-35 years)	HQ	2w. 6w, 3m, 6m, 1y	Arthroscopy
2	(Bottoni et al., 2008)	Randomized Control Trial	Hawaii, America.	35	35	34	35	2-17 days	42-192 days	27.3 (18-43 years)	HQ	6m – 2y	Arthroscopy
3	(Eriksson et al., 2018)	Randomized Control Trial	Swedish	34	35	32	32	8 days	6-10 weeks	26.9 (18-40 years)	HQ	3m, 6m	Arthroscopy
4	(Chen et al., 2015)	Randomized Control Trial	China	27	28	27	28	3-7 weeks	6-11months	Early: 29.4 Delayed: 31.9	LARS	1y and 5 y	Arthroscopy
5	(Manandhar et al., 2018)	Randomized Control Trial	India	110 (Not Stated)		53	51	4-21 days	42-60days	30 (18-55 years)	HQ	6m	Arthroscopy
6	(von Essen et al., 2020)	Randomized Control Trial	Swedish	33	35	28	29	8 days	6-10 weeks	26,9 (18-40 years)	HQ	6m, 1y,2y	Arthroscopy
7	(Hur et al., 2017)	Prospective Non-Randomized Control Studies	Korea	48	43	48	43	1-3 weeks	12-74 weeks	Early: 30.1 Delayed: 30	HQ	2y	Arthroscopy
8	(Herbst et al., 2017)	Prospective Non-Randomized Control Studies	Austria	50	50	50	50	1.2 days (average)	53.9 ± 68.4 days (average)	Early: 27.6 Delayed: 27.8	HQ	6m, 1y, 2y	Arthroscopy
				30	30	30	30	0.8 ± 0.8 days (average)	49.2 ± 86.3 days (average)	Early: 24.9 Delayed: 24.7			

(HQ: Hamstring Quadriple, LARS: Ligament Advanced Reinforcement System, w: weeks; m: months; y: year)

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Table 4. Results of both Tegner and Lysholm score in 8 eligible studies.

Author	Timing	Tegner	*P* Value	Lysholm	*P* Value
(Meighan et al., 2003)	Early ACL Reconstruction	NR		NR	
	Delayed ACL Reconstruction	NR		NR	
(Bottoni et al., 2008)	Early ACL Reconstruction	5.8 (Work related to activity and/or recreational sport)	0.34	80.6 (fair)	0.61
	Delayed ACL Reconstruction	4.9 (work related to activity and/or recreational sport)		83.4 (good)	
(Eriksson et al., 2018)	Early ACL Reconstruction	4.5* (work related to activity and/or recreational sport)	NR	76 (fair)	n.s
	Delayed ACL Reconstruction	4.25* (work related to activity and/or recreational sport)		79 (fair)	
(Chen et al., 2015)	Early ACL Reconstruction	6.3 (a competitive/organized sport)	0.413	93.37 (excellent)	0.164
	Delayed ACL Reconstruction	6.1 (a competitive/organized sport)		91.64 (excellent)	
(Manandhar et al., 2018)	Early ACL Reconstruction	4.15 (work related to activity and/or recreational sport)	0.064	NR	
	Delayed ACL Reconstruction	3.72 (work related to activity and/or recreational sport)		NR	
(von Essen et al., 2020)	Early ACL Reconstruction	7* (a competitive/organized sport)	NR	88.05 (good)	n.s

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	Delayed ACL Reconstruction	8.25* (a competitive/organized sport)		86.46 (good)	
(Hur et al., 2017)	Early ACL Reconstruction	6.0 (a competitive/organized sport)		94.5 (good)	
			0.27		0.28
	Delayed ACL Reconstruction	5.6 (work related to activity and/or recreational sport)		96.3 (excellent)	
(Herbst et al., 2017) (A)	Early ACL Reconstruction	6.7 (a competitive/organized sport)		Not Stated	
			n.s		n.s
	Delayed ACL Reconstruction	6.3 (a competitive/organized sport)		Not Stated	
(Herbst et al., 2017) (B)	Early ACL Reconstruction	6.6 (a competitive/organized sport)		Not Stated	
			n.s		n.s
	Delayed ACL Reconstruction	6.3 (a competitive/organized sport)		Not Stated	

(NR; No Reference) (NS: Not Significant) (*, Conversion from (Hozo et al., 2005))

compared to pre-injury activity rate on both groups with early and delayed groups showed similar outcomes. Meighan et al. preferred that the reconstruction could be done by delayed reconstruction because it was associated with a more rapid return of movement and muscle function.

According to Chen et al., the acute phase was described as the time required to properly manage rehabilitation and develop a positive mental attitude after the ACL ruptures. They categorized acute ACL reconstruction as reconstruction that occurred within 3-7 weeks after injury and delayed ACL reconstruction as reconstruction that occurred within 6-11 months after injury. Both the acute and delayed groups had a pre-operative rehabilitation. They believed that initiating rehabilitation earlier increased quadriceps and hamstring muscle strength, which was essential in determining knee function following ACL reconstruction in terms of flexion and extension. They reported that both Tegner and Lysholm score results were not statistically significant in the 1-year and 5-year follow-ups. The cut-off point for delayed ACL reconstruction was longer than any of the included studies, which might affect the outcome of the study. However, the study reported that patients in the delayed group that underwent ACL reconstruction for more than six months had a pre-operative rehabilitation to gain maximal ROM, which was the same

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criteria as the acute group. According to the study, 25% of patients had recurrent episodes of instability prior to surgery in the chronic group, and 32% of patients had persistent pre-operative pain. These symptoms persisted for six months before the patients had their first operation. The unpleasant series could be alleviated quickly with an acute intervention.

Manandhar et al. defined early ACL reconstruction as less than three weeks from injury to surgery, while delayed ACL reconstruction was defined as 42 until 60 days from injury to surgery. They stated that the mean Tegner score in early and delayed groups with a follow-up of six months was statistically not significant. Both early and delayed groups also had the same condition to undergo ACL reconstruction, which was the patient knee flexion with at least 120 degrees with or without pre-operative rehabilitation in the early group. In contrast, the delayed group had a pre-operative rehabilitation. They reported that even though the Tegner activity rating score did not differ statistically, it might be because the knee had to achieve a pre-operative 120 degree of flexion. That was why they concluded that patients should have surgery sooner rather than later, once they have restored 120 ° of knee flexion.

Both Eriksson et al., and Von Essen et al., had the same cut-off point of reconstruction, which was less than eight days from injury to surgery for early ACL reconstruction and six to 10 weeks from injury to surgery for delayed ACL reconstruction, and had the same sample population. The differences between the studies were that the patients' follow-up time with Eriksson et al. were followed up for 6 months while Von Essen et al., were followed up for 24 months. In a six-month follow-up, they reported that both groups' Tegner and Lysholm scores had improved. Surprisingly, the acute repair did not cause stiffness to rise. The acute group performed better on one-leg hop tests and improved in the subscales of pain, symptoms, and quality of life, but there were no significant differences after 24 months of follow-up.

Hur et al., defined early ACL reconstruction as the reconstruction of the ACL within three weeks after injury while delayed ACL reconstruction as the reconstruction of the ACL more than three months after injury. They excluded patients that underwent reconstruction more than three weeks until three months after an injury as they referred to the timing as an intermediate period, not acute or chronic. In the 24 months of follow-up, they reported that there were no significant differences in Tegner and Lysholm score. They also reported that there was a decreased Tegner score between pre-operative and post-operative in both groups as they assumed that the patients were reluctant to do more demanding activities. They hypothesized from their study that early ACL reconstruction had an advantage in muscle power and proprioception over delayed ACL reconstruction. However, in their study, they did not find any significant differences in the recovery of muscle power and proprioception between two groups.

Herbst et al., in their study, divided the patients into two groups which were patients who had an isolated tear of the ACL and patients who had an ACL injury with meniscus repair or meniscectomy. They defined early ACL reconstruction as the reconstruction of the ACL within 48 hours, while delayed ACL reconstruction was defined as reconstruction of the ACL after 6 weeks. They reported that in both groups, the Tegner score of early and delayed ACL reconstruction was not significant. For the Lysholm score, they only reported in the form of a graphic, and they concluded that there was no significant between early and delayed ACL reconstruction in both groups. Only 4.9 percent of patients with an isolated ACL reconstruction and 4.2 percent of patients with a combined ACL reconstruction and meniscus

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repair had a clinically relevant extension and flexion loss after acute surgery, according to this study. There was no discernible change in ROM between acute surgery within 48 hours and delayed surgery within the inflammation-free interval.

There were six studies (Bottoni et al., 2008; Eriksson et al., 2018; Hur et al., 2017; Manandhar et al., 2018; Meighan et al., 2003; von Essen et al., 2020) that reported the meniscus injury. Two of the eight studies (Chen et al., 2015) had no reference regarding the meniscus injury. Other studies (Eriksson et al., 2018; von Essen et al., 2020) reported the same outcome.

One study (Meighan et al., 2003) reported the meniscus injury without differentiating lateral meniscus or medial meniscus. Other studies (Bottoni et al., 2008; Eriksson et al., 2018; Hur et al., 2017; Manandhar et al., 2018; von Essen et al., 2020) differentiated the meniscal injury and reported that the total injury of the medial meniscus for early ACL reconstruction were 41 tears, while delayed ACL reconstruction was 61 tears. The lateral meniscus injury for early ACL reconstruction was 58 tears, while delayed ACL reconstruction was 36 tears. Early ACL reconstruction had fewer medial meniscus tears than delayed ACL reconstruction, while for lateral meniscus tears, early ACL reconstruction had more tears than delayed ACL reconstruction. Two studies (Hur et al., 2017; Manandhar et al., 2018) also reported bilateral tears, which were the lateral and medial meniscus injuries. The total tears of early and delayed ACL reconstruction in the two studies were 12 and 8 tears, respectively.

Our findings in these reviews about chondral damage showed that in three studies (Eriksson et al., 2018; Hur et al., 2017; Manandhar et al., 2018). Eriksson et al. reported greater chondral damage in early ACL reconstruction, while Manandhar et al. and Hur et al., reported a more serious chondral damage in delayed ACL reconstruction.

According to Eriksson and Von Essen, delaying ACL reconstruction surgery increases the risk of meniscal and chondral damage. However, both studies found no significant differences in terms of related injuries, even though the early group had a slightly higher accident rate. The insignificant differences were most likely due to a smaller sample size or a variation in time to surgery between the groups that were too low to affect subsequent injury outcomes.

Manandhar et al. also reported that the early group had a greater rate of lateral meniscus tears, and the delayed group had a higher rate of medial meniscus tears. The higher incidence rate of lateral meniscus tears in the early group from the study is possible not because of the time interval, but as mentioned in most journals, it is associated with the mode of injury (Briem & Snyder-Mackler, 2009; Lohmander et al., 2007; Simon et al., 2015). From the demography of the study, approximately 30% of the patient were in traffic accidents, while the rest were sport-related activity injuries. The traffic accident patient could predispose to the tears of meniscus and chondral damage. The patient could regain knee stability and reduce the chance of additional meniscal and chondral injury, leading to early degenerative joint change, if the ACL reconstruction was done sooner.

Hur et al., reported a higher incidence rate of meniscus tears and chondral damage in the delayed group than in an early group. They concluded that the patients that underwent early ACL reconstruction had a higher chance of repairment for the meniscus tears than delayed ACL reconstruction. For the chondral damage, they found that the insignificant differences between the two groups were more likely due to the time from injury to surgery, more than three months which might be too short as it did not influence the incidence rate of cartilage

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Table 5. Medial Meniscus tears from 4 eligible studies.

No	Author	Medial Meniscus Tear		*P* Value
		Early	Delayed	
1	(Bottoni et al., 2008)	14	15	1
2	(Eriksson et al., 2018)	7	2	NR
3	(Manandhar et al., 2018)	6	20	NR
4	(Hur et al., 2017)	14	24	0.06

Table 6. Lateral Meniscus tears from 4 eligible studies.

No	Author	Lateral Meniscus Tear		*P* value
		Early	Delayed	
1	(Bottoni et al., 2008)	18	9	0.025
2	(Eriksson et al., 2018)	13	10	NR
3	(Manandhar et al., 2018)	12	8	NR
4	(Hur et al., 2017)	15	9	0.06

Table 7. Meniscus Tears from 1 eligible RCT studies.

No.	Author	Meniscus Tears		*P* value
		Early	Delayed	
1	(Meighan et al., 2003)	3	4	NR

(NR: No Reference)

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Table 8. Chondral/Cartilage damage from 3 eligible studies.

No.	Author	Chondral/Cartilage Damage		*P* value
		Early (n)	Delayed (n)	
1	(Eriksson et al., 2018)	10	4	NR
2	(Manandhar et al., 2018)	10	28	NR
3	(Hur et al., 2017)	15	20	0.14

(NR: No Reference)

Table 9. Chondral/Cartilage damage from 1 eligible RCT study.

No	Types of Chondral damage (Bottoni et al., 2008)	Early ACLR (n)	Delayed ACLR (n)	*P* Value
1	Medial Femoral Condyle	0	4	0.11
2	Lateral Femoral Condyle	3	0	0.11
3	Patella	5	0	0.023
4	Femoral Trochlea	1	1	1

damage. The study concludes that early ACL reconstruction is more preferable as the torn of the meniscus in the early group increases the chance of repairment.

Bottoni et al. defined early ACL reconstruction as less than 21 days until three weeks from injury to surgery, while delayed ACL reconstruction was defined as more than six weeks from injury to surgery. They reported an increased incidence rate in lateral meniscus tears and the lateral femoral condyle in the early group, while the delayed group showed an increased incidence rate in the medial meniscus and medial femoral condyle. The increased incidence rate in the delayed group showed that when we delayed the injury to surgery, it could cause instability of the knee which resulted damaged in other structures, in this case, the medial meniscus and medial femoral condyle, because we know that the medial compartment of the knee represents the main weight-bearing of the knee (Briem & Snyder-Mackler, 2009). When there is an insufficiency of the ACL, the medial compartment, which is the medial meniscus and medial femoral condyle, is more stressed,

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which results in more prone to injury (Simon et al., 2015). From the demography of the studies, it was shown that several patients of both early and delayed groups had some traffic accidents that could affect the outcomes of the reconstruction and meniscal and chondral damage. Traffic accidents could cause massive damage/trauma to the knee joint's integrity, resulting in a severe arthrofibrosis and difficult rehabilitation (David Magit et al., 2007). Some patients also had different activity rates, such as active people, athletes, and soldiers, slightly affecting the outcomes. They also stated that meniscus tears in the early group are more manageable to heal than those in the delayed group, owing to the delay in surgery and the possibility of increased damage to the meniscus, which could predispose the inability to repair these tears. The conclusion of the study indicates that ACL reconstruction can be done in the early stage because the result of the functional outcome, Tegner dan Lysholm score, would give an insignificant difference compared to the delayed ACL reconstruction. However, the study stated that not all the reconstruction should be performed in the acute phase with the knee is still inflammation, swelling and having a limited ROM.

DISCUSSION

The main findings of this review show that the early ACL reconstruction has a higher score in both Tegner and Lysholm score than a delayed ACL reconstruction but are not statistically significant. There are three studies by (Bottoni et al., 2008; Chen et al., 2015; Manandhar et al., 2018) that use the Tegner score, and the others are two studies by (Bottoni et al., 2008; Chen et al., 2015) with Lysholm score that reported the probability score which was the statistically insignificant outcome with the value $P > 0.05$. The results obtained from this review show that there are no significant differences in the functional outcome as measured by Tegner and Lysholm.

Early ACL reconstruction is defined as performing ACL reconstruction within six weeks post-injury, while delayed ACL reconstruction is more than six weeks post-injury. This corresponds with previous studies. A study conducted by Goradia et al. showed that patients who had had early ACL reconstruction six weeks after injury had a higher score on the Lysholm scale; however, the difference was not statistically significant (Goradia & Grana, 2001). The mean acute pre-operative period was similarly established as six weeks by Noyes et al. (Noyes & Barber-Westin, 1997). Cipolla et al. also suggested that performing ACL reconstruction within 3-6 weeks after injury is well-timed (Cipolla et al., 1995). A meta-analysis by Smith could not identify any significant differences in functional outcomes score between early reconstruction performed within one month from injury and delayed reconstruction (Smith et al., 2010). They found that the severity of the injury, rather than the time interval between injury to surgery, is an essential aspect to consider when reconstructing the ACL.

The risk of performing early reconstruction is associated with arthrofibrosis development. The definition of arthrofibrosis is not generally acknowledged. Historically, it has been described as stiffness following a knee injury or reconstructive surgery. Past studies found an association between a pre-operative range of motion and arthrofibrosis development. For instance, Mayr et al.. found a correlation between limited pre-operative knee motion and stiffness after ACL reconstruction in a study. They noted that undergoing early ACL reconstruction during the inflammation stage could increase the risk of arthrofibrosis more than delayed ACL reconstruction and caused limited knee ROM. Mayr et al. reported that after ACL reconstruction in 223 patients with

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autologous BPTB graft (75%), the risk of arthrofibrosis incidence was increased when time injury to surgery was within four weeks; however, they also noted that the more crucial risk factors for the incidence of arthrofibrosis than the time between injury to surgery were inflamed knee (swelling, effusion, hyperthermia) and inadequate range of motion before surgery (Mayr et al., 2004) Pre-operative stiffness has been shown to be associated with past operative stiffness. Gage et al., recommended that ACL reconstruction should be delayed until full passive extension with an average time to achieve extension after 18 days after an ACL injury to avoid arthrofibrosis post-operatively (Gage et al., 2019). Arthrofibrosis remains a rare but potentially devastating complication after an ACL reconstruction, an estimation of 2% of patients who had post-operative stiffness required an intervention. Contrary, according to Sander et al., patients who underwent ACL reconstruction beyond four weeks of injury had a significantly higher risk of arthrofibrosis than patients treated surgically within four weeks (Sanders et al., 2017). A systematic review by Kwok et al., stated that when an ACL reconstruction was performed as early as possible, within one week after an injury, there is no increased risk of the knee stiffness if a modern surgical technique and an accelerated rehabilitation are used (Kwok et al., 2013).

An increase in the meniscus and the chondral lesion may be associated with delayed ACL reconstruction. The result of this review also found an increased incidence rate of the medial meniscus and medial femoral condyle. Ghodadra et al. evaluated 709 individuals who had their ACLs reconstructed. The time from injury to surgery was divided into three cut-offs which were less than four weeks, between 4 and 8 weeks, and more than eight weeks. They discovered that the chronic group (>8weeks) had a considerably higher rate of meniscal tears, particularly in the medial meniscus and medial chondral lesions than the early group (Ghodadra et al., 2013). In their study, Michalitsis et al. found that the risks of developing a high-grade cartilage lesion which was grade III and IV Outerbridge in an ACL-deficient knee repaired more than 12 months from injury to surgery were 5.5 and 12.5 times greater, respectively, as compared to knees that underwent ACL reconstruction less than three months and between 3 and 12 months from injury to surgery (Michalitsis et al., 2015). Chaddia et al. evaluated time to surgery in ACL reconstruction as one of the risk factors for meniscus and cartilage injury and concluded that the increased risk of the injured medial meniscus and decreasing repair rate had a strong relationship with the increasing time to surgery (Chhadia et al., 2011).

A retrospective study by Bierke et al., concluded that if an anatomical surgical technique was used and the patient was operated on in the acute phase without meniscus repair, there was no increased risk of arthrofibrosis. Early and forced movement should be considered while refixing the meniscus at the same time. Before surgery, symptoms of inflammation such as effusion, discomfort, and a motion deficit of fewer than 90 degrees should have resolved, although, in the study, aggressive rehabilitation should be evaluated in ACL reconstruction with simultaneous meniscus repair patients (Bierke et al., 2021).

The findings also showed an increased incidence rate in the lateral meniscus, lateral femoral condyle, and femoral trochlea in the early group compared to the delayed group. The possibility of the increased incidence rate is associated with the mode of injury rather than the time interval from injury to surgery. Feucht et al. retrospectively reviewed 268 patients who had undergone ACL reconstruction. The results indicate that the time interval between injury and surgery has

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no effect on lateral meniscus tears and that other factors other than surgical delay must be responsible for lateral meniscus tears in ACL-injured subjects. In contrast, delayed surgery increases the incidence of medial meniscus tears due to instability (Feucht et al., 2015).

From the previous systematic review that has been published, the majority of them (Deabate et al., 2020; Ferguson et al., 2019; Smith et al., 2010) concluded that the functional outcome of early and delayed ACL reconstruction, particularly Tegner and Lysholm score have no significant differences which are similar to the results of this systematic review although one of them (S. H. Kim et al., 2021) concluded that the Tegner and Lysholm score increased in the early group compared to the delayed group. Increased meniscus tears and cartilage were also found in two systematic reviews (Ferguson et al., 2019; S. H. Kim et al., 2021), although other systematic reviews (Deabate et al., 2020; Smith et al., 2010) stated that there were no significant differences between the two timings. The difference between this systematic review with others is that the cut-off point is six weeks from injury to surgery and the year of the publication.

The review suggests that the ACL reconstruction can be performed in the early phase. With the advance in surgical methods, understanding of grafts, and the anatomy of the knee for drilling structure and others, it can also be performed safely with rehabilitation and minimum side effects. With a proper and accurate diagnosis and immediate intervention, patients can return to sport or work sooner. Regardless of the timing of reconstruction, pre-operative management, early mobilization, and aggressive rehabilitation are important and should be done in both early and delayed ACL reconstruction.

The strength of the systematic review is that it mostly used RCT studies which are relatively objective in terms of bias compared to other studies. Another strength of the review is that the cut-off point in the timing of the studies is well defined as early ACL reconstruction is less than six weeks while delayed ACL reconstruction is more than six weeks. The studies can provide a better understanding of the cut-off timing of early and delayed ACL reconstruction. Unfortunately, the studies have some limitations. The limitation of this review is associated with the outcome of this review that only describes descriptively, not analytically, using a meta-analysis review which will be more objective. Second, there is a heterogeneous time regarding post-operative follow-up in each RCT study. Third, there is a limited amount of RCT studies published throughout the years, resulting in limited information regarding when the optimal time for surgery. Therefore, it is still debatable until now. Furthermore, some of the studies included in the systematic review have some bias concerns that still need improvement.

CONCLUSION

The review concludes that whether the patient performs early or delayed ACL reconstruction, the Tegner and Lysholm scores are similar. Therefore, early ACL reconstruction can be optimal for patients who will undergo reconstruction since delayed ACL reconstruction increases the risk of medial meniscus tears and medial femoral condyle damage. The following systematic review can be done with a meta-analysis approach as the analysis can be more objective.

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Literature Review

The role of social support on resilience in people living with HIV/AIDS: A Systematic literature review

Firman Firman[1], Sri Yona[2], Allenidekania Allenidekania[3]

1) Master Program in Faculty of Nursing, Universitas Indonesia
2) Department of Surgical Medical Nursing Faculty of Nursing, Universitas Indonesia

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Correspondence:

ns.firman92@gmail.com

ABSTRACT

During the COVID-19 pandemic, it had a fairly heavy psychological impact, so resilience or resilience was needed, especially for people with HIV/AIDS (PLWHA). This study is to determine the role of social support on resilience in people with HIV/AIDS. Resilience is a person's ability to adapt, survive and thrive in difficult situations. This study used a systematic literature review, which was carried out by means of a systematic review of several articles discussing social support and resilience in people with HIV/AIDS. Article criteria include international publication in English and full text. Article searches were carried out in February 2022 through 4 databases, namely PubMed, Wiley, Proquest, and Springer. Search using keyword ("PLWHA" AND "Social Support" OR "Perceived Social Supports" AND "Resilience" OR "Resiliences"). Articles were analyzed using JBI and Prisma tables. Based on the search for articles in the database, 217 articles were found, then selected through systematic stages so that eight selected journals were obtained. This systematic literature review found that social support was an important factor in increasing resilience in PLWHA. The most influential source of support was support from the family, namely: 30.4%, with (P=0.001). The perceived social support can reduce the impact of stress experienced. With high social support, it can reduce the use of harmful substances and increase ART adherence and contribute to improving the patient's health condition. In conclusion, perceived social support can play an important role, especially in increasing resilience, so it impacts the physical and psychological well-being of people living with HIV/AIDS.

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INTRODUCTION

HIV/AIDS (Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome) was one of the world's health problems, which required serious attention from various parties, and a holistic approach. The problems experienced by PLWHA are not only physical health problems but also psychosocial problems that are often experienced by them. Therefore, resilience or resilience was needed for PLWHA to be able to adapt. However, if PLWHA has low resilience, it will be difficult to adapt to changing conditions (Pai et al., 2020).

Based on data reported by UNAIDS (2021), the cases of HIV/AIDS in the world reached 37.7 million people. And it was estimated that as many as 680,000-1 million people died of HIV/AIDS. According to WHO data, in 2020, there will be 78% of new HIV infections in the Asia Pacific region. The number of People Living With HIV/AIDS (PLWHA) in Indonesia over the last eleven years reached it was peak in 2021, namely 558,618 cases, 427,201 HIV, and 131,417 AIDS (Direktur Jenderal P2P, 2021).

People with HIV/AIDS were a vulnerable group who experienced several physiological and psychological symptoms, both caused by the disease they were experiencing, as well as the side effects of Antiretroviral (ART) and other drugs related to comorbidities (Ibragimov et al., 2021). This vulnerability exceeded the vulnerability of people with other chronic diseases such as Diabetes Mellitus and Hypertension. Generally, people with HIV/AIDS will experience symptoms such as fatigue, fever, headache, nausea/vomiting, diarrhea, weight loss, pruritus/itching, chills, rash, sweating, dyspnea, cough, muscle aches/ joint pain, and lack of sleep (CDC., 2021).

In it was development, Antiretroviral treatment (ART) is carried out on people who have been diagnosed with HIV positive, if treatment is carried out regularly, it can suppress the viral load in the blood, and the CD4 cell count will increase, so as to reduce as well as overcome various complaints that arise. Thus, the Human Immunodeficiency Virus (HIV) disease can be controlled properly (Rooney et al., 2019). Effective symptom management was essential for people with HIV to maintain their quality of life (Gangi et al., 2020).

Another aspect that was needed was social support. Social support is the presence of certain people who personally provide advice and motivation when individuals experience problems (Rzeszutek et al., 2017). For this reason, if there is poor social support and there is rejection and discrimination against PLWHA, it will exacerbate the stressful conditions they experience (Abimbola et al., 2021). Social support increases resilience in PLWHA so that they remain enthusiastic and optimistic in undergoing treatment (Wang et al., 2021). Resilience is an ability possessed by individuals that can be used to overcome difficulties experienced (Connor & Davidson, 2003).

In a study, it was explained that having high resilience was an important factor for individuals to be able to deal with stressful situations and was used as a protective factor for both physical and mental health (Julian et al., 2021). Resilience is very important for PLWHA so that they can assist in the process of adaptation to the conditions of the disease they are experiencing (Wu et al., 2015). High resilience can reduce symptoms of stress and depression (As of et al., 2020).

Efforts to increase resilience/resilience for PLWHA were very important to continue, one of which was through social support (Julian et al., 2021; Huang et al., 2018; Wani, 2020). The problem of decreasing physical health in HIV patients was caused by the psychological impact

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experienced (Prabhu et al., 2020). Therefore, the treatment of HIV patients was not enough with a medical approach; a social approach was needed, namely by providing social support. Many studies have described the form of social support, but there were still some differences regarding the most meaningful form of support for PLWHA, especially in increasing resilience for PLWHA. For this reason, this systematic literature review will determine social support's role on resilience in people living with HIV/ AIDS.

METHODS

Data Source

This literature review study was conducted using PRISMA to determine the role of social support on resilience in people with HIV/ AIDS. Article searches were carried out in February 2022 through 4 databases, namely PubMed, Wiley, ProQuest, and Springer. Then the articles are selected through 3 stages. First selected based on duplication of articles from several sources found. Second, choose articles by reading the title and abstract. The third was by reading the full article.

Inclusion Criteria

Articles included in this study with the following inclusion criteria: articles with quantitative studies which explain social support and resilience for people with HIV/ AIDS, international publication articles so that the articles that will be included in this study were articles of very good quality, articles in English and full text. While the articles that were not included were systematic review articles, literature reviews, and meta-analyses.

Tracing Strategy

To get articles that match the research topic, the researchers used the keywords ("PLWHA" AND "Social Support" OR "Perceived Social Supports" AND "Resilience" OR "Resiliences"), found 217 articles, and then selected through systematic stages in order to obtain 8 selected journals.

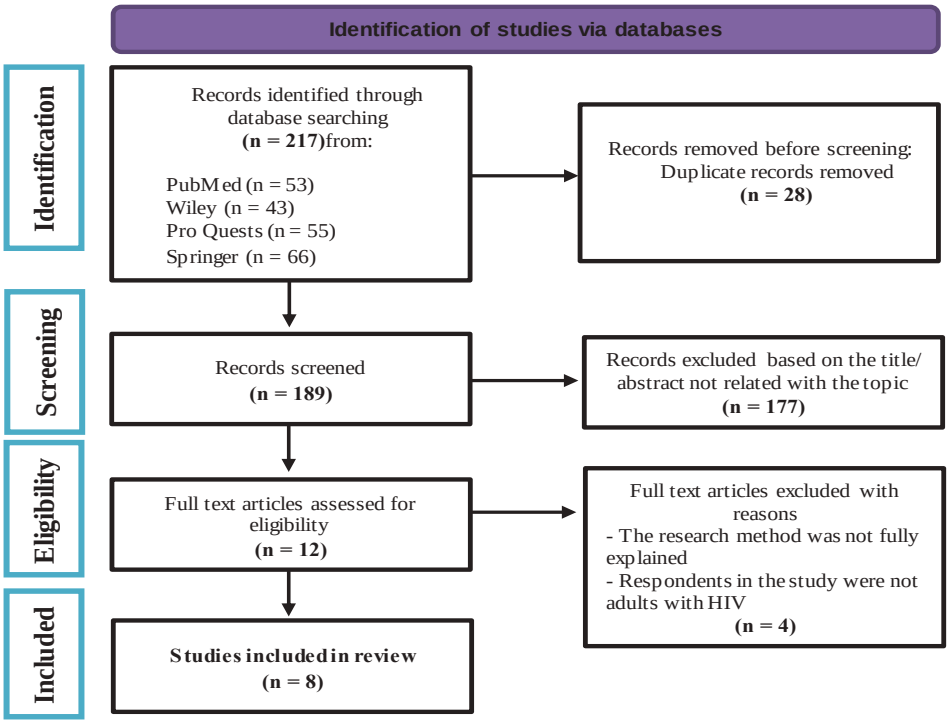

Figure 1. Workflow Literature Searching

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RESULT

In this systematic literature review based on search results, 217 articles were found and then selected through a rigorous screening process and stages, so that 8 articles were obtained for systematic review. The article discusses social support and resilience in people with HIV/AIDS (PLWHA), as described in the following description:

Sources of Social Support

Based on the results of research conducted by Xu et al. (2018), 212 people with HIV/AIDS were recruited from the Hospital. From the results of the study, it was explained that support from the family was positively related to resilience. The score for family support was 12.6 (SD = 2.54), while the score for resilience was 13.2 (SD = 2.31). These data show that social support that comes from the family can increase individual resilience. This was in line with the research results (Lyons et al., 2016) in Australia, in 402 men and women living with HIV, subjects aged 18 years and over. The results of the study explain that the support that came from family was 30.4%, close friends 29.8%, and other people 28.4%. Finding this showed that the type of support that had the most significant effect was the support that came from the family with (P=0.001).

Likewise research by Rzeszutek et al. (2017) in 290 people with HIV persons who were receiving care in a voluntary participating hospital, subjects aged 18 years or older, it was explained that family support was positively related to the global PTG (Post Traumatic Grow) score in the follow-up assessment (beta = .38) and for the level of resilience in the first assessment (r = .25). Finding this showed that the form of social support that came from the family has a very important role in increasing their resilience.

Another found (Huang et al., 2018) in China on 160 people with HIV also explained that the results of the study showed that better marital and family relationships were a source of individual resilience and higher well-being. With a source of individual resistance can increased general welfare among PLWHA that was (B = .27, p < .05) physical well-being (B = .25, p < .01) and mental well-being (B = .23, p < .01). There were implications for interventions to increase resilience with the aim of improving the welfare of PLWHA by incorporating interpersonal strategies to strengthen the protective role of marital relations, which play a role in facilitating the process of resilience in PLWHA.

The Role of Social Support

In the results of research conducted by (Catabay et al., 2019) in 310 people who were recruited at the Hospital. The study results explained that the score with a high level of social support was as much as 35%, and a moderate or high level of resistance was 72%. For each point increase in social support scores (OR = 0.95; 95% CI: 0.91-1.00) and resilience scores (OR = 0.91; 95% CI: 0.85-0.97), there was each decreased the likelihood of experiencing major depressive symptoms. At each point increase in the resilience score, there was a decrease in the likelihood of having major depressive symptoms (OR = 0.92; 95% CI: 0.88-0.97). Social support can reduce mental health effects.

In line with the results of research conducted by (Wen et al., 2020) in 223 people with HIV. The results showed that social support directly affected resilience by 0.11, while a direct effect on depression was 0.19. These findings suggest that social support can increase a person's resilience as well as reduce symptoms of depression. The same thing was also found in the article by (Adamu et al., 2019) that social support is a buffer of resilience so as to prevent the effects of life stress experienced. The results

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showed the average score of social support (52.36 ± 10.17), resilience (60.14 ± 12.67), and perception of stress (26.46 ± 4.81). This finding showed that the relationship between social support and resilience among women with HIV is a significant relationship, as evidenced by (P=0.01).

In a study conducted by (Lyons et al., 2016) on 402 HIV people, it was explained that social support from family and close friends mediated resilience with health and well-being for PLWHA. In other research by Hena Khan, 2015) that the average score of social support among men was 46.85(19,00) and girls 44.15(18.89), while the average male endurance score was 29.05(5.79), the female was 29.55(8.08). These findings showed a significant correlation between social support and resilience (P=0.01). This was in line with research by Xu et al. (2018) that there was no difference in support from family for male and female respondents, for males 12.6 (2.64), females 12.6 (2.26) with (P-value 0.85). However, it showed different scores on resilience, with males 13.4 (2.36) and females 12.5 (2.07) with (P-value 0.02).

From research results by Rzeszutek et al. (2017), the perceived level of support and need for support, expressed in the intensity of seeking support, may also facilitate the use of more adaptive stress coping strategies (r = .25). The most common stress coping strategies were meaning-focused coping strategies, particularly positive reassessment (also referred to as positive re-evaluation). Besides that, perceived social support will mediate the relationship between perceived support acceptance and use of the substance. This was in line with the research of Wen et al., 2020) also explained that social support has an indirect effect on increasing ART adherence, which was 0.03 so that it can improve physical health. This was also supported by research by Hena Khan, 2015) that the regression analysis results for the influence of contributions showed that social support and resilience predicted immunity in PLWHA. Social support accounted for 43.9 percent of the variance in CD4 scores. Meanwhile, resilience accounted for 4.8 percent of the variance in CD4 scores.

DISCUSSION

Several research results explained that there are several sources of social support for people with HIV/AIDS, including support from family, friends, and other people. However, the support that was most needed and very meaningful for PLWHA was a support that came from the family (Xu et al., 2018). This was because the family was the closest person to their family members, so it became the main source of strength. The presence of the family to provide support was very important so that the individual did not feel alone when facing challenges and difficulties. Likewise explained by (Huang et al., 2018; Luo et al., 2013) that the presence of the family becomes very important for people with HIV to stay close and support each other as they face HIV-related challenges. Adequate family support can encourage the development of the ability to adapt to adversity and maintain a better quality of life.

According to Lipira et al. (2019), family support is a resource that individuals can use to develop resilience. Older PLWHA who received higher levels of family support were more likely to develop resilience that endured aging and improved quality of life. Family traditions in China form an important safety umbrella for PLWHA (Luo et al., 2013), and family members were primary caregivers for medication, psychosocial and financial support, and child care. This was especially true for older PLWHA as they usually have limited social networks and rely heavily on their families to develop strategies for responding to HIV infection and aging, most of

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Table 1. Characteristics of articles

Title, Author, and Country	Aims	Methods	Sample	Findings
Social support, stress coping strategies, resilience and post-traumatic growth in a Polish sample of HIV-infected individuals: results of a 1-year longitudinal study (Marcin Rzeszutek, Włodzimierz Oniszczenk, Ewa Firląg-Burcka, 2017). Poland.	This study aimed to investigate post-traumatic growth rates (PTG) and their relationship to levels of social support, stress coping strategies, and resilience among people living with HIV (PLWHA).	Cross-sectional study, the data collection procedure was carried out using a questionnaire instrument	The sample in this study was 290 people who participated voluntarily. Eligibility criteria were PLWHA aged 18 years or older, a confirmed medical diagnosis of HIV infection, and receiving treatment from a hospital. Exclusion criteria included HIV-related cognitive impairment, which was screened by a psychiatrist working in the Hospital where the study was conducted.	• The results of the study explained that the form of social support comes from family support. And the support felt by PLWHA has a very important role in increasing their resilience. • It was found that received support was positively related to the global PTG score in the follow-up assessment (beta = .38) as well as to the level of resilience at the first assessment (r = .25). • Perceived level of support and need for support, expressed in the intensity of support seeking, may also facilitate the use of more adaptive stress coping strategies (r = .25) • Perceived social support will mediate the relationship between received support and substance use
Close relationships, individual resilience resources, and well-being among people living with HIV/AIDS in rural China (Huang et al., 2018) China	This study aimed to examine the mediating role of individual resilience resources in the relationship between marital and family relationships with the welfare of PLWHA.	In cross-sectional research, the data collection procedure was carried out using a questionnaire instrument	The sample size was 160 people, and the sample selection randomly selected five villages from among 22 villages where the HIV prevalence was greater than 10% in Henan province, China. Inclusion criteria were: (1) HIV positive, (2) Married more than five years.	• The results show that better marital and family relationships were a source of higher individual resilience and well-being. • With the existence of a source of individual resilience can improve general welfare,(B = .27, p < .05),physical well-being(B = .25, p < .01)and mental well-being(B = .23, p < .01)betweenPLWHA • There are implications for interventions to increase resilience with the aim of improving the welfare of PLWHA by incorporating interpersonal strategies to strengthen the protective role of marital relations, which play a role in facilitating the process of resilience in PLWHA
Perceived stress and mental health: The mediating roles of social support and resilience	This study aims to examine social support and resilience as mediators of the relationship between	Retrospective cohort research design and data collection procedures were carried out using	The sample in this study was 310 black women seeking health services recruited in the waiting rooms of two public STD clinics in the City of Baltimore. The inclusion criteria were as follows:	• This study found that social support can reduce negative mental health effects • It was found that 35% had a high level of social support, and 72% had a moderate or high level of resilience. • For each point increase in the resilience score, there was a decrease in the likelihood of having major depressive

among black women exposed to sexual violence. (Christina J. Catabaya, Jamila K. Stockmana, Jacquelyn C. Campbellb, Kiyomi Tsuyuki, 2019). *United States*	perceived stress and mental health.	questionnaires, documents, and interviews	biologically female, between the ages of 18-44, self-identifying as Black.	symptoms (OR = 0.92; 95% CI: 0.88–0.97). • For each point increase in social support scores (OR = 0.95; 95% CI: 0.91-1.00) and resilience scores (OR = 0.91; 95% CI: 0.85-0.97), there was decreased likelihood of experiencing major depressive symptoms, respectively.
Resilience, self-esteem, self-efficacy, social support, depression, and ART adherence among people living with HIV in Sichuan, China (Wen et al., 2020) China	This study aimed to examine the relationship between resilience, self-esteem, self-efficacy, social support, depression, and antiretroviral therapy (ART) adherence in people living with HIV.	The research design is cross-sectional, and the data collection procedure is carried out using a questionnaire instrument	The sample was 223 people, and the sample collection procedure was carried out on patients who visited the hospital regularly. The inclusion criteria were: (1) aged 18 years and over; (2) diagnosed HIV positive; (3) willing to be a respondent	• The results showed that social support had a direct effect on the resilience of 0.11, while a direct effect on depression was 0.19. These findings suggest that social support can increase a person's resilience as well as reduce symptoms of depression. • In addition, social support was also found to have an indirect effect on increasing ART adherence, which was 0.03.
Ageism, resilience, coping, family support, and quality of life among older people living with HIV/AIDS in Nanning, China (Xu et al., 2018) China	The purpose of this study was to assess the interrelationships between age, resilience, coping, family support, and quality of life of PLWHA	In a cross-sectional study, the data collection procedure was carried out using a questionnaire instrument	The study sample was 212 PLWHA who were recruited from the Hospital. Eligibility criteria for PLWHA include PLWHA who are at least 50 years old and able to participate in face-to-face interviews.	• The results showed that family support was positively related to resilience.Family support score 12.6 (SD = 2.54), score for resilience or resilience 13.2 (SD = 2.31). Thus support that comes from the family can increase individual resilience. • The support from the family for male and female respondents did not show any difference, for males 12.6 (2.64), females 12.6 (2.26) with (P-value 0.85). But showed different scores on resilience, male 13.4 (2.36), female 12.5 (2.07) with (P-value 0.02).
Psychosocial Factors Associated with Resilience in a National Community-Based Cohort of Australian Gay Men Living with HIV (Anthony Lyons, Wendy	This study aims to provide a complete picture of resilience and mental health	Cohort study design, the data collection procedure was carried out using	A sample of 402 men and women living with HIV, aged 18 years and over, and residents in Australia identified as gay men, reflecting the demographic	• The results of the study explained that the type of support that has the most significant effect is the support that comes from30.4% from family, 29.8% from close friends, 28.4% from other people, with P=0.001. • Social support from family and close friends mediated resilience with health and well-being for PLWHA.

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Heywood, Tomas Rozbroj, 2016) Australia	among HIV-positive gay men	a questionnaire instrument	distribution of HIV infection in Australia	
Stress, social support, and resilience among women living with HIV in Nigeria (Aliyu Adamu, Gugu Mchunu, Joanne R. Naidoo, 2019). Nigeria	The aim of this study was to explore the relationship between social support, HIV-related psychological stress, and resilience among women living with HIV	The research design is cross-sectional, and the data collection procedure is carried out using a questionnaire instrument	The sample in this study was WLWH, as many as 748 people who attended three selected hospitals in the state of Niger, Nigeria. The inclusion criteria were as follows: participants had to be women diagnosed with HIV for not less than 4 months, were 18 years and over, and had not been on ART for less than 3 months.	• The results of the study obtained an average score of social support (52.36 ± 10.17), resistance (60.14 ± 12.67), stress perception (26.46 ± 4.81) • These findings indicate that the relationship between social support and resilience among women with HIV showed a significant relationship with (P=0.01) • Social support is a buffer of resilience so as to prevent the effects of life stress experienced.
Effect of Resilience and Social Support on Immune - Activation in HIV-Positive People (Hena Khan, 2015) India	The aim of the study was to examine the effect of resilience and social support factors on immune activation among people with symptoms of HIV and AIDS.	In cross-sectional research, the data collection procedure was carried out using a questionnaire instrument	The number of samples was 40 people living with HIV, with criteria ranging from 21 to 55 years old, taking ARV drugs or antiretroviral therapy (ART) for a duration of at least six months. The sample was selected by purposive sampling.	• The results obtained the average score of social support between men 46.85 (19.00)and girls44.15 (18.89), while the average endurance score for males is 29.05 (5.79) for females 29.55 (8.08). • These findings showed a significant correlation between social support and resilience with (P=0.01) • The regression analysis results for the influence of contributions showed that social support and resilience predict immunity in PLWHA. • Social support accounted for 43.9 percent of the variance in CD4 scores. Meanwhile, resilience accounted for 4.8 percent of the variance in CD4 scores.

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whom disclose their HIV status to their partners and other family members. (Zang et al., 2014). However, families can not meet all the social and medical needs of PLWHA. They may seek support from others, especially medical professionals, outside the family. However, support from family became the most important thing for people with HIV.

Social support played an important role in increasing resilience, as several articles have found (Rzeszutek et al., 2017; Huang et al., 2018; Catabay et al., 2019; Wen et al., 2020) explained that social support came from the family as a buffer for high resilience. If the perceived support is high, then a person's resilience will also be high. The role of social support in increasing resilience has a positive effect on people living with HIV/AIDS, including from research by Wen et al., 2020) that social support has a direct effect on depression 0.19. These findings suggested that social support can increase a person's resilience as well as reduce symptoms of depression. When the resilience of people living with HIV develops and increases, the individual will show optimism and positive thinking so that it will create a calm atmosphere and reduce psychological symptoms such as stress and depression. Adamu et al. (2019) also explained that social support is a buffer of resilience so as to prevent the effects of life stress experienced.

In addition, social support was also an intermediary in reducing the use of drugs and harmful substances. As explained by Rzeszutek et al. (2017), social support increased resilience and contributed to preventing the use of harmful substances. A study revealed that psychosocial stress among PLWHA may be related to socioeconomic status, poor family and support systems, stigma, and discrimination. (Aransiola et al., 2014) increasing resilience is a very important thing that must be improved to prevent mental health problems and improve health and well-being (Lyons et al., 2016). Therefore, social support was very important because of the presence of someone, both family and friends, who provide support for PLWHA, so that they can share with each other and can create positive feelings and not feel lonely, so as to reduce the psychological symptoms they feel. As a result, people with HIV did not need more sedatives. Besides, according to Wen et al., 2020), good social support will form good resilience and can positively increase adherence to ART therapy. This was in line with Hena Khan (2015) that social support also contributed to an increase in the CD4 count of people living with HIV/AIDS.

The limitations of this study include the number of articles used in 8 articles, besides that the results of this study were not strong enough to conclude a causal relationship between social support and resilience in people living with HIV/AIDS because the articles obtained were generally cross-sectional, although there were several articles. Others used a cohort study. Meanwhile, the strength of this research was that it went through a systematic literature review process, starting from determining keywords to searching for literature and then filtering and selecting quality articles that can meet the requirements for critical appraisal. For this reason, further research was needed on social support and resilience with an approach of *Randomized Controlled Trial* (RCT) to find an accurate causal relationship between these variables.

CONCLUSION

Based on a systematic literature review process that has been carried out, several things can be concluded. The first sources of social support came from family, friends, and other people. But the most felt source of support is support coming from the family by 30.4%. Finding this showed that the type of support that had the most significant effect was the support that came from the family with (P=0.001). The

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family was the closest person family member, so they became the main source of strength. The presence of the family to provide support was very important so that the individual did not feel alone when facing challenges and difficulties.

The second is the role of social support in increased resilience in PLWHA. Social support from family and close friends mediated resilience with health and well-being for PLWHA because social support acted as a buffer for an individual's resilience so as to prevent the effects of life's stressors. Perceived support may also facilitate the use of more adaptive stress coping strategies (r = .25) to prevent and suppress the impact of psychological stress felt by PLWHA so that they can demonstrate the ability to adapt to change and rise and thrive in difficult situations experienced. It will have an effect on reducing the use of drugs or harmful substances. Social support has an indirect effect on increasing ART adherence, which was 0.03 so that social support and resilience predict immunity in PLWHA.

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Research Articles

The potential of ethanol extracts 96% mature Papaya fruit seeds (*Carica papaya L*) as anti-diarrhea medicine

Wilujeng Suciati[1], Sri Wahyu Basuki[2*]

1,2) Faculty of Medicine, University Muhammadiyah of Surakarta

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Correspondence:

swb191@ums.ac.id

ABSTRACT

Mature papaya fruit seeds (*Carica papaya L.)* reduce diarrhea because of phytochemical compounds. This study aimed to determine the potential of 96% ethanol extract of mature papaya fruit seeds as antidiarrhea. This study used experimental laboratory research with pre and post-test with control group design. The research subjects were 25 mice divided into 5 groups, KI group (negative control), KII (positive control) loperamide, and KIII-KIV-KV given treatment with a dose (200 mg; 400 mg; 800 mg). A decrease in diarrhea is known by observing the consistency of feces, stool weight, and stool diameter. Data were analyzed by the Kruskal Wallis test and the Mann Whitney Post Hoc test. The results of the consistency of feces in group K(I) were compared with groups of K(II), K(III), K(IV), K(V) p=0.046, 0.083, 0.014, and 0.014. In stool weight K(I) compared to K(II), K(III), K(IV), K(V) with p=0.053, 0.102, 0.016, and 0.053. In the observation of absorption diameter K(-) compared to K(+), KI(200), KII(400), KIII(800) the p=0.121, 0.0197, 0.051 and 0.21. In conclusion, the mature extract papaya fruit seeds can reduce diarrhea seen from the stool consistency in the group extract 400 and 800 mg/Kilograms body weight and fecal weight in the 400mg/Kilograms body weight extract group.

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INTRODUCTION

Diarrhea is still a global disease that occurs in developing and developed countries. Diarrhea increases the expenditure of feces with a softer or more fluid consistency. It can even be water and occurs at least three times in 24 hours (Anggreli *et al*., 2015). Approximately 1.8 billion people die every year worldwide due to diarrhea with complications such as malnutrition and impaired immunity (Kemenkes RI, 2012). Of all child deaths due to diarrhea, 78% occur in Africa and Southeast Asia (Farthing *et al*., 2012). The prevalence of diarrhea in Indonesia is still fluctuating. There are five provinces with the highest incidence of diarrhea; Papua (6.3% and 14.7%), South Sulawesi (5.2% and 10.2%), Aceh (5, 0% and 9.3%), West Sulawesi (4.7% and 10.1%), and Central Sulawesi (4.4% and 8.8%) (Candrasari *et al*., 2011.).

Bacterial and viral infections are the leading causes besides parasites and fungi. The most common bacteria are *Escherichia coli* and *Salmonella* sp. while for the virus most often found in cases of acute diarrhea is Rotavirus (Nurhalimah *et al*., 2014). Based on the results of Bonkoungou's study in Ouagadougou, Burkina Faso with subjects under five years of age found *Escherichia coli* bacteria ranked second in diarrhea at 24% after *Rotavirus* by 30%, *Salmonella* sp. at 9%, *Shigella* sp. at 6%, *Adenovirus* by 5 % *and Campylobacter* by 2% (Marcdante, *et al.*, 2014). Acute diarrhea is caused by an inflammatory process in the intestine or infection that directly affects the secretion of enterocytes and absorption function (Riskesdas, 2013).

Salmonella sp. bacteria adaptive hosts in animals and infections in humans in the gastrointestinal tract, including the stomach, small intestine, and large intestine. Eight to forty-eight hours after food contaminated by *Salmonella* sp., sudden pain arises with soft or runny diarrhea, sometimes accompanied by mucus, blood, nausea, vomiting, fever with a temperature of 38 to 39 degrees Celsius (Siti *et al*., 2015).

Some previous studies explained that some medicinal plants effectively treat diarrhea because of the content of tannins, phenols, saponins, essential oils, alkaloids, and flavonoids such as guava leaves (Bonkoungou *et al*., 2013). Other medicinal plants still not utilized by the community are papaya seeds. The number of papaya production from year to year is increasing. This is in line with the increasing number of papaya seeds produced by the community. Papaya seeds have many benefits as an antibacterial effective against the bacteria *Escherichia colli*, *Salmonella*, and *Staphylococcus* (Irianto, 2013).

The administration of *beluntas* leaf extract contains tannins in male mice induced by *Salmonella typhimurium* bacteria to reduce the antidiarrheal effect (Nurhalimah et al., 2015). In addition, *Carica pubescens* seeds had been proven effective in lowering the diarrheal frequency in mice. Previous research by Purwaningdyah. *et al*. (2015) using papaya seeds can provide antidiarrheal effects. The study showed that papaya seeds with plant compounds could reduce the best dose 800mg / Kilograms body weight. Based on this, researchers are interested in testing the potential of mature ethanol extract 96% papaya seeds as an antidiarrheal drug in mice. The difference from the previous research was the production of 10^7 CFU / ml suspension with 0.2 ml of feed, using mature papaya fruit, and using 96% ethanol. Therefore this study aims to determine the potential of papaya fruit seeds (*Carica papaya L*) mature as an antidiarrheal drug and to know the potential of using dried papaya seeds as a diarrhea drug with the correct dose of use to reduce the use of chemical drugs for the treatment of diarrhea.

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METHOD

This research used experimental research design pretest and post-test with control group design methods. This study was conducted in the Pharmacology laboratory of the Faculty of Medicine, Muhammadiyah University, Surakarta. This study has passed ethical clearance No: 1204 / A-1 / KEPK-FKUMS / V / 2018. This research used the mature papaya fruit seeds (*Carica papaya L*) from the Mojosongo area, Boyolali. This study used 25 Swiss strains of mice using the Federer formula (Pangesti *et al*., 2013).

Making ripe papaya seed extract

The mature papaya fruit seeds (*Carica papaya L*) were washed, weighed, and dried. After washing and drying, the extraction process was carried out on papaya seeds. The process of extracting the dried papaya (*Carica papaya L*) fruit seeds was mashed and immersed in 96% ethanol. It stirred evenly and left to settle filtered with filter paper. Then rotatory evaporator was carried out at 60° C and evaporated with a water bath at 60 ° C until an extract was obtained thick.

Determination of dosage and treatment in test animals

Mice were divided into five groups consisting of 5 mice each group. They were weighed before treatment and then given a suspension of *Salmonella typhimurium* bacteria with a dose of 10^7cfu / ml as much as 0.2 ml (Marcdante, et al., 2014). The mice were observed to have diarrhea. After that, the consistency of feces, stool weight, and feces absorption diameters were observed.

The positive control group was a group of mice treated with loperamide. The recommended dose for diuretic effects is 4 mg/day. Thus, the dose of loperamid for mice was 0.01 mg / 20 grams body weight of mice. Loperamide 0.01 mg is then dissolved in 2 ml of water and given orally.

The negative control group was a group of mice given oral treatment with aqua dest. Group III, IV, and V groups of mice given 96% ethanol extract of papaya seeds ripened at a dose of 200 mg/kilograms body weight, a dose of 400 mg/kilograms body weight, and a dose of 800 mg/kilograms body weight were dissolved in 2 ml of aqua dest orally. Then observe the mice until the mice do not experience diarrhea for 10 hours.

RESULTS

The yield is 11.91% because it gets 123 grams of thick extract of ripe papaya fruit seeds from 1033 grams of Simplicia. Stool weight observations were made from the beginning before the diarrhea was 0.1 to 0.4. At the time of administration with *Salmonella* bacteria, the mice were diarrhea on filter paper. The feces of mice weighed with an average of 1.03grams, the positive control group averaged 1.04 grams, ripe papaya seed extract 200 mg/kilograms body weight averaged 1.025 grams, papaya fruit extract 400 mg/Kilograms body weight mean stool weight of 1.042gram and ripe papaya fruit seed extract 800 mg/Kilograms body weight with an average of 1.033 grams. Observation of feces consistency and feces absorption diameters on filter paper showed stool consistency in *Salmonella*-induced mice, which was soft and runny after administration of extract papaya fruit seeds did not get stool consistency and diameters of feces uptake in mice, or the result is zero.

Chi-square test results on the addition of feces consistency p-value = 0.005 and expected value of less than five there is 100% number of cells. The results of stool consistency did not meet the chi-square requirements, so an alternative test with the Kruskal Wallis test results p-value = 0.007. It showed a relationship between fecal consistency in the treatment group followed by the post hoc test.

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Shapiro Wilk test results on feces weight value p = 0.000 and feces absorption diameter p = 0.266. After extracting, the drug obtained stool weight p = 0.000 and absorption diameter p = 0.000. The distribution of feces weight data after extract and drug treatment obtained a value of p <0.05, indicating that the data distribution is not normal.

Based on Table 5, the Kruskal Wallis test of each group by observing the consistency of feces, feces weight, and diameter of feces absorption showed no statistically significant differences. In Table 6, there is a significant difference because mice do not experience diarrhea. This shows that mature papaya fruit extract (*Carica papaya L*) has the potential to reduce diarrhea by observing fecal consistency, absorption diameter, and stool weight.

Table 1. Results of Kruskal Wallis Test After Giving Medication and Extract

Antidiarrheal observation	P-Value	Interpretation
Stool consistency after administration of extracts and drugs	0.007 *	There are differences
Stool weight after administration of extracts and drug	0.008 *	There is a difference
Diameter of fecal absorption after administration of extracts and drugs	0.008 *	There are differences

* Different meaningful (p <0.05)

Table 2. Results of the Mann Whitney Antidiare Test on Stool Consistency Observations

Group	P-Value	Interpretation
Negative controls - Positive controls	0.046 *	There are differences
Negative control - 200 mg extract	0.083	There is no difference
Negative control - Extract 400 mg	0.014 *	There is a difference
Negative control - Extract 800 mg	0.046 *	There are differences
Positive control - Extract 200 mg	1000	There is no difference
Positive control - Extract 400 mg	1000	There is no difference
Positive control - 800 mg extract	1000	There is no difference
200 mg extract - Extract 400 mg	1000	There is no difference
200 mg extract - 800 mg extract	1000	There is no difference
400 mg extract - 800 mg	1000	extract There is no difference

* Different meaningful (p <0.05)

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Table 3. Mann Whitney Antidiare Test Results in Observation of Absorption Diameter

Group	P-Value	Interpretation
Negative control - Positive control	0.121	There is no difference
Negative control - 200 mg extract	0.197	There is no difference
Negative control - Extract 400 mg	0.051	There is no difference
Negative control - 800 mg extract	0.121	There is no difference
Positive control - Extract 200 mg	1000	There is no difference
Positive control - Extract 400 mg	1000	There is no difference
Positive control - 800 mg extract	1000	There is no difference
200 mg extract - Extract 400 mg	1000	There is no difference
200 mg extract - 800 mg extract	1000	There is no difference
400 mg extract - 800 mg extract	1000	There is no difference

* Different meaningful ($p < 0.05$)

Table 4. Mann Whitney Antidiare Test Results in Stool Weight Observation

Group	P-Value	Interpretation
Negative control - Positive control	0.053	There is no difference
Negative control - 200 mg extract	0.102	There is no difference
Negative control - Extract 400 mg	0.016 *	There are differences
Negative control - 800 mg extract	0.053	There is no difference
Positive control - Extract 200 mg	1000	There is no difference
Positive control - Extract 400 mg	1000	There is no difference
Positive control - 800 mg extract	1000	There is no difference
200 mg extract - Extract 400 mg	1000	There is no difference
200 mg extract - 800 mg extract	1000	There is no difference
400 mg extract - 800 mg extract	1000	There is no difference

* Different meaningful ($p < 0.05$)

To find out the differences between before and after extracts administration can be seen in Tables 5 and 6 below:

Table 5. Results of Kruskal Wallis Test Before Giving Medication and Extracts

Antidiarrheal Observation	P-Value	Interpretation
Stool consistency before administration of extracts and drugs	0.499	There is no difference
Stool weight before administration of drugs and drugs	0.889	There is no difference
Diameter of fecal absorption before administration of extracts and drugs	0.873	There was no difference

* Different meaningful ($p < 0.05$)

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Table 6. Results of the Kruskal Wallis Test After Giving Medication and Extracts

Antidiarrheal Observation	P-Value	Interpretation
Stool consistency after administration of extracts and drugs	0.499	There is no difference
Stool weight after administration of adhesives and drugs	0.889	There is no difference
Diameter of fecal absorption after administration of extracts and drugs	0.873	There was no difference

* Different meaningful ($p < 0.05$)

DISCUSSION

This study observed stool consistency of diarrhea mice. The parameters of this diarrhea are marked with stool along with the diameter of feces absorption on filter paper. This study found that feces consistency in Salmonella-induced mice was soft and runny due to bacterial infection, which caused intestinal hyper peristaltic and released a lot of fluid (Nurhalimah, 2014). In the chi-square test, fecal consistency was obtained $p = 0.005$, and the expected value of less than five there were 100% of cells. The results of stool consistency did not meet the chi-square requirements, so an alternative test with the Kruskal Wallis was obtained $p = 0.007$, which showed a relationship between fecal consistency in the treatment group then followed by the post hoc test.

The Mann-Whitney Post Hoc test showed a value of $p < 0.05$ found in the ratio between negative controls with positive controls, negative controls with extracts of 400 mg / Kilograms body weight, and 800 mg/ Kilograms body weight. These findings indicate significant differences in the observation of stool consistency. This is in line with the research of Purwaningdyah *et al.* (2015), where there was a decrease in stool consistency after administering papaya fruit extract.

Mice experience diarrhea after administration of *Salmonella* bacteria. The *Salmonella typhimurium* bacteria invaded the small intestinal mucosa, expelling the toxin to stimulate the intestinal epithelium. This stimulation can increase the intestinal peristaltic and secretes a lot of fluid. In the Kruskal Wallis test, the stool weight between diarrhea and after administration of extracts of loperamide and drug showed significant differences. These results are in line with Purwaningdyah. *et al.* (2015). The study showed decreased fecal weight after administering extracts and loperamide (Wijayanti *et al.*, 2017). The extracts and loperamide slow down the movement of intraluminal fluid and allow more absorption and reduced motility (Purwaningdyah *et al.*, 2015).

The Mann-Whitney Test aimed to compare between groups of fecal weight treatment, namely the negative control group-group III extract of 400 mg/Kilograms body weight obtained $p = 0.016$ ($p < 0.05$). It means that there was a difference in the weight of stool without treatment and given papaya fruit extract ripe at a dose of 400 mg/Kilograms body weight. This result is different from the previous study. The most effective dose to reduce fecal weight is papaya seed extract at a dose of 800 mg/ Kilograms body weight (Wijayanti *et al.*, 2017).

The Mann-Whitney test was also used to compare the positive control group of extracts of papaya fruit (*Carica papaya L*) ripe. There is no difference between the groups. These results are similar to the research conducted by Fristia

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(2011). The study tested the antidiarrhea effect with ethanol of papaya leaves in mice. The study showed that papaya leaves did not have antidiarrheal effects by not reducing the weight of feces.

From the results of this study in the positive control group (extracts of papaya fruit seeds with doses of 200 mg, 400 mg, and 800 mg), the stool production was zero. Loperamide drugs and extracts can slow gastrointestinal motility through the circular and longitudinal muscles of the intestine. Tannin from papaya fruit seeds extracts functions as an astringent that can bond and form a membrane on the microbial reaction. So that condensed oil can be used for treatment in a mixture of less lost liquid from the digestive tract. Tannin binds to the tannate protein to facilitate the amino acid to be absorbed by the body, then attaches to the malein through the body to reduce the secretion of liquid and nasal mucus, which results in constipation (Riddle *et al*., 2016).

The p-value = 0.08 was obtained at the stool weight after drug administration and papaya seed extract in the Kruskal Wallis test. Statistically, it shows a significant difference from diarrhea until after the extract and loperamide drug was given. This research aligns with previous research conducted by Nurhalimah *et al.* (2015). This shows that ripe papaya seeds contain tannins which can suppress intestinal motility so that fluid discharge decreases (Enda, 2017). This study is also in line with Nurhalimah's research *et al*. (2015), which decreases fecal diameter after administration of *beluntas* leaf extract (Riddle *et al*., 2016).

Antidiarrheal studies can be shown to reduce diarrhea compared to the negative control group by observing feces weight and diameter of feces uptake. While the statistical test of the ethanol extract group of ripe papaya fruit seeds at doses of 400 mg/Kilograms body weight and 800 mg/Kilograms body weight can reduce the effects of diarrhea by decreasing fecal weight and stool consistency.

Papaya seeds contain alkaloids as antibacterial. Papaya seeds contain alkaloids, steroids, phenols, tannins, essential oils, terpenoids, and saponins (Irianto, 2013). The mechanism of action of phenols as an antibacterial is by denaturing cell proteins. Hydrogen bonds formed between phenols and proteins cause protein structures to become damaged (Zarghami *et al*., 2017). The mechanism of action of alkaloids as an antibacterial disrupts the constituent components of peptidoglycan in bacterial cells. The cell wall layers are not formed intact and cause cell death. The mechanism of action of flavonoids as an antibacterial can be divided into three: inhibiting the synthesis of nucleic acids, inhibiting the function of cell membranes, and inhibiting energy metabolism. The mechanism of action of saponins as an antibacterial is by causing leakage of proteins and enzymes in cells, and cell death occur (Enda, 2017).

A limitation in this study is that no quantitative phytochemical tests were carried out to find out what percentage of tannin was obtained from the extraction results and observations when diarrhea occurred in each test animal.

CONCLUSION

The mature extract papaya fruit seeds have the potential to reduce diarrhea. This study showed that feces weight and diameter of feces uptake reduced compared to the negative control group in animal tests. In addition, the statistical test of the ethanol extract group of ripe papaya fruit seeds at doses of 400 mg/Kilograms body weight and 800 mg/Kilograms body weight can reduce the effects of diarrhea by decreasing feces weight and stool consistency.

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Research Articles

Mapping of antibiotic resistance in multi-drug resistance tuberculosis at RSUD Arifin Achmad, Riau Province

Andralia Mayangsasati[1] , Sri Sundari[2]

1,2) Department of Hospital Administration, Universitas Muhammadiyah Yogyakarta, DIY Yogyakarta, Indonesia

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Correspondence:

swb191@ums.ac.id

ABSTRACT

Tuberculosis is a disease caused by the bacteria *Mycobacterium tuberculosis*. Resistance is a condition where an antibiotic is not able to kill *Mycobacterium tuberculosis*. The type of research used is descriptive with a mixed-method approach. It was found that most MDR-TB patients were male (67.2%), aged 41-50 years (26.9%), and lived in Pekanbaru City (65.7%). There were 30 patients (44.8%) who underwent microscopic examination, 12 patients (44.4%) who had a previous medical history of TB disease who had been informed finished taking medication by their doctors. Nine patients (33.3%) with a history of inadequate TB treatment. Three patients (11.1%) were confirmed as a treatment failure. Three patients (11.1%) were primary TB and confirmed the result of laboratory tests for resistance to anti-TB drugs. MDR TB patients who smoke were nine patients (33.3%), and DM patients were two people (7.4%). So, information about the characteristics of Multi-Drug Resistance Tuberculosis is needed, and it is hoped that appropriate treatment can be given.

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INTRODUCTION

Tuberculosis is a disease caused by the bacterium *Mycobacterium tuberculosis* . This disease can affect all ages and genders. This disease worldwide shows morbidity and mortality that increases with age. (Marçôaa, Ribeirob, & I. Zãoc, 2018). The occurrence of resistance of M. tuberculosis to Anti Tuberculosis Drug (ATD) is a problem encountered in TB treatment. This resistance is a condition where ATD is not able to kill M. tuberculosis germs (Kemenkes, 2013). The resistance of TB bacteria to ATD has been around for a long time.

Indonesia is ranked 8th out of 27 countries with the highest MDR TB burden in the world with an estimated MDR TB patient in Indonesia there are 6,800 new cases of TB with Multi Drug Resistant Tuberculosis (MDR TB) every year (WHO, 2017). The MDR TB rate is estimated at 2% of new TB cases and 12% of re-treated TB cases. 55% of Multi Drug Resistant Tuberculosis (TBMDR) patients have not been diagnosed or received treatment properly (Ministry of Health, Technical Instructions for Integrated Management of Drug Resistant Tuberculosis Control, 2013). The Data and Information Center of the Ministry of Health of the Republic of Indonesia (2014) recorded that in 2009 there were 66 patients with MDR TB in Indonesia, in 2010 there were 216 patients, in 2011 there were 460 patients, in 2012 there were 696 patients, in 2013 there were 1,094 patients, in 2014 as many as 1,752 patients, in 2015 as many as 1,860 patients. The data shows an increase in the number of MDR TB sufferers every year in Indonesia (Kemenkes, 2016). The number of deaths per week is 52,000 people or every day more than 7000 people die (Rattan, Kalia, & Ahmad, 1998).

The presence of multiple drug resistance (MDR=multiple drug resistance) against Mycobacterium tuberculosis is reflected in the increasing number of new cases and mortality rates and the lack of successful treatment of tuberculosis. Treatment of tuberculosis requires a long and adequate time, this is a public health problem throughout the world.

METHODS

This study was done from January to March 2021. The type of research used is descriptive with a mix method approach. The mix method research is a research that uses two methods, two methods, namely quantitative, namely the prevalence of patients suffering from MDR TB and qualitative, namely the results of interviews with specialist doctors to determine the cause of resistance in a single study.

The data was processed with the help of data processing application software and analyzed univariately to describe the characteristics of the respondents (gender and education) and to determine the frequency distribution of each variable, and bivariate analysis. Then use the type of qualitative descriptive research with a phenomenological approach. Data obtained by conducting in-depth interviews. Interviews were conducted for approximately 30 minutes, conducted online in January 2021. The number of questions asked to the respondents was 39 questions.

Inclusion criterias for this research are inpatient and outpatient of RSUD Arifin Achmad with Multidrug Resistance Tuberculosis from 2020 to 2021 who are willing to be the object of research and interviewed. Meanwhile exclusion criterias are patients who are sensitive to ATD and who are rejected to be the object of research

Ethical Clearance: No: B/005/ UNI9.5.1.1.8/ UEPKK/2021

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Table 1. Characteristics of Research Subjects

Variable	Frequency	Percentage
Sex		
Male	45	67,2
Female	22	32,8
Age		
< 21 tahun	3	4,5
21-30 tahun	11	16,4
31-40 tahun	12	17,9
41-50 tahun	18	26,9
51-60 tahun	16	23,9
> 60 tahun	7	10,4
Residence		
Bengkalis	1	1,5
Indragiri Hulu	3	4,5
Kampar	10	14,9
Kodya Jakarta Timur	1	1,5
Kota Pekanbaru	44	65,7
Kota Tebing Tinggi	1	1,5
Kuantan Singingi	1	1,5
Pelalawan	2	3,0
Rokan Hilir	2	3,0
Rokan Hulu	1	1,5
Siak	1	1,5
Total	67	100,0

RESULTS

This research was conducted at Arifin Achmad Hospital, Riau Province in December 2020 - January 2021. The data of this study were obtained through recording from the medical records owned by the hospital. This study involved 67 patients as research subjects. The characteristics of the subjects of this study are shown in the table below.

It is shown in the table above that the majority of the research subjects are male age 41-50 years old and live in Pekanbaru

Theme Determination Process

The process of determining the theme in this study was obtained from the results of FGD (focus group discussion) data analysis using a qualitative data processing scheme from Creswell in 2017. Based on the results of data analysis, 4 themes were obtained (4 or 5), Theme 1) Previous TB history, supported by 3 categories, namely primary TB, secondary TB, and suspected secondary TB. Theme 2) Risk factors for MDR TB are supported by 4 categories, namely Primary TB, Relapsed Patients, Inadequate Medication History, and Treatment Failure. Theme 3) Patient knowledge of TB treatment methods which is supported by 4 categories, namely; patients who know that if they discontinue the treatment, they have to start from the beginning, patients who do not know if they discontinue the treatment, they have to start from the beginning, patients who know that TB treatment must be complete (uninterrupted), and patients who do not know that treatment TB must be complete (uninterrupted). Theme 4) Medication compliance, which is supported by 2 categories, compliant patients and non-compliant patient. Theme 5) Patient

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compliance to repeat sputum tests, supported by 2 categories namely; patients who know the need for repeated sputum tests and patients who do not know the need for repeated sputum tests.

Theme I: Medical Record/History of previous TB

A. Primary TB

The respondents are MDR TB patients who sought treatment at the Arifin Achmad Hospital. He told about his history of previous illnesses. The patient admitted that this was the first time they had TB without a previous medical history of TB disease. There were 3 patients who immediately suffered from MDR TB.

B. Secondary TB

The next respondents told about their previous medical history of TB. It was not their first time had TB. The patient had experienced a similar illness and had completed his treatment.

Patient 1 had a previous medical history of TB category 1, and had been on treatment for 6 months, but after the treatment, the patient was not advised by the doctor to do a sputum test. There is a possibility that the patient's treatment was not successful and the patient is a patient with MDR TB from the beginning.

Patient 2 had a medical record/history of previous TB category 1, but the patient performed sputum test regularly for treatment evaluation. At the end of the treatment the patient had finished taking the medicine and was confirmed cured by the test results. But in early 2020 the patient experienced similar symptoms and later developed MDR TB.

C. Secondary TB suspects

The next respondent told about his medical history of previous illnesses that had similar symptoms of TB but had never been diagnosed with TB.

Patient 3 had a medical history of a prolonged cough before, but when he went to the doctor, the patient was diagnosed with bronchitis and was programmed to take medicine for 6 months. There was no treatment for bronchitis for 6 months, which means that the patient had TB but the doctor did not tell and inform the patient the actual diagnosis and disease, and how to take medication, so the patient stopped the treatment himself after 1 month.

Patient 4 has the possibility of being misdiagnosed, she was diagnosed with the fungal disease which led to mistreatment that caused the patient to become resistant to first-line anti-TB drugs.

Theme II: Risk Factors of TB MDR

A. Primary TB

The respondent said that this was the first time he had been sick with MDR TB. The patient previously had no history of similar illness and inadequate TB treatment. He did not have a medical history of coughing for a long time since his childhood until he got the illness.

This was the first time Patient 5 had TB, the doctor checked for sputum and drug resistance and the results were positive, the patient was directly being put in the MDR TB treatment program for 2 years.

Just like patient 5, patient 6 also had no previous history of TB disease. The patient immediately suffered from drug-resistant TB for the first time. But the patient had a history of a long cough that was not diagnosed by the doctor when the patient was young.

Patient 7 said that there was a neighbor who had lingering cough, it was possible that the patient was exposed to TB but did not realize that he was infected and then did not take any medicine, or he was infected MDR TB from his neighbor

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B. Relapsed Patients

The next respondent told that he had a previous medical history of TB (Category 1), then he experienced the same symptoms and was diagnosed with TB again but this time it is MRD TB.

According to patient 8, there was no repeated sputum test and the patient had been confirmed cured by the doctor and did not need any further treatment.

In contrast to patient 8, patient 9 had completely recovered, which was confirmed by laboratory results but later she is reinfected.

C. Inadequate Medical History

Patient 10 has a history of TB disease but he had an inadequate treatment. The patient dropped out of treatment because he had difficulty to pay for the transportation, and the patient did not have a companion to assist him during treatment.

Patient 11 had been sick with TB before (10 years ago) but he experienced disturbing side effects every time he took the medicine, so that the patient felt unable to continue the treatment, and stopped it by himself without telling or consulting with the doctor.

D. Failed treatment

Patient 12 was diagnosed with a category 1 TB patient, but at the end of the treatment, there was no improvement in the sputum test result, then the patient was referred and tested for drug resistance and the result was positive.

Theme III: Patient knowledge of TB treatment

A. Patients know that if they drop out, they have to start over

The following informant tells about what he knows about TB treatment

Patient 13 knew that treatment must be repeated from the beginning if he missed taking the medicine. He knew this because his doctor had provided him with good education/knowledge about TB.

B. Patients do not know that if they stop taking the drug/medication, they have to start the treatment from the beginning

The following respondent differs from the previous respondent regarding what he knew about TB treatment.

Patient 14 did not know that if a patient stops taking the drug before completing the treatment program, he must start again from the beginning. The patient did not remember the doctor ever inform/educate him about this.

Patient I5 said he didn't know if he dropped out of treatment he had to start from the beginning. This happened due to the lack of information from the doctor.

C. Patients know that TB treatment must be complete and should not be interrupted

This respondent said that he knew the treatment of TB. This treatment must be completed and patients should not stop the treatment by themselves without consulting with the doctor.

Patient 16 knew that TB treatment must be carried out according to the specified time, cannot be discontinued, which is 6 months for category 1 and 2 years for MDR TB

D. Patients do not know that TB treatment must be complete and should not be discontinued

The following respondent tells about his experience of dropping out of medicine before the due date.

Due to a lack of education from the doctor, patient 17 did not know that TB treatment must be completed for 6 months, which caused the patient to stop taking medicine once the medicine from the doctor ran out.

At the beginning of the treatment, patient 18 was actually given education by the doctor,

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but the patient admitted that he did not really understand that TB treatment must be done completely.

Theme IV: Medication Adherence

A. Patients medication adherence is good

The next respondent told how he took his medicine correctly and regularly

Patient 19 said that he had never missed taking TB drugs or missed going to the puskesmas (Community Health Center) during his illness

b. Patients do not comply taking medication

The following respondents told the reasons why they were not obedient in taking medicine

Patient 20 said that he had forgotten to take his medicine so it caused the patient missing one schedule

Patient 21 said that he had missed taking medicine once because he had not had time to take medicine at the *puskesmas* (Community Health Center), but then he continued to take medicine accordingly.

Patient 22 said that due to financial problem, he could not afford to go to the *puskesmas* (Community Health Center) to take the medicine.

Theme V: Patients' compliance with repeated sputum tests

A. patient knows the need for re-examination of sputum

The next respondent said that he did not know about the need for a repeat sputum examination/test

Patient 23 did not know the need for a sputum examination for treatment evaluation. The doctor did not suggest him to do it.

B. patient does not know the need for re-examination of sputum

Unlike the previous respondent, the following respondent E always checks sputum regularly.

Patient 24 received good information/education to check sputum for evaluation of the treatment

DISCUSSION

The results of this study indicate that most of the subjects in this study were male (67.2%), the majority aged 41-50 years (26.9%), and the majority lived in Pekanbaru (65.7%). One study that showed relatively identical results was a study conducted by Huda (2017) at RSUD (Regional Public Hospital) Dr. H. Abdul Moeloek Lampung Province. This descriptive study involving 246 people aims to determine the description of patients with Multi Drug-Resistant Tuberculosis (MDR TB) in RSUD dr. H. Abdul Moeloek Lampung Province period January-December 2015. The result of this study showed that patients who experienced rifampicin resistance based on the age of MDR TB patients were the group 26-45 years with 15 patients (51.72%), group 12-25 years with 9 patients (31.03%), group 46-65 years with 5 patients (17.24%), and the lowest > 66 years 0 patients (0%). Based on sex, most MDR TB patients were female which were 15 patients (51.72%), while male 14 patients (48.27%) (Huda, Safitri, & Marhamah, 2018)

Productive age is an age group that is a risk factor for MDR TB. This age group is the group that is more easily exposed and infected by MDR TB because they interact more with other people and have high mobility. Male are more at risk of developing MDR TB than female. This is presumably because women are more easily worried about being ostracized by their family and environment if they are proven to have a contagious disease such as TB. In addition, the male is generally the breadwinner of the family and is more active outside the home, so it is easy to be exposed and infected with MDR TB from other people (Nunkaidah, Lestari, & Afa, 2017)

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However, different results were obtained in Fadlilah's (2021) study, which showed that the majority of MDR TB patients were aged 26-33 years old. In terms of age characteristics, it can be seen that the results of the research conducted by the researcher are in line with (Fadlilah, 2021) study, in which was the majority of MDR TB patients were male.

Smoking habit is more common in male patients. Smoking makes a person more susceptible to tuberculosis, and the death rate from TB is higher in smokers compared to nonsmokers. Smoking habits can also damage the lung defense mechanism called mucociliary clearance. In addition, cigarette smoke increases airway resistance and causes easy leakage of blood vessels in the lungs will also damage macrophages which are cells that can eat nuisance bacteria. The increasing number of TB patients can create a new problem: the increasing number of patients with MDR-TB. Several other studies have found that children who are exposed to cigarette smoke (passive smoker) are also more likely to get TB later. It was also found that TB in smokers is more contagious than TB patients who do not smoke. Smoking habit is also a factor in the progression of pulmonary tuberculosis and the occurrence of fibrosis (Suyastri, Ermayanti, & Russilawati, 2019). In this study, MDR TB patients who smoke are 9 out of 15 male patients (60%).

The Identical results were also obtained in a study conducted by Hendra (2017) at the Haji Adam Malik General Hospital in Medan. This descriptive study with a cross-sectional design involving 178 people was aimed at knowing the characteristics of MDR-TB patients with comorbid DM. The results of this study showed that resistance to rifampin was found in all TBMDR patients with DM (Hendra, 2017).

This study showed that there were only 24 patients (35.8%) who underwent HIV testing. The study subjects who underwent HIV test, the majority showed negative results, there was only 1 person (4%) who showed a positive result. Globally, there were 10.4 million TB cases in 2016, and 10% of them were co-infected HIV. In individuals with HIV, the risk of developing TB is up to 26 times higher than in the general population, even in HIV patients who have relatively high CD4 cells (Tornheim & Dooley, 2018). TB-HIV coinfection occurs through several mechanisms, namely HIV-1 inhibition of the development of T cells that are reactive to M. tuberculosis, inhibition of phagocytosis and autophagy in macrophages, macrophage death and tissue necrosis in HIV-1 coinfection, and hypersensitivity reactions known as TB immune reconstitution inflammatory response syndrome (TB-IRIS) (Bell & Noursadeghi, 2018)

Furthermore, based on in-depth interviews conducted to 27 patients, it was found that 12 patients had a history of category 1 TB, which then relapsed, 9 patients had a history of drug withdrawal, 3 patients had a failed treatment and 3 patient were primary cases. In 12 patients who relapsed, mostly due to there was no follow-up after the completion of treatment, it is impossible to know the treatment results for 6 months, whether it works or not. The doctor who treated the patient did not recommend re-examination and stated that the patient had finished treatment after 6 months. There is a possibility that the patient has not recovered and is not continuing treatment. Then the patient was reinfected and became a case of MDR TB.

However, a few patients have been confirmed cured by repeated examinations, but then they were reinfected. Drug resistance is related to previous treatment history. In patients with a history of previous treatment, developing resistance is 4 times higher, while the occurrence

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of MDR is 10 times or more compared to patients who have never been treated (Nofizar, Nawas, & Burhan, 2010).

According to many studies the strongest risk factor for MDR TB is the history of previous treatment with Anti Tuberculosis drugs. One of the studies that prove a very strong relationship between risk factors of previous TB treatment and MDR TB is a study conducted (Balaji, 2010). In 9 patients who had a history of dropping out of treatment, there were patients who were not informed/educated by doctors about TB treatment, patients with poor economic conditions and patients who could not handle the side effects of the medicine that caused inadequate treatment and the patients became resistant to anti-TB drugs.

TB patients with inadequate previous treatment and experiencing higher anti-TB drugs resistance (96.2%) than TB patients who recovered (23.1%). Statistical test results obtained p value = 0.001 and OR = 40.0 (95% CI: 4.66 - 343.14), meaning that the previous treatment was inadequate as a cause of anti-TB drugs resistance. TB patients with inadequate previous treatment were at risk of developing resistance 40 times higher compared to TB patients with adequate treatment (analytical journal).

Sri Melati's research (2010) showed that the results of treatment carried out on MDR-TB patients at the pulmonary polyclinic were 32 (34.5%) MDR-TB dropouts, 26 (27.9%) failed MDR-TB, and 16 (17.2%) %) patients are still on MDR-TB treatment. Patients with complete treatment of MDR-TB 11 patients (11.8%), MDR-TB patients who were considered completed MDR-TB treatment 6 (6.0%) and MDR-TB patients who recovered were 2 (2.1%). It can be concluded that patients with a history of dropping out of treatment are the most common risk factors for MDR TB (Munir, 2010).

Inadequate management of TB as a cause of resistance can be viewed from the side of the service provider/health worker due to incorrect diagnosis, the treatment that does not use the right combination of dose, type, and inadequate amount of medication, duration, and counseling to the patients. Most of the respondents who suffered from MDR TB had an accurate diagnosis status in the previous TB treatment. Only 7 respondents were not right in carrying out the initial diagnosis of TB treatment (only used chest X-rays photo without carrying out the bacteriological examination.)

In research subjects who showed positive results on microscopic examination, there were 2 people (3%) positive 1, 5 people positive 2 (7.5%), and 1 person (1.5%) positive 3. A positive result 1 means that 10-99 Acid Fast Bacilli (AFB) is obtained in 100 fields of view, a positive result 2 means that 1-10 AFB is obtained per field of view, and a positive result 3 means that more than 10 AFB is obtained per field of view (Bakti, Mertaniasih, Ernawati, Soebadi, & Hadi, 2018). Uniquely, all patients who were the subjects of this study were MDR TB patients, so microscopic examination should have shown positive results. However, this result is reasonable, similar to the results found in the Rasool (2019) study in Pakistan. The study found that 34.52% of culture-positive TB patients showed negative results on AFB examination (Rasool, Khan, Mohy-Ud-Din, & Riaz, 2019). This result may be due to inadequate sputum samples used as examination material so that the results of the smear examination cannot describe the actual conditions in the lungs.

Several previous studies have shown different results from the research that researchers have done. One study that showed different results was obtained in a study in Southeast Sulawesi. This descriptive study involving 40 people aims to explain the characteristics of MDR TB patients in Southeast Sulawesi in 2014-2017.

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The results of the study showed that the majority of MDR TB patients in Southeast Sulawesi in 2014-2017 showed positive microscopic examination 1 (Aini & Rufia, 2019)

This study shows the result from mapping the MDR TB patient in RSUD Arifin Achmad and shows the characterictic of the patients, also shows an in-depth interview to find the risk factors of MDR TB. However, since there's no limitation to when the patients diagnosed with TB, the interview relied on the patients' memory. It would be better if there is a future study with longer period of time and has patients with ongoing treatment as subjects.

CONCLUSION

Most of the MDR-TB patients at the Arifin Achmad Hospital, Riau Province, were male (67.2%), aged 41-50 years (26.9%), and lived in Pekanbaru City (65.7%). There were 30 patients (44.8%) who underwent microscopic examination; the majority (73.3%) showed negative results. Twenty-five patients (37.3%) underwent culture examination; the majority (76%) showed negative results. Most MDR-TB patients in Arifin Achmad Hospital, Riau Province (80.6%) had rifampin resistance results based on TCM examination. 7 patients (10.4%) underwent LPA Line II examination. All patients showed positive results. There were 24 patients (35.8%) who underwent HIV testing. In patients who underwent HIV testing, the majority (96%) showed negative results. There were 12 patients (44.4%) who had a previous history of TB disease who had been declared finished taking medication by a doctor. 9 patients (33.3%) with a history of inadequate TB treatment. 3 patients (11.1%) were declared treatment failure. 3 patients (11.1%) were primary TB and confirmed the laboratory examination results for resistance to OAT. Smoking and DM are not very influential as risk factors for MDR TB. Nine MDR TB patients smoke (33.3%) and 2 DM patients (7.4%).

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Research Articles

Mapping and determining priority areas interventions for toddler diarrhea in Surabaya

Yuli Puspita Devi[1], Sofwatun Nida[1], Muthmainnah Muthmainnah[2,3], Martya Rahmaniati Makful[1]

1) Faculty of Public Health, Universitas Indonesia, Depok, Indonesia
2) Doctoral Program, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
3) Department of Epidemiology, Demography Biostatistics and Health Promotion and Behaviour, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

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Correspondence:

yuli.puspita@ui.ac.id

ABSTRACT

Diarrhea is still the second leading cause of death in toddlers besides pneumonia. The highest number of cases of diarrhea in toddlers in East Java is Surabaya. This study aimed to describe the distribution of toddler diarrhea based on risk factors using a regional mapping approach in Surabaya. This study was an ecological study with a regional mapping approach. The independent variables used as risk factors for toddler diarrhea were healthy latrines, drinking water facilities, open defecation free (ODF), and complete basic immunizations. The unit of analysis used was the districts that were processed from the Surabaya Health Profile data in 2019. Results showed most cases of diarrhea under five occurred in Wonokromo, Sawahan, Tambak Sari, and Kenjeran Districts. There was a significant relationship between toddler diarrhea and complete basic immunization (p = 0.008), while the relationship with healthy latrines, ODF, and drinking water sanitation was insignificant. This study concluded that 8 of 31 districts were prioritized for handling toddler diarrhea in Surabaya. In addition, there is a need for dissemination to the community through optimizing the role of health workers at the Puskesmas regarding complete basic relationships and the incidence of diarrhea in toddlers.

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INTRODUCTION

Diarrhea is the second leading cause of death in toddlers. Toddlers with persistent diarrhea are three times more likely to die (Talbert et al., 2019). Globally, every year deaths from diarrhea occur around 525,000 toddlers with cases of diarrheal disease in toddlers, almost 1.7 billion cases every year (World Health Organization, 2017). In Indonesia, diarrheal disease is an endemic disease and a potential outbreak often accompanied by death. In 2019, the age group with the highest prevalence of diarrhea (based on the diagnosis of health workers) was in the age group 1-4 years at 11.5% and in infants at 9%. In Indonesia, there were 314 deaths (10.7%) in children aged 12 – 59 months caused by diarrhea, this figure is the highest when compared to other causes such as pneumonia and fever (277 deaths and 215 deaths) in 2019 (Kementerian Kesehatan RI, 2020). Under-five mortality due to diarrhea in Indonesia is the second-highest in East Java Province after West Java Province (Kementerian Kesehatan RI, 2020). While the Health Profile of East Java in 2019, diarrhea for toddlers served was mostly in the Surabaya City, namely 19,906 toddlers (Dinkes Jawa Timur, 2020). In addition, Surabaya City was also the area with the highest number of under-five deaths due to diarrhea in East Java Province, which was 7 toddlers (Dinkes Jawa Timur, 2020).

Various causes of diarrhea in toddlers, one of which was the sanitation factor (Azis et al., 2021). The worse the household sanitation, the higher the incidence of diarrhea in toddlers (Imadudin et al., 2021). Sanitation is related to environmental health, which affects the degree of public health. According to the Indonesian Health Profile, the indicator of proper sanitation was people accessing latrines (Kementerian Kesehatan RI, 2020). In 2019, there were 957,260 (98.21%) families with access to proper sanitation (healthy latrines) in Surabaya City. (Dinas Kesehatan Kota Surabaya, 2020). This shows that healthy latrines in Surabaya City were quite good, which means that there were sanitation factors or other factors that impacted the incidence of diarrhea in Surabaya.

Improvements in sanitation facilities have an impact on reducing the prevalence of diarrhea among toddlers in India. However, due to maximally enhanced water coverage, it did not show such an impact on diarrhea prevalence. So policymakers need to focus on coverage and broaden the proper use of sanitation facilities (Mallick et al., 2020). To contribute to designing targeted policies and to reduce the incidence of diarrhea among children, a previous study emphasized that the key is the availability and accessibility of clean water, water storage facilities, and better fecal disposal facilities (Omotayo et al., 2021).

One of the efforts to increase access to sanitation by the Ministry of Health is to change the direction of the sanitation approach policy from previously providing subsidies to community empowerment which focuses on changing the behavior of Open Defecation Free (ODF) which is one of the five pillars of CBTS (Community-Based Total Sanitation) (Dinkes Jawa Timur, 2020). Surabaya City had not been able to reach the CBTS village category because Surabaya City was still implementing 2 of the 5 pillars of CBTS, namely Open Defecation Free (ODF) and Washing Hands with Soap (Dinas Kesehatan Kota Surabaya, 2020). Previous research recommended that government organizations and relevant stakeholders strengthen urban WASH programs to focus on increasing the availability of sufficient water for daily consumption and promoting safe disposal of child waste and good handwashing practices at critical times. Further efforts are needed to make mothers/caregivers aware of diarrhea prevention through effective WASH activities to reduce the burden of this problem on toddlers

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(Getahun & Adane, 2021).

A study developed a model that showed better water sources were strongly associated with diarrhea incidence, while better sanitation had a marginal relationship. Improved water sources and sanitation were necessary to get the maximum benefit from reducing diarrhea in children (Kumie, 2020). A previous study explored the diarrhea prevention awareness of rural communities using a questionnaire survey. A significant association was found between drinking untreated water and the occurrence of diarrhea (Ko & Sakai, 2022).

A previous study stated that drinking water consumed without prior treatment was significantly associated with the incidence of diarrhea in toddlers (Vasconcelos et al., 2018). Regulation of the Minister of Health Number 492 in 2010 states that safe (decent) drinking water for health is drinking water that meets physical, microbiological, chemical, and radioactive requirements. In 2019, there were 106,482 (49.55%) drinking water facilities in Surabaya City with low and medium risk, and 1,649 of them were sampled and examined, with the result that only 1,115 (67.62%) eligible drinking water facilities (Dinas Kesehatan Kota Surabaya, 2020). In addition to sanitation, other factors cause diarrhea in toddlers, both the environment and individuals (Ulfa et al., 2017).

The main source of drinking water, washing hands before taking water from storage containers, domestic waste disposal sites, and soap for washing hands were the most important factors for the prevention of diarrhea in children (Soboksa et al., 2020). Likewise, previous research also showed a relationship between access to drinking water and inadequate sanitation with the incidence of diarrhea found in East Java (Prakoso, 2020).

The risk factors for diarrhea were quite a lot, such as poor personal hygiene, low application of clean and healthy living behavior, low availability of clean water, not getting immunizations, and poor environmental sanitation, including environmental pollution groups (Ira, 2019). Many studies stated toddler diarrhea was also caused by incomplete basic immunization. The previous study stated that there was a significant relationship between the completeness of immunization and the incidence of diarrhea in toddlers (Santoso & Kasman, 2018). In 2019 the coverage of UCI districts in Surabaya was 100% or all districts in Surabaya had achieved complete basic immunization coverage of at least 80% (Dinas Kesehatan Kota Surabaya, 2020).

Based on the background, this study aimed to describe the distribution of cases and their causes with the support of mapping so that it can be seen which areas are priority interventions for diarrhea problems under five in Surabaya in 2019.

METHODS

This was an ecological study with a cross-sectional design supported by mapping (Laksono & Kusrini, 2020; Mahendra et al., 2021). The population in this study is all districts (31 districts) in Surabaya City, East Java province, so the unit of analysis is the district. The data for each district was obtained by adding up the data from each *puskesmas* and then combining them in the same district. The data source in this study was from the Surabaya City Health Profile in 2019. This study used a total sample technique where the number of samples was the same as the total population. The independent variables were the percentage of families having healthy latrines, the percentage of villages having open defecation free, eligible drinking water facilities, and complete basic immunization coverage for infants. While the dependent variable was the number of cases of diarrhea under five. The dependent variable was categorized based on equal intervals to determine the distribution of

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the number of cases in each district. While the independent variables were categorized into two categories based on the equal count mode from the percentage value of each independent variable for diarrhea in toddler.

Mapping was obtained by combining two layers in the form of polygons and geometric points so that the distribution of two variables in one map can be known (Imadudin et al., 2021). The scoring technique is carried out to determine priority areas for handling cases of diarrhea under five in Surabaya City, where the dependent variable was weighted twice that of the independent variable, this weighting aims to more clearly identify the area at the level/classification (Fuada et al., 2012). The classification for determining priority areas for handling toddler diarrhea was made based on the number of cases of diarrhea under five, healthy latrines, open defecation free, and complete basic immunization coverage, then divided into three categories, namely low, medium, and high. However, this study did not research other internal risk factors (such as habit of washing hands in running water). A correlation test was used in this study to determine the significant effect of risk factors on toddler diarrhea. Meanwhile, analysis by mapping was carried out to determine the priority areas intervention for toddler diarrhea (Pertiwi & Widayani, 2019). Data processing in this study was carried out using Quantum Geographic Information System (QGIS) 2.8.1 software to describe conditions based on the distribution of cases and their risk factors. This study was approved by Health Ethics Research Committee from Faculty of Ners, Universitas Airlangga, ref: 1773-KEPK (29 September 2019).

RESULTS

Surabaya is the capital of East Java Province. Surabaya City is located between 112^0 36' until 112^0 54' Bujur Timur and 7^0 9' until 7^0 21' South Latitude. The area of Surabaya City is directly adjacent to the Madura Strait in the north and the east, while in the south, it is bordered by Sidoarjo Regency and bordered by Gresik Regency in the west. The Surabaya City has 31 districts grouped into 5 sub-mayors, namely North Surabaya, East Surabaya, South Surabaya, West Surabaya, and Central Surabaya. The total area of Surabaya is 326.81 $km^{2,}$ with Benowo District being the district with the widest area of 23.73 km^2 located in West Surabaya. Meanwhile, Simokerto District is the district with the smallest area of 2.59 km^2 located in Central Surabaya (Badan Pusat Statistik Kota Surabaya, 2021).

Table 1. Descrip of Toddler Diarrhea Cases and Percentage of Risk Factors in Surabaya 2019

Variables	Minimum	Maximum	Mean	Std. Deviation
Toddler Diarrhea	55	1847	657.12	452.45
Complete Basic Immunization	94.59	103.9	97.34	2.02
ODF Village	0	100	45.24	30.45
Healthy Latrine	91.94	100	98.28	1.71
Eligible Drinking Water Facility	.22	1	.69	.16

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Table 2. Correlation betwen the number of cases of diarrhea in a todler with the risk factors

Variables	r	p-value
Healthy Latrine	0.116	0.534
Complete Basic Immunization	-0.470	0.008*
ODF Village	0.177	0.342
Eligible Drinking Water Facility	0.001	0.997

Table 1 shows that the lowest cases of diarrhea under five in Surabaya were 55 cases in Gunung Anyar District and the most cases were 1847 cases in Tambak Sari District. Based on Table 2, complete basic immunization coverage was significantly associated with diarrhea in toddlers (p = 0.008). The value of r shows an inverse relationship, which means that the lower the complete basic immunization coverage in an area/district, the more cases of diarrhea occur in toddlers (r = -0.470).

Mapping Toddler Diarrhea with Healthy Latrines

The distribution of the percentage of healthy latrines in Surabaya City spread in the northern and central areas of Surabaya City, where several adjacent areas had a low percentage of families with latrines. The percentage of households with healthy latrines that had a high risk of diarrhea cases in toddler was Sawahan and Wonokromo Districts. This can be seen on the map showing cases of diarrhea toddlers in dark red color and the percentage of healthy white latrines, which means it was quite low (Figure 1). Meanwhile, Semampir and Wonocolo districts had a moderate risk of diarrhea toddlers caused by healthy latrines. Semampir and Wonocolo districts had a very high number of cases of toddler diarrhea characterized by a deep red color, even though it had a high percentage of healthy latrines. This can happen because these two districts were surrounded by districts with a low percentage of healthy latrines (white dots).

Mapping of Toddler Diarrhea with ODF Villages

The distribution of the percentage of villages with open defecation free in Surabaya City was low (marked with a red dot) tends to be in the central and southern parts of Surabaya. Table 1 shows that some districts still have not implemented open defecation free. Similar to healthy latrines, Sawahan and Wonokromo districts also had a high risk of cases of diarrhea toddler caused by the ODF factor. In these two districts, villages that have implemented open defecation free were quite low, and the incidence of diarrhea in toddlers was very high, as indicated by a solid red color (Figure 2). In addition, the map shows that the open defecation-free factor was at moderate risk for cases of diarrhea toddlers in Wonocolo District.

Mapping of Toddler Diarrhea with Eligible Drinking Water Facilities

The distribution of the low of eligible drinking water facilities tends to spread in the northern and eastern parts of Surabaya City, where many adjacent districts in the north and east of Surabaya were white dots which indicated that eligible drinking water facilities were low. Figure 3 shows that there were still many districts that had drinking water facilities that did not meet the requirements. Areas that had a high risk of diarrhea toddlers because of the low of eligible drinking water facilities were Kenjeran District and Tambak Sari District. It can be seen on the map that in that district, the cases of diarrhea in toddlers were very high, indicated by a solid red color, and the

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percentage of drinking water facilities was quite low (Figure 3). Meanwhile, the moderate risk of diarrhea in toddlers caused by the low of eligible drinking water facilities was in Semampir and Sukolilo Districts.

Mapping of Toddler Diarrhea with Complete Basic Immunization

The distribution of complete basic immunization coverage has a pattern of spreading in the central Surabaya and North Surabaya areas, where several districts in the region have complete basic immunization coverage, which tends to become low. The high risk of diarrhea in a toddler is caused by the relatively low coverage of complete basic immunization in Sawahan, Kenjeran, and Tambak Sari districts. The spatial picture on the map shows the three districts in solid red, and the coverage of complete basic immunization is lower than in the other districts (Figure 4). 5 areas had a moderate risk of diarrhea for toddlers due to complete basic immunization, namely Tandes District, Wiyung District, Wonocolo District, Sukolilo District, and Semampir District.

Mapping of Priority Areas Interventions for Toddler Diarrhea

The distribution of cases of diarrhea in toddler shows that cases of diarrhea in toddler had a pattern of spreading in the areas of Central Surabaya and North Surabaya, where there were two districts in each region that had a very high number of cases of diarrhea in toddler marked by a solid red color (Figure 1-4). After scoring the cases of diarrhea toddler by considering the factors of healthy latrines, open defecation free, drinking water facilities, and complete basic immunizations, the priority areas for handling toddler diarrhea were obtained. Based on Figure 5, it can be seen that 8 areas were priority areas for intervention for toddler diarrhea cases in Surabaya, namely Kenjeran District, Pakal District, Wiyung District, Tandes District, Jambangan District, Wonokromo District,

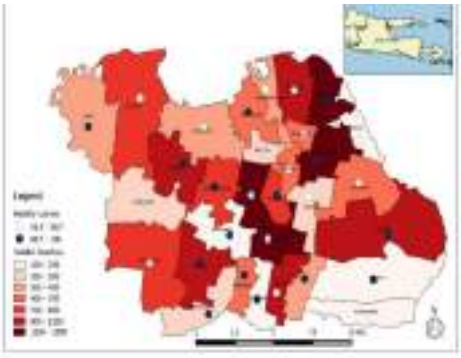

Figure 1. Distribution Map of Toddler Diarrhea Cases and Healthy Latrines in Surabaya in 2019

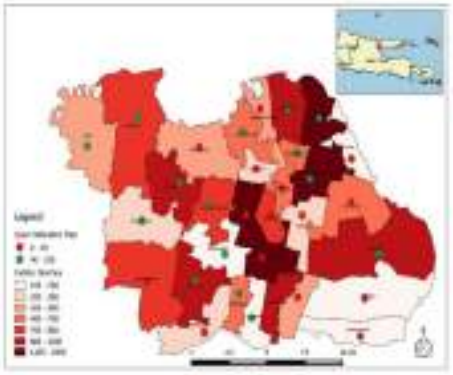

Figure 2. Distribution Map of Toddler Diarrhea Cases and Open Defecation Free in Surabaya in 2019

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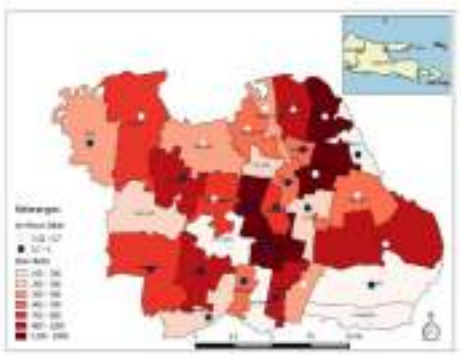

Figure 3. Distribution Map of Toddler Diarrhea Cases and Eligible Drinking Water in Surabaya in 2019

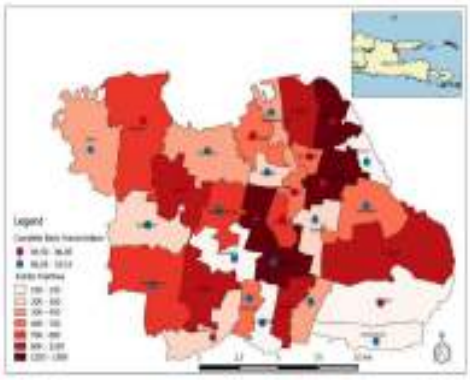

Figure 4. Distribution Map of Toddler Diarrhea Cases and Complete Basic Immunization in Surabaya in 2019

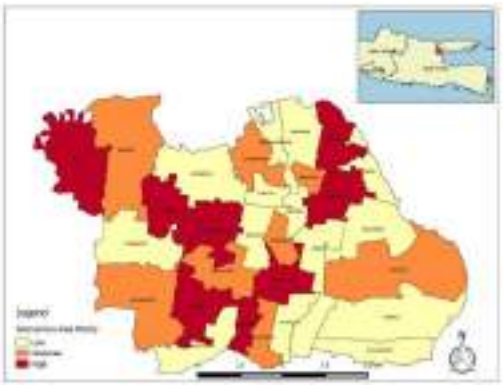

Figure 5. Map of Priority Areas Interventions for Toddler Diarrhea in Surabaya in 2019

Sukomanunggal District, and Tambak Sari District.

DISCUSSION

Diarrhea is a disease that is transmitted through contaminated food or drink. Eligible drinking water facilities were one of the efforts to prevent diarrhea in toddlers. Previous studies have found that eligible drinking water was significantly related to the incidence of diarrhea in toddlers, including types of drinking water, namely Municipal Waterworks and Non-Municipal Waterworks (Pertiwi & Widayani, 2019; Syaputra & Syamsir, 2020). Households that got water from ineligible sources were more at risk for diarrhea in toddlers (Alemayehu et al., 2020). The results of this study indicate that areas with very high cases of diarrhea were caused by the lack of adequate drinking

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water facilities. Similar to the previous study which described areas with a moderate risk of diarrhea in toddlers also had a moderate risk of drinking water facilities that met the requirements (Dyah Nurmarastri Sasabil Sidqi, Novia Anasta, 2021).

Spatial analysis is very important in mapping the spread of disease and assisting in policymaking. Targeting diarrhea transmission hotspots was one potential strategy to reduce diarrhea cases. The spatial pattern of the percentage of children with persistent diarrhea was related to households with sanitation facilities (Mahendra et al., 2021).

Increasing latrine coverage is generally believed to reduce exposure to fecal pathogens and prevent disease (Clasen et al., 2014), especially diarrhea in toddlers (Nilima et al., 2018). Previous studies have shown that houses with unhealthy latrines were three times more likely to have diarrhea in toddlers than those with healthy latrines (Kurniawati et al., 2021). Healthy latrines are latrines that animal vectors cannot enter, were made of waterproof floors, and do not cause unpleasant odors (in enclosed spaces), the distance between the latrine and the source of clean water must be > 10 meters from a septic tank. In principle, healthy latrines did not lead to the direct distribution of materials that were harmful to humans due to the disposal of human waste and preventing the spread of disease vectors to users and the surrounding environment (Peraturan Menteri Kesehatan RI Nomor 3 Tahun 2014 Tentang Sanitasi Total Berbasis Masyarakat, 2014). However, the results of this study showed a weak and insignificant positive correlation between the availability of healthy latrines and diarrhea in toddler. This is shown in Figure 1, which tends to have no difference in the distribution between districts with low or high cases of diarrhea in toddler on the percentage of healthy latrine availability. This finding is in line with the results of a meta-analysis study which stated that there was no effect of sanitation, availability of latrines, on the incidence of diarrhea in toddler. The study stated that to overcome the problem of diarrhea, it was not enough to intervene in sanitation alone but also at the same time as improving access to clean water and waste water management (Contreras & Eisenberg, 2020). Likewise with the research in India, they cannot assume that promoting targeted latrine coverage alone is effective for reducing exposure to fecal pathogens and preventing disease, there need to be interventions on exposure and health promotion (Clasen et al., 2014).

Diarrhea is an environment-based disease. Diarrhea in Indonesia has the potential to cause an outbreak because diarrhea is endemic and environment-based, which is often accompanied by death. The results of the previous study concluded that there was a very strong relationship between the CBTS program and the coverage of diarrhea services in NTB and there was a strong relationship between the open defecation-free program and the coverage of diarrhea services in NTB. (Saprudin & Syahrul, 2021).

ODF is a condition when every individual in a community no longer had open defecation that has the potential to spread disease (Peraturan Menteri Kesehatan RI Nomor 3 Tahun 2014 Tentang Sanitasi Total Berbasis Masyarakat, 2014). Areas that were already ODF will reduce the risk of diarrhea in toddlers (Ayalew et al., 2018). The results of this study indicate the opposite. ODF status was known to have an insignificant positive correlation with the incidence of diarrhea in toddler in Surabaya City. The distribution of districts with ODF coverage of more or less than 40% did not look different in districts with high and low cases of diarrhea in toddler. The range of ODF coverage in the Surabaya City was quite varied

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with a fairly high standard deviation value. In fact, the coverage of healthy latrine ownership in households was more than 90 percent in all districts. Further studies need to be carried out to understand this phenomenon. Therefore, several previous studies have shown that there was a relationship between the CBTS Program and the incidence of diarrhea in people who did not have latrines so people were obliged to have healthy latrines that are effective as sanitary ware (Sinum, 2021).

Complete basic immunization is a government program for compulsory health services for toddler (Dinkes Jawa Timur, 2020). Some of the causes of completeness of basic immunization were maternal education, place of delivery, distance to health facilities (Jama, 2020). Maternal factors significantly affected the completeness of basic immunization in terms of knowledge, attitudes, and perceptions (Dillyana, 2019). Meanwhile, complete basic immunization coverage is correlated with poor population, neonatal visits, and *posyandu* activity (Devi et al., 2021).

Complete basic immunization can protect toddlers' immunity so it was useful for preventing toddlers from diseases, one of which was diarrhea (Santoso & Kasman, 2018). Previous studies have shown that most toddler had a complete history of basic immunization and did not experience diarrhea, this had a significant impact on the nutritional status of toddler (Sartika et al., 2021). Even so, there were studies that state that there was no significant relationship between complete basic immunization and the incidence of diarrhea in toddler (Himawati & Fitria, 2020). Complete basic immunization in Indonesia did not include rotavirus vaccination because it was still the immunization of choice or not mandatory (Kementerian Kesehatan RI, 2015), even though rotavirus vaccination had an impact on preventing diarrhea in toddlers (Chissaque et al., 2018; Vinandyanata et al., 2021). A Cochrane review found that rotavirus vaccination can prevent diarrhea (Soares-Weiser et al., 2019). IDAI stated that rotavirus vaccination can be given to children three times, at the ages of 2 months, 4 months, and 6 months (Soedjatmiko et al., 2020).

A country had experienced a major decline in child deaths from diarrheal diseases in recent decades. The factors that had the most impact on the DSMR (Diarrhea specific mortality rate) were the coordinated efforts of the government with non-governmental organizations and the private sector to enable rapid implementation and interventions such as oral rehydration solutions and zinc, promotion of breastfeeding, handwashing and latrine sanitation, and improvement of women's education and nutrition (Billah et al., 2019; Devi et al., 2022).

However, previous studies showed that improved sanitation did not directly affect water treatment and was not associated with the incidence of diarrhea. At the community level, increased water coverage had no direct effect, but increased sanitation coverage was associated with lower diarrhea prevalence. The interaction analysis of this study shows that the protective effect of better sanitation at the community level is enhanced by better drinking water at the community level. This illustrates the importance of simultaneously improving drinking water and sanitation (Komarulzaman et al., 2017).

CONCLUSION

Based on the mapping results, it can be seen that the high cases of diarrhea toddlers in the Sawahan and Wonokromo districts were caused by the relatively low percentage of households with healthy latrines and villages with open defecation free. Meanwhile, the high cases of diarrhea in a toddler in Tambak Sari and Kenjeran districts were predicted to be caused by the low percentage of eligible drinking water facilities. However, the internal

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factors of toddler diarrhea were not included in this study such as hygiene habituation of family include habit of washing hands in running water, rotavirus vaccination, allergy factor, and other infection with chronic diarrhea. Mapping cases of diarrhea toddler based on the four risk factors (healthy latrines, ODF, drinking water facilities, and complete basic immunization) obtained 8 of 31 districts that were priority areas for handling toddler diarrhea in Surabaya, namely Kenjeran, Pakal, Wiyung, Tandes, Jambangan, Wonokromo, Sukomanunggal, and Tambak Sari. The districts of Sawahan, Tambak Sari, and Kenjeran also have relatively low complete basic immunization coverage. Therefore, it is necessary to prevent diarrhea through optimizing the CBTS program and increasing the coverage of basic immunization for toddler.

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Research Articles

Characteristics of laryngopharyngeal reflux: a retrospective descriptive study

Rizka Fathoni Perdana[1], Reyna Cesariyani Rahmadianti Rusuldi[2*], Husin Thamrin[3], Rosa Falerina[1]

1) Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga, Soetomo General Hospital, Surabaya, Indonesia.
2) Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
3) Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Soetomo General Hospital, Surabaya, Indonesia.

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Correspondence:

reyna.cesariyani.rahmadianti-2018@fk.unair.ac.id

ABSTRACT

Laryngopharyngeal reflux (LPR) is a condition of reverse flow of gastric and duodenal fluid that reaches the aerodigestive tract, causing inflammation in the upper respiratory tract. Reflux Symptoms Index (RSI) and Reflux Finding Score (RFS) have been used as instruments to determine the symptoms and signs in LPR patients. This study aims to find out the characteristics of patients with LPR. A retrospective descriptive study was performed using medical records as a source of information to obtain the characteristics of patients with LPR in ENT Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya. The study population is all patients that have been diagnosed with LPR based on RSI >13 and RFS >7 in the period 2018-2019. Our finding shows the total number of patients diagnosed with LPR was 58. There were 45 patients diagnosed solitarily according to the results of the RSI score, while the RFS was 34 patients. The total number of patients diagnosed according to RSI and RFS was 21. In this study, 67.24% of patients with LPR were female, while the male patients were 32.76%. Most patients with LPR belonged to 50 – 59 years (25.86%). The occupation distribution shows the highest number of patients is unemployed (43.10%). In conclusion, the number of female LPR patients is higher compared to that of males. The middle age group dominated LPR. The distribution of occupation in LPR patients was dominated by housewives. The most frequent and severe complaints from LPR patients were throat clearing, the sensation of something sticking in the throat or lump, and excess throat mucus or postnasal drip. The laryngoscopy findings compiled on the RFS showed that the most common signs in LPR patients were subglottic edema, thick endolaryngeal mucus, and posterior commissure hypertrophy.

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INTRODUCTION

Laryngopharyngeal reflux (LPR) is a condition of reverse flow of gastric and duodenal fluid that reaches the aerodigestive tract, causing inflammation in the upper respiratory tract (Jerome R. Lechien, Saussez, & Karkos, 2018). Around 11% of the India population was estimated to have symptoms of LPR (Mishra, Agrawal, Chauhan, & Kaushik, 2020), research in Greece, around 18.8% (Spantideas, Drosou, Bougea, & Assimakopoulos, 2015), and research in the United Kingdom around 34.4% (Kamani, Penney, Mitra, & Pothula, 2012). LPR is commonly found in the productive age. Male and female patients show no significant difference (Kamani et al., 2012; Spantideas et al., 2015).

LPR could occur due to weakening of the upper esophageal sphincter, resulting in gastric fluid reflux more easily. If recurrent reflux occurs, the mucosa in the pharyngeal and laryngeal areas can be inflamed because these tissues tend to be sensitive to acid exposure (Johnston et al., 2016).

Symptoms caused by this condition might vary. Hoarseness, a lumpy sensation, annoying cough, thick mucus, and painful swallowing are commonly reported. Several factors might contribute to this condition, for instance, smoking habits, drinking alcohol, excess food portions, and high-fat intake. Symptoms of LPR are not specific because these can also be found in allergies, irritant exposure, and even in healthy people (Yuksel & Vaezi, 2012).

There has been no agreement on the gold standard examination. Hence it is more difficult to give a definite diagnosis of LPR. Belafsky developed Reflux Symptoms Index (RSI) and Reflux Finding Score (RFS), instruments that have been used to diagnose LPR clinically. The RSI questionnaire consists of LPR symptoms that the patient should fill in during history taking. While RFS is a questionnaire that the doctor fills out after a laryngoscopy examination (Belafsky, Postma, & Koufman, 2001, 2002).

Studies about LPR in Indonesia are still uncommon. Therefore, the study of LPR characteristics is conducted to determine patients' frequency distribution based on demographic (i.e., age, gender, and occupation), RSI, and RFS.

METHODS

This research is a retrospective descriptive study, using medical records in the period 2018 – 2019 as a source of information to obtain the characteristics, RSI, and RFS in ENT Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya. This research has received an ethical clearance 0200/LOE/301.4.2/XI/2020 from the Research Ethics Commission of Dr. Soetomo General Academic Hospital Surabaya.

RSI was taken during history taking to assess the symptoms of the patients. There are nine questions given. Each question has a scale of 0 (no problem) to 5 (severe). The maximum total score for this assessment is 45. The patient is diagnosed with LPR if their total score is >13.

RFS is an assessment tool that contains signs in LPR patients. Findings obtained by laryngoscopy will be inserted into the RFS. The maximum total score for RFS is 26. The patient is diagnosed with LPR if the total score is >7.

An otorhinolaryngologist conducted laryngoscopy at Dr. Soetomo General Academic Hospital Surabaya, a consultant in broncho-esophagology. The procedure was carried out with fiber optic XION nasopharyngoscopy model EF-N. The laryngeal area was examined after passing the flexible scope from the nasal cavity to the throat.

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Table 1. Reflux Symptoms Index

No	Within the last month, how did the following problems affect you?	0 = No problem 5 = Severe problem					
1.	Hoarseness or problem with voice	0	1	2	3	4	5
2.	Throat clearing	0	1	2	3	4	5
3.	Excess throat mucus or postnasal drip	0	1	2	3	4	5
4.	Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5.	Cough after eating or after lying down	0	1	2	3	4	5
6.	Breathing difficulties or coughing episodes	0	1	2	3	4	5
7.	Troublesome or annoying cough	0	1	2	3	4	5
8.	Sensation of something sticking in the throat or lump	0	1	2	3	4	5
9.	Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

Source: Belafsky, Postma and Kaufman, 2002

Table 2. Reflux Finding Score

No	Lesion	RFS
1.	Subglottic Edema	0 = Absent 2 = Present
2.	Ventricular Obliteration	0 = None 2 = Partial 4 = Complete
3.	Erythema/Hyperemia	0 = None 2 = Arytenoid only 4 = Diffuse
4.	Vocal Fold Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Polypoid
5.	Diffuse Laryngeal Edema	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Obstructing

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No	Lesion	RFS
6.	Posterior Comissure Hypertrophy	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Obstructing
7.	Granuloma/Granulation Tissue	0 = Absent 2 = Present
8.	Thick Endolaryngeal Mucus	0 = Absent 2 = Present

Source: *Bealfsky, Postma and Kaufman, 2001*

Inclusion and Exclusion Criteria

The inclusion criteria of this research are patients with LPR that have the following data: demographic (i.e., age, gender, occupation), either or both RSI and RFS. While sample may be excluded from this research if any of the following criteria are present: incomplete data and malignancy.

RESULTS

During the period 1 January 2018 – to 31 December 2019, the total number of patients diagnosed with laryngopharyngeal reflux was 58. There were 45 patients diagnosed solitarily according to the results of the RSI score, while the RFS was 34 patients. The total number of patients diagnosed according to both RSI and RFS was 21 patients.

Demography

Thirty-nine (67.24%) patients with LPR were female, while the male patients were 19 (32.76%). In this study, most patients with LPR belonged to 50 – 59 years, which had 15 patients (25.86%). This number is followed by the age groups of 40 – 49 and 30 – 39, who had the same number of patients, i.e., 12 (20.69%). While the age group of 70 – 79 had the least number of patients, which was 4 (6.90%). No LPR patient was found in ages >80 and <20. In this study, the occupational group with the highest number of patients is unemployed, with 25 patients (43.10%) reported. Unemployed patients were dominated by the female (23 out of 25 patients).

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Table 3. Distribution and Frequency of Patients Based on Gender and Age

Characteristics of Subjects	N	%
Gender		
Male	19	32.76
Female	39	67.24
Age		
≤19	0	0
20 – 29	9	15.52
30 – 39	12	20.69
40 – 49	12	20.69
50 – 59	15	25.86
60 – 69	6	10.34
70 – 79	4	6.90
Total	100	100

Table 4. Distribution and Frequency of Patients with LPR Based on Occupation

Characteristic of Subjects Occupation	Male (n=19)	Female (n=39)	N (%)
Unemployed	2 (10.53)	23 (58.97)	25 (43.10)
Private Employee	6 (31.58)	4 (10.26)	10 (17.24)
Civil servant	3 (15.79)	3 (7.69)	6 (10.34)
Retired	5 (26.32)	1 (2.56)	6 (10.34)
Teacher	1 (5.26)	3 (7.69)	4 (6.90)
College Student	1 (5.26)	1 (2.56)	2 (3.45)
Farmer	0	2 (5.13)	2 (3.45)
Entrepreneur	0	2 (5.13)	2 (3.45)
Parking Attendant	1 (5.26)	0	1 (1.72)
Total	(100)	(100)	(100)

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Reflux Symptom Index

In this study, the most common symptom is throat clearing (95.56%). This number is followed by a sensation of something sticking in the throat or lump (91.11%) and excess throat mucus or postnasal drip (84.44%). The RSI also showed that the sensation of something sticking in the throat or lump had the highest mean score of 3.64, followed by throat clearing with a mean score of 3.36 and excess throat mucus or postnasal drip with a mean score of 3.07.

Reflux Finding Score

In this study, the most common laryngeal findings were subglottic edema and thick endolaryngeal mucus, which had the same number of patients, 23 patients (67.65%). This number is followed by posterior commissure hypertrophy (64.79%). Between RFS with a range score of 0 – 4, erythema/hyperemia (2.76) has the highest mean score. While subglottic edema and thick endolaryngeal mucus have equal high mean scores (1.35) amongst RFS with a range score of 0-2.

Table 5. Distribution and Frequency of Patients with LPR Based on RSI

Symptoms Range Score RSI (0-5)	Frequency (n=45)	%	Mean Score of RSI
Hoarseness or problem with voice	29	64.44	1.87
Throat clearing	43	95.56	3.36
Excess throat mucus or postnasal drip	38	84.44	3.07
Difficulty swallowing food, liquids, or pills	32	71.11	2.36
Cough after eating or after lying down	24	53.33	1.47
Breathing difficulties or coughing episodes	21	46.47	1.29
Troublesome or annoying cough	26	57.78	1.49
A sensation of something sticking in the throat or lump	41	91.11	3.64
Heartburn, chest pain, indigestion, or stomach acid coming up	34	75.56	2.51

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Table 6. Distribution and frequency of Patients with LPR based on RFS

Signs and Range Score of RFS		Frequency (n=34)	%	Mean Score of RFS
Subglottic Edema	0 – 2	23	67.65	1.35
Ventricular Obliteration	0 – 4	3	8.86	1.71
Erythema/Hyperemia	0 – 4	13	38.26	2.76
Vocal Fold Edema	0 – 4	15	44.18	1.44
Diffuse Laryngeal Edema	0 – 4	11	32.35	1.38
Posterior Comissure Hypertrophy	0 – 4	22	64.79	1.82
Granuloma/Granulation Tissue	0 – 2	3	8.86	0.78
Thick Endolaryngeal Mucus	0 – 2	23	67.65	1.35

DISCUSSION

Demography

Table 3 shows the distribution and frequency of patients with LPR based on gender. The results showed that LPR was more common in females (67.24%) than males (32.76%). The ratio of female to male patients was found to be 2:1. This result is consistent with a previous study by Munifah *et al.* (2020); there were a higher number of female patients with LPR (64.29%) than males. A study by Widiantari and Sucipta (2019) showed there was a 1.2 times higher number of female patients than male patients. A study by Junaid (2020) also indicates LPR patients were more dominated by female patients (56.9%). Likewise, a study by Misha *et al.* (2020) showed that the number of female patients (54%) was higher than that of male patients.

To date, there is no definite reason why female dominates LPR. The hormonal factor is thought to have a role in increasing the frequency of reflux. In gastroesophageal reflux disease (GERD), which has similar pathophysiology to LPR, patients that received hormone replacement therapy (HRT), i.e., estrogen, are found to have lower the esophageal sphincter pressure. Estrogen mediates the relaxation of the esophageal sphincter, thereby increasing the frequency of reflux. However, several studies have shown that estrogen could protect the mucosa from GERD injury. This matter still needs further analysis (Kang, Khokale, Awolumate, Fayyaz, & Cancarevic, 2020; Zia & Heitkemper, 2016).

Table 3 shows the results of the distribution and frequency of LPR patients based on age. The age groups that had the highest number of patients in this study were 50 – 59 (25.86%), 40 – 49 (20.69%), and 30 – 39 (20.69%). This

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study's three age groups constituted 67% of all LPR cases. These results were also obtained in a study conducted by Spantideas *et al.* (2015), where the 50 – 64 and 35 – 49 age groups contributed the most (75%) of the total LPR cases. Likewise, Kamani's (2012) study showed high LPR patients in the 41 – 60 age group.

The percentage of up to 67% in this study's 30 – 59 age group showed that LPR was dominated by middle age. This age group is a productive age. It is suspected that stress has a role in the high number.

Furthermore, this study found no LPR patients in the age groups >80 and <20. This may be due to the small number of patients in those age groups. The absence of patients in the age group <20 might occur due to the inability of children and teenagers to visit a doctor without a guardian. As a result, it is suspected that the complaints experienced tend to be ignored if it is not intrusive. Stress levels in this age group may also not be as high as in the productive age group. While the age group of >80 years has a declining quality of life, it is suspected the patients had more severe health problems, so complaints about LPR tend to be ignored.

Table 4 shows the results of distribution and frequency of LPR patients based on occupation. The occupational group that had the highest number of LPR patients was unemployed (43.10%). These unemployed patients were dominated by women, described as housewives on medical records. Housewives amongst total female patients had a percentage of 58.97%. There has been no research on the relationship between LPR with occupation. However, several GERD studies showed that housewives had the highest prevalence (Bor, Kitapcioglu, & Kasap, 2017; Puspita, Putri, Rahardja, Utari, & Syam, 2017).

The high number of housewives experiencing LPR might be due to prolonged stress. Housewives play an essential role in managing household finances as well as familial needs. More research is needed on this matter.

Another study shows LPR is related to work that requires the ability to use voice frequently (e.g., vocal artist). Heavy use of voice could result in weakness in the vocal fold. However, no patients in this study were found to be working as vocal artists (J. R. Lechien, Schindler, Robotti, Lejeune, & Finck, 2019).

Result of RSI

RSI is an instrument used to diagnose LPR. A study conducted in the UK by Kamani *et al.* (2012) used RSI >10 as the diagnostic criteria. Another study in Greece by Spantideas *et al.* (2015) used RSI ≥13 as the diagnostic criteria. Meanwhile, this study uses the RSI score >13 as the diagnostic criteria following Belafsky's (2002) study, which developed RSI for the first time.

Table 5 shows the results of the distribution and frequency of LPR patients based on RSI. Throat clearing as the most common complaint was found in the study by Sirajuddin (2020), with a percentage of 86.00%. Another study by Spantideas *et al.* (2015) showed the most complaints were throat clearing with a percentage of 48.2%, and the sensation of something sticking in the throat or lump in 40.6% of patients. Meanwhile, in the study of Widiantari and Sucipta (2019), throat clearing was also the most common complaint. Still, complaints of the sensation of something sticking in the throat or lump ranked third in that study after complaints of excess throat mucus or postnasal drip.

Throat clearing, the sensation of something sticking in the throat or lump, and excess throat mucus or postnasal drip are the most severe complaints in patients with LPR. Research by Spantideas *et al.* (2015) showed throat clearing was the most severe complaint. Meanwhile, Spyridoulias's (2015) research shows sensation

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of something sticking in the throat or lump is the most common complaint, with a severity score of 5/5.

Reflux that reaches the laryngeal area could result in irritation, so that throat clearing occurs in response to relieve discomfort. Pepsin as the reflux content would irritate by damaging the gaps between the laryngeal epithelial cells. Prolonged reflux could cause inflammation of the laryngeal mucosa, which increases mucus production, causing throat clearing. Complaints that initially only in the form of discomfort can develop into excessive mucus production. When retained or thickened, the excess mucus would then result in a sensation of something sticking in the throat or lump (Kowalik & Krzeski, 2017; Jerome R. Lechien et al., 2018).

Result of RFS

RFS is an instrument for diagnosing LPR which was made based on the findings of laryngoscopy. Laryngoscopy was performed by inserting a tube that has a camera to the laryngeal area (i.e., epiglottis, aryepiglottic fold, cuneiform cartilages, vocal cords, arytenoids, postcricoid region, and piriform sinus). The examiner observed and filled in the RFS afterward. Belafsky (2001) developed RFS for the first time by assessing the results of laryngocopy of LPR patients and stated that 95% of patients have RFS >7. Therefore, this study uses that cut-off number as diagnostic criteria.

Table 6 shows the results of the distribution and frequency of LPR patients based on RFS. The RFS results in this study showed that subglottic edema, thick endolaryngeal mucus, and posterior commissure hypertrophy were the most common findings. Previous research conducted by Sirajuddin (2020) showed that posterior commissure hypertrophy was the most common finding, with a percentage of 99.10%. Meanwhile, the study by Widiantari and Sucipta (2019) showed that thick endolaryngeal mucus was the second most common finding after erythema/hyperemia. In addition, erythema/hyperemia, subglottic edema, and thick endolaryngeal mucus were the most severe findings due to high mean scores.

As one of the highest findings in RFS, thick endolaryngeal mucus showed a compatible result with RSI2 and RSI3, i.e., throat clearing and excess throat mucus or postnasal drip, which were the most common complaint in patients as well. The presence of thick mucus would make the patients do throat-clearing to relieve the excess throat mucus. In addition, RSI8, i.e., the sensation of something sticking in the throat, is also in accordance with the presence of posterior commissure hypertrophy. Posterior commissure hypertrophy is a finding due to chronic reflux into the larynx (Kowalik & Krzeski, 2017).

Limitation of The Study

RSI and RFS were collected on different days. RSI was performed during the history taking, while the laryngoscopy examination was scheduled after the first appointment so that several patients only have RSI data without RFS. Thus, the data were not complete due to the nonattendance of patients after being scheduled.

CONCLUSION

In conclusion, the number of female LPR patients is higher compared to that of males. The middle age group dominated LPR. Housewives dominated the distribution of occupation in LPR patients, so LPR could not be associated with the occupation.

The results of RSI in this study showed that the most frequent and severe complaints from LPR patients were throat clearing, the sensation of something sticking in the throat or lump, and excess throat mucus or postnasal drip. The laryngoscopy findings compiled on the RFS showed that the most common signs in LPR patients were subglottic edema,

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thick endolaryngeal mucus, and posterior commissure hypertrophy.

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Research Articles

Relationship of knowledge and attitude with smoking habits at low healthy family index

Aisyah Lahdji[1*], Hema Dewi Anggraheni[2], Nina Anggraeni Noviasari[3], Muhammad Ridhwan Hamdani[4]

1,2,3,4) Faculty of Medicine, Muhammadiyah Semarang University

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Correspondence:

lahdjiaa@unimus.ac.id

ABSTRACT

Smoking is one of the habits that are often done by the people of Indonesia. Smoking habits are influenced by several things, such as knowledge and attitudes. Having good knowledge will tend to avoid smoking habits, and having a positive attitude will make someone stop smoking. This study aims to determine the relationship between knowledge and attitudes toward smoking habits in Tugu District residents with a Low Healthy Family Index. This research is an observational study with a cross-sectional approach carried out in Tugu District with residents with a low Healthy Family Index. The samples used were 81 samples. The analysis used is the Spearman test. The results showed that 34 respondents (42%) had sufficient knowledge, 64 respondents had a negative attitude (79%), 36 respondents were heavy smokers (44.4%), and 45 respondents were moderate smokers (55.6%). The results of the relationship between knowledge and attitudes toward smoking habits are each with p values of 0.000 and 0.005. This study concludes that there is a relationship between knowledge and attitudes toward smoking habits in Tugu District residents with a Low Healthy Family Index.

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INTRODUCTION

Smoking is a habit that many people often do. Globally, 1.1 billion people smoke over the age of 15, with 945 million male and 180 million female smokers. ASEAN data shows that there are 122 million adult smokers, and the number of smokers in Indonesia is 65 million (Lian & Dorotheo, 2018). The prevalence of smoking in Indonesia has increased from 7.2% in 2007 to 9.1% in 2018. This is contrary to the 2019 RPJMN target of 5.4% (Kementerian Kesehatan RI Badan Penelitian dan Pengembangan, 2018). The Central Java Health Profile shows the proportion of the smoking population aged 10 years in Central Java has increased from 2013 by 22.9% to 23.19% in 2018 (Profil Kesehatan Provinsi Jawa Tengah, 2019).

No family member who smokes is one of the 12 indicators of the Healthy Indonesia Program with a Family Approach (PIS-PK). In Central Java, the indicator that no family member smokes has decreased in percentage, from 44.58% in 2018 to 44.01% in 2019, while for the City of Semarang, it is 54.86% and is the four lowest of the 12 indicators. . Tugu District has the lowest prevalence of non-smoking family members, which is 45.37% (Kemenkes, 2017).

Smoking habits are influenced by several factors, namely predisposing factors (predisposing factors), enabling factors, and reinforcing factors. Predisposing factors include knowledge, attitudes, beliefs, beliefs, and individual values. Supporting factors (enabling factors) are manifested in the physical environment, such as health facilities and information media, and reinforcing factors are manifested in reference groups from the habits of the person concerned, such as parents and community leaders. (Notoatmodjo, 2014). Smoking habits are influenced by knowledge which is an important thing in the formation of one's actions. Someone who has good knowledge will tend to avoid smoking. In addition to knowledge, attitudes also affect smoking habits. A positive attitude towards smoking habits can make a person's intention to quit smoking low, and a negative attitude towards smoking habits can make a person's intention to quit smoking high. (Alamsyah, 2017). This study aimed to determine the relationship between knowledge and attitudes toward smoking habits in Tugu District residents with a Low Healthy Family Index.

METHODS

This research is an observational study with a cross-sectional design. This research was carried out in February 2021 in Mangunharjo Village and Mangkang Wetan Village. The sample of this study was 81 samples with the sampling technique of consecutive sampling according to the inclusion and exclusion criteria. The inclusion criteria for this study were (1) PIS-PK members who smoked, (2) had an unhealthy/low Healthy Family Index, (3) over 17 years of age, and (4) registered in the work area of the Mangkang Health Center. The exclusion criteria for this study were PIS-PK members who were passive smokers and had a pre-healthy and healthy index. Data was collected through a questionnaire of knowledge, attitudes, and smoking habits. The data that has been collected was analyzed using the Spearman test on SPSS version 26, with a degree of significance was less than 0,05. This research has received ethical approval with the number 082/EC/FK/2020.

RESULTS

Data on knowledge, attitudes, and smoking habits in the sample are in table 1. The table shows that the majority of respondents have sufficient knowledge as many as 34 respondents (42%), negative attitudes 64 respondents (79%), and moderate smokers as many as 45

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respondents (55.6 %).

In table 2, the data were analyzed using the Spearman test. The results showed that the majority of respondents who are heavy smokers have less knowledge as much as 20 (55.6%) of the 36 respondents who are heavy smokers. In comparison, moderate smokers have sufficient knowledge; as many as 24 (55.3%) of 45 respondents were moderate smokers and no light smokers were found. Statistical test results obtained p-value of 0.000 (p<0.05). This shows that there is a relationship between knowledge and smoking habits. The correlation coefficient value was 0.444, indicating a moderate level of relationship between knowledge and smoking habits.

Table 3 shows that the majority of respondents who are heavy smokers have a negative attitude; as many as 25 (69.4%) of the 36 respondents who are heavy smokers, moderate smokers have a negative attitude as many as 39 (86.7%) of 45 respondents who are moderate smokers and not found light smoker respondents. Statistical test results obtained a p-value of 0.005 (p<0.05). This shows that there is a relationship between attitudes and smoking habits. The correlation coefficient value is 0.311, indicating a low level of relationship between attitudes and smoking habits.

Table 1. Individual Characteristic

No	Variable	Category	N=81
1	Knowledge	Poor	24 (29.%)
		Moderate	34 (42%)
		Good	23 (28.4%)
2	Attitude	Very Positive	0 (0%)
		Positive	10 (12.3%)
		Negative	64 (79%)
		Very Negative	7 (8.6%)
3	Smoking Habits	Heavy Smoker	36 (44.4%)
		Moderate Smoker	45 (55.6%)
		Light SMoker	0 (0%)

Table 2. Relationship between Knowledge and Smoking Habits

Knowledge	Heavy Smoker	Moderate Smoker	Light Smoker	p-value	Correlation Coefficient
Poor	20 (55.6%)	4 (8.9%)	0		
Moderate	10 (27.8%)	24 (53.3%)	0	0.000	0.444
Good	6 (16.7%)	17 (37.8%)	0		
Total	36 (100%)	45 (100%)	0		

Table 3. Relationship between Attitude and Smoking Habits

Attitude	Heavy Smoker	Moderate Smoker	Light Smoker	p-value	Correlation Coefficient
Very Positive	0	0	0		
Positive	9 (25%)	1 (2.2%)	0		
Negative	25 (69.4%)	39 (86.7%)	0	0.005	0.311
Very Negative	2 (5.6)	5 (11.1%)	0		
Total	36 (100%)	45 (100%)	0		

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DISCUSSION

In this study, it was found that there was a relationship between knowledge and smoking habits of Tugu District residents who had a low/unhealthy family index in PIS-PK. Based on the questionnaire, the majority of respondents who are heavy smokers have less knowledge. They believe that smoking is a habit that is difficult to break and accept that smoking is not harmful to health and cigarette smoke is not detrimental to those around them. The majority of respondents who are smokers have sufficient knowledge. They believe that smoking causes dependence, but they think that smoking is harmful to health and cigarette smoke is detrimental to those around them (Huong et al., 2016). This study's results align with research conducted by Yan, which shows that smoking is caused by low knowledge (Yan et al., 2014).

In this study, it was found that there was a low-level relationship between knowledge and smoking habits of Tugu District residents who had a low/unhealthy index in PIS-PK. Based on the questionnaire, the majority of respondents who were heavy smokers had a negative attitude. They believe that smoking is free anywhere and will not stop smoking even if sick. While smokers have a negative attitude, they believe quitting smoking is not easy, but it is not impossible. Then they believe that they are more confident when smoking, but they will stop smoking if there are people who are bothered by cigarette smoke. This study's results align with research conducted by Lake, which states that there is a relationship between attitudes and smoking behavior (Lake, Hadi, & Sutriningsih, 2018).

Based on behavioral theory, according to Notoatmojo, before someone adopts a new behavior, within that person, a sequential process occurs, namely awareness, in the sense that the individual knows in advance about the stimulus (object). Furthermore, the subject feels interested in the stimulus or object, then weighs whether or not the stimulus is good for him. Furthermore, the subject begins to try to do something according to what is desired by the stimulus. And in the last stage, the subject has new behavior according to their knowledge, awareness, and attitude towards the stimulus.

One of the most important factors for the formation of a person's behavior is because, from experience, it turns out that behavior is based on knowledge, and attitudes will be more lasting than behavior that is not based on knowledge (Maseda DR, et al. 2013). The limitation of this research is that this research was conducted during the COVID-19 pandemic, thus limiting the scope of the research, and has not examined in depth other behavioral factors on health status.

CONCLUSION

This study concludes that there is a relationship between knowledge and attitudes toward smoking habits of Tugu District residents with a low family index.

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Research Articles

Health protocol implementation with Scabies at Junior High School Kebumen during the COVID-19 pandemic

Adibah Zahra[1], Farindira Vesti Rahmasari[2,3], Gina Puspita[4], Kanti Ratnaningrum[5], Tri Wulandari Kesetyaningsih[2]

1) School of Medicine, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia
2) Department of Parasitology, School of Medicine, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia
3) Department of Molecular Tropical Medicine and Genetics, Tropical Medicine, Mahidol University, Thailand
4) Pediatric Department, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia

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Correspondence:

adibahzahra0626@gmail.com

ABSTRACT

Scabies is a skin disease that is very difficult to get rid of in Islamic boarding schools. Even with the implementation of a fairly strict health protocol during the COVID-19 pandemic, it has not been able to stop its spread. This study aimed to determine the relationship between the implementation of health protocols and scabies cases that occurred at the VIP-Al Huda Junior High School Kebumen during the COVID-19 pandemic. This was an analytic observational study with a case-control research design. The data was collected from December 2021 to February 2022. There were 100 male and female students in grades 7 and 8 who became the study's sample, consisting of 50 students in the case group and 50 students in the control group. Chi-square was used to analyze the data. The results reported that there is a relationship between adherence to the implementation of health protocols (OR 4.750; p 0.001) and scabies cases at the VIP Al-Huda Junior High School Kebumen during the COVID-19 pandemic. It was concluded that compliance with the implementation of health protocols related to scabies cases that occurred at the VIP Al-Huda Junior High School Kebumen during the COVID-19 pandemic.

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INTRODUCTION

Scabies is a skin disease that is an obligate parasitic infection in humans caused by Sarcoptes scabiei var hominis (Thomas et al., 2017). Scabies is a skin disease with a high prevalence worldwide, with an estimated 200 million cases annually (So et al., 2021). In Indonesia, based on Riskesdas 2018, the number of cases of scabies is still an infectious disease that is ranked 3rd out of the 12 most skin diseases in Indonesia (Prasasty, 2020).

Specific symptoms of scabies are in the form of erythematous papules and itching due to mites and products produced by mites such as sputum, eggs, and scabies that cause type I and type IV hypersensitivity (Salavastru et al., 2017). The main reason for the easy spread of scabies is population density, low awareness of clean living, sleeping together, and sharing clothes and towels (Sara et al., 2018). During the COVID-19 pandemic, public awareness of a cleaner life tends to increase to prevent the transmission of COVID-19 (Makruf & Farhan, 2021). Nevertheless, the spread of scabies cases during the pandemic is still quite high. This can be seen in Turkey, where scabies cases became 5.59 times in April 2020 and in the following month became 12.91 times compared to 2019 (Kutlu & Metin, 2020). In Germany, scabies increased by two times in the first four months of 2020 compared to the previous year (Turan & Metin, 2021). In addition, cases of scabies in Spain also drastically increased from March to May 2020 than five years ago (Martínez-Pallás et al., 2020). A study in Indonesia on handling skin health during the COVID-19 pandemic in Ranah Village, Riau, showed that during the COVID-19 pandemic, the most common skin disease was scabies with an estimated 59.18%. One of the reasons for the increase in cases was that during the COVID-19 pandemic, there was a stay-at-home policy so that learning activities were carried out at home online. This has led to a new cluster of intrafamilial scabies cases spreading because, at the beginning of the COVID-19 pandemic, Islamic boarding school students returned to their home areas where scabies cases in Islamic boarding schools were still quite high (Zahtamal et al., 2020).

Prior to the COVID-19 pandemic, the number of scabies cases in Islamic boarding schools was quite high. For example, in Islamic boarding schools in Central Java, the prevalence of scabies reached 54.1% (Istikomah, 2020). Student behavior that can cause easy transmission of scabies disease such as using toiletries, clothes, prayer tools, and towels in turn, and frequently changing beds such as pillows, bolsters, bed linen, and blankets (Widuri et al., 2017). The cleanliness of the boarding school environment that is not maintained is also one of the factors that can facilitate the transmission of scabies disease (Rina, 2017).

During the COVID-19 pandemic, there has been no research on the number of scabies cases in Islamic boarding schools. Policies at Islamic boarding schools are different both before the pandemic and during the COVID-19 pandemic. Islamic boarding schools that have carried out offline learning activities during the COVID-19 pandemic must adhere to strict health protocols. Some health protocols must be implemented include social distancing, not borrowing personal tools, and washing hands (Kemendikbud, 2020). Based on this background, the researcher considers it necessary to conduct research related to the relationship between the application of health protocols and cases of scabies at the VIP Al-Huda Junior High School during the COVID-19 pandemic.

METHODS

This was an analytic observation with a case-control research design which was conducted

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at VIP Al-Huda Junior High School from December 2021 to February 2022. Purposive sampling was applied in this study. The inclusion criteria in this study were students aged 13-14 years, living in Islamic boarding schools for 6 months during the COVID-19 pandemic, and having symptoms of scabies disease (for the case group). As well as for the exclusion criteria, namely students who lived in Islamic boarding schools before the COVID-19 pandemic. There were 100 students from classes 7 and 8, both female and male.

The independent variable in this study was compliance with the implementation of health protocols, while the dependent variable was scabies cases during the COVID-19 pandemic. The respondent's compliance in implementing the health protocol was measured by the respondent's compliance in maintaining distance, not crowding and washing hands which was assessed using 14 questionnaires with a Likert scale. Respondents suffering from scabies were determined based on anamnesis and physical examination conducted by a doctor. Data analysis was carried out in the form of univariate analysis and bivariate analysis with chi-square test and odds ratio. The analysis was carried out using the SPSS16.0 for Windows program, which has a 95% confidence level.

The questionnaire used has been tested for validity and reliability by previous researchers. Before the research was conducted, prospective respondents were given an informed consent form and signed it as an agreement to participate in the study. Then, a scabies examination by a doctor took 50 respondents who suffered from scabies (case) and 50 healthy respondents (control) to fill out the research questionnaire. The data that has been collected will be analyzed using univariate and bivariate analysis with chi-square test and odds ratio. The analysis was carried out using the SPSS16.0 for Windows program, which has a 95% confidence level. This research was conducted after obtaining approval from the ethics committee of the Faculty of Medicine and Health Sciences, Muhammadiyah University of Yogyakarta with number 301/EC-KEPK FKIK UMY/XI/2021

RESULTS

Table 1 shows that the respondents in this study were homogeneous; most of the respondents who suffered from scabies aged 13 years were 30 students. The respondents in this study who suffered from scabies mainly were male, as many as 30 students.

Based on table 2 shows that most of the students, as many as 42 students (42%), are still not compliant with implementing the COVID-19 health protocol.

Based on table 3, the number of respondents who are less compliant in implementing health protocols and suffer from scabies is 30 (60%), more than respondents who do not suffer from scabies, namely 12 (24%). The Chi-Square test results that have been corrected by Fisher Exact obtained P Value Sig. 0.001 < 0.05 means that there is a relationship between health protocol compliance and scabies cases at the VIP Al-Huda Junior High School Kebumen during the COVID-19 pandemic. The odds ratio value shows that students who have low adherence have a 5.758 times risk of developing scabies compared to students who are obedient in implementing health protocols. The results of the Confident Interval (CI) state that respondents who have a low level of compliance have a risk of at least 2,008 times up to a maximum of 11,453 to suffer from scabies disease.

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Table 1. Distribution of subjects by age and gender

Characteristic	Case	Control	Amount
Age			
13	30	25	55
14	20	25	45
Gender			
Male	30	22	52
Female	20	28	48

Table 2. Frequency distribution of compliance with health protocols

Category	Amount	Percentage
Less	42	42%
Compliance	58	58%

Table 3. The relationship between students compliace in implementing health protocols during the COVID- 19 Pandemic with cases of scabies at the VIP Al-Huda Junior High School kebumen

Adhere	Scabies Cases				P	95% CI	OR
	Case	%	control	%			
Less	30	60%	12	24%	0.001	2.008-11.453	4.750
Compliance	20	40%	38	76%			
Total	50	100%	50	100%			

DISCUSSION

In Indonesia, scabies is still a significant concern because in 2013 cases ranged from 3.9-6%, and in 2016 there were 4.60%-12.95% cases, and in 2018 cases of scabies were 6.9% (Prasasty, 2020; Sunarno & Hidayah, 2021). The prevalence of scabies in each region in Indonesia is also quite varied. The prevalence of scabies cases in East Java was recorded at 72,500 cases (Puspita et al., 2018). In addition, the number of scabies cases in 2008 in flats and landfills in Jakarta was 6.20%. The prevalence of scabies cases in Boyolali Regency reached 7.36%, Semarang reached 5.80%, and Pasuruan Regency reached 8.22% (Sembodo et al., 2021).

Before the COVID-19 pandemic, the number of scabies cases in Islamic boarding schools was still quite high. It can be seen in several Islamic boarding schools in Central Java, for example, at the Matholiul Huda Al Kausar Islamic Boarding School, Pati, which showed very high cases of scabies, as many as 84.8% (Mayrona et al., 2018). At the An-Najach Islamic Boarding School, Magelang, scabies cases were up to 43%. In addition, cases of scabies in East Jakarta also showed a relatively high number of 51.6% (Avidah et al., 2019). This can be caused because transmission occurs very quickly through direct skin contact, for example, by shaking hands and sleeping together, or indirectly through clothing (Salavastru et al., 2017). Now, the COVID-19 pandemic has increased public awareness for a cleaner life, which can be seen from public awareness in implementing health protocols (Makruf & Farhan, 2021). Increased clean living behavior can affect the spread of scabies cases (Cletus., 2014).

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The results reported that more cases of scabies occurred in men. These results are also in accordance with the research conducted by Anggraeni & Indira in 2019 and the research of Juliansyah & Minartami in 2017, where these two studies show a relationship between gender and scabies cases (Anggreni & Indira, 2019; Juliansyah & Minartami, 2017). In addition, research conducted by Ratnasari & Sungkar in 2014 also supports the results of this study because it shows that gender is associated (Ratnasari & Sungkar, 2014). This can happen because men are more active than women, thereby increasing the possibility of interacting directly with many people, including people with scabies so that they can become a means of transmitting scabies disease (Anggreni & Indira, 2019). In addition, women tend to pay more attention to their appearance and keep their skin clean than men (Ratnasari & Sungkar, 2014).

The results also show that most cases of scabies occur in younger respondents, namely 13 years. This is in accordance with research conducted by Yudhaningtyas in 2018, which showed that age had a relationship with scabies cases (Yudhaningtyas, 2018). Similar results were also found in a study by Imartha et al in 2017, indicating that age is associated with scabies cases. A study by Suparmi & Supriatna in 2017 also showed a relationship between age and scabies cases. Age can be related to scabies cases because the individual's way of thinking about a disease will improve with increasing age (Imartha et al., 2017; Suparmi & Supriatna, 2015). Therefore, humans will do better things in maintaining cleanliness and preventing and dealing with scabies disease (Ramadhan et al., 2019).

Although there has been no previous research regarding the relationship between implementing health protocols and scabies cases during COVID-19, based on the results of the analysis above, it shows that there is a relationship between student compliance in implementing health protocols for scabies cases at VIP Al-Huda Junior High School during the COVID-19 pandemic. The application of the health protocol referred to in this study is not crowding, washing hands, and maintaining distance. Not crowding can prevent the transmission of scabies cases because crowded locations can be a strategic place for the spread of scabies cases either directly or indirectly (Sfeir & Munoz-Price, 2014). This can be caused by direct transmission through skin contact, which only takes a short time of 15-20 minutes (Banerji, 2015). In addition, transmission without direct contact can occur through sharing personal tools such as clothing and toiletries because mites can live outside the host's body for 24 to 36 hours (Chandler & Fuller, 2019; Tidman & Tidman, 2013).

The second health protocol is to wash hands with an alcohol-based hand sanitizer or soap for 20 seconds to kill the COVID-19 virus (WHO, 2020). The use of water, soap and alcohol can actually not kill scabies mites in the human body (Leistner et al., 2017). However, the use of alcohol as well as soap and water can prevent secondary infection because it can kill microorganisms, including bacteria (Ataee et al., 2017). Soap used for washing hands can be divided into antimicrobial soap and ordinary soap. The difference between the two is that antimicrobial soap contains antimicrobial properties such as triclosan which has been shown to be more selective by inhibiting enoyl-acyl-carrier protein (ACP) reductase, which causes a decrease in fatty acid synthesis. Fatty acids are important ingredients in cell membranes; if reduced, fatty acids will cause cells to die (Giuliano & Rybak, 2015). However, the effectiveness of antimicrobial soap and ordinary soap in killing bacteria did not significantly differ (Kim & Rhee, 2016). However, soap is more recommended than alcohol-based hand sanitizer because of its

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ability to kill bacteria better. Most alcohol-based hand sanitizers contain isopropanol, ethanol, n-propanol, or a mixture of them as active ingredients. The power of alcohol to kill microbes is due to its ability to cause protein denaturation and coagulation which causes the loss of the protective layer on the microbe so that it loses its function (Gold et al., 2022). Soap and water are considered more effective than hand sanitizers because when using soap and water, bacteria will be released from the hands along with the water used to wash hands. Meanwhile, in the use of hand sanitizers, not all bacteria are lost from the hands (Cordita et al., 2019).

Lastly, during the COVID-19 pandemic, there is a policy of maintaining a distance, commonly referred to as social distancing of at least one meter when standing, sitting, or walking with other people to prevent the transmission of COVID-19 (WHO, 2020). This policy can prevent physical contact between individuals. The existence of distance between individuals can prevent transmission of scabies because although female mites can move at a speed of 2.5 cm/min, the mites cannot jump or fly (Gunning et al., 2019; Richards, 2021). The results of this study reveal a relationship between the application of health protocols and cases of scabies during the COVID-19 pandemic. Unfortunately, research on compliance with health protocols and cases of scabies during the COVID-19 pandemic is still limited, so little literature has been obtained to serve as a reference in research. In addition, the sample in this study was quite small because it only obtained data of 100 respondents and was not generalized to the general population.

CONCLUSION

There is a relationship between compliance with the implementation of health protocols and cases of scabies at the VIP Al-Huda Junior High School Kebumen during the COVID-19 pandemic and students with low compliance risk of developing scabies compared to students who comply in implementing health protocols.

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Research Articles

Description of complaints/clinical symptoms and examination results of the SARS-CoV-2 rapid test in Brata Medika Laboratory Clinic Pare - Kediri in February 2021

Acivrida Mega Charisma[1], Arif Rahman Nurdianto[2,3*], Rizal Fauzi Nurdianto[4], Fery Setiawan[5], Heribertus Agustinus B. Tena[6]

1) Lecturer in Universitas Anwar Medika Hospital, Sidoarjo, Jawa Timur, Indonesia
2) Lecturer in Universitas Anwar Medika Hospital, Sidoarjo, Jawa Timur, Indonesia
3) Head of Education and Training Section, Rumah Sakit Umum Sidoarjo Barat, Jawa Timur, Indonesia
4) Student of Medical Faculty, Universitas Wijaya Kusuma Surabaya, Jawa Timur, Indonesia
5) Doctoral Student, Faculty of Medicine, Universitas Airlangga
6) Head of Biodokkes Polda Nusa Tenggara Timur

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Correspondence:

didins99@gmail.com

ABSTRACT

SARS-CoV-2 antigen rapid test is one of the examinations widely used for early detection of Covid-19 infection. Rapid test is considered to have more advantages, is faster, and is cheaper than molecular PCR testing, and more accurate than rapid antibody tests. Its weakness is especially in detecting samples with small quantities of the virus. The study was conducted using a retrospective method. The data was taken from the patient's medical record of the SARS -CoV-2 antigen rapid swab test at Brata Medika Pare Clinical Laboratory for the period of February 2021. Data inclusion criteria including the examination, complete identity, results of anamnesis examination and rapid test examinations. Data were analyzed in a tabular form containing frequency and percentage. There were 18 (22.5%) patients with positive SARS-CoV-2antigen rapid swab test results, 16 (89%) with complaints/symptoms, and 2 (11%) without complaints/symptoms. Meanwhile, 62 (77.5%) were found with negative SARS-CoV-2 antigen rapid swab test results where 18 (29.0%) were patients with complaints/symptoms and 44 (71.0%) were patients without complaints/symptoms. The high percentage of negative SARS-CoV-2 antigen rapid swab test results in patients with complaints/symptoms (29.0%), it is recommended that a confirmatory examination with the molecular PCR test be carried out.

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INTRODUCTION

The Covid-19 disease was first reported at the end of December 2019 in Wuhan, China. Later in early 2020, the World Health Organization (WHO) announced the Covid-19 disease as a pandemic that had spread in more than 200 countries. This disease is caused by the virus Severe Acute Respiratory Syndrome Coronarius-2 (SARS-CoV-2), which is round with a diameter ranging from 60-200 nm with many spikes in the viral capsid and is classified as a single-stranded RNA virus (26-32 kb) (Xiaolong, 2020). This disease is transmitted between humans through droplets from the nose or mouth of a person infected with Covid-19 when coughing, sneezing, or talking (World Health Organization, 2020a). WHO estimates SARS-CoV-2has a relatively high reproductive number (RO) ((RO: 1,4-2,5) although not as high as SARS-CoV (RO: 2-5), but higher than MERS-CoV (RO: <1) (Chen 2020; Setiawan et al. 2020; Setiawan and Nurdianto 2021; Setiawan et al. 2021; Nurdianto AR, Tena HAB 2021).

Standard recommendations to prevent the spread of this viral infection are through washing hands regularly using soap and clean water, wearing a mask, establishing the ethics of coughing and sneezing, and carrying out social boundaries. In addition, it has been recommended to maintain distance when in crowded areas or with other people showing symptoms of respiratory diseases such as coughing and sneezing (Guo et al., 2020). In respiratory viruses, diagnosis depends on two clinical manifestations such as fever, fatigue, dry cough, dyspnea, and gastrointestinal symptoms, as well as an accurate diagnostic examination (Burhan E, Isbaniah F, Susanto A, Yoga Y, Tjandra A, 2020). According to WHO, the latest symptoms of Covid-19 include fever, dry cough, and fatigue. Other symptoms of losing taste/smell, runny nose, conjunctivitis (red eye), sore throat, headache, muscle or joint pain, skin rashes, nausea, vomiting, diarrhea, dizziness, chills, and shortness of breath, and many more. The symptoms experienced are usually mild and appear gradually (M. K. Rohmah & Rahman Nurdianto, 2020; M. Rohmah & Nurdianto, 2020; World Health Organization, 2020a)

At the beginning of the Covid-19 pandemic, WHO only recommends laboratory tests with nucleic acid amplification (NAAT) such as real-time Reverse Transcription-Polymerase chain reaction (RRT-PCR) to detect SARS-CoV-2which is the disease maker virus (World Health Organization, 2020b). The RT-PCR method detects the presence of the virus in the patient's body through a polymerase chain reaction with a primer or probe that specifically targets the SARS-CoV-2genome so that the amount of SARS-CoV-2 DNA in the specimen can be counted (Xiaolong, 2020). The other tests that are much simpler, cheaper, and faster, often called rapid diagnostic tests (RDT). RDT is a rapid test for detecting antibody (IgG and Ig M) SARS-CoV-2 where the blood sample is developed. The response of human antibodies to fight the virus in early infection can be used to support the diagnosis of a viral infection. Detection of IgM antibodies can indicate recent exposure to SARS-CoV-2, whereas detection of IgG antibodies indicates long-standing viral exposure (Li et al., 2020; The Association of Indonesian Clinical Pathology and Laboratory Medicine Specialists (PDS PatKLIn), 2020)

Most of the rapid atomic tests for Covid-19 use the sandwich immunodetection method with the easy-to-use lateral line test format and are commonly used for testing for HIV, malaria, and influenza. The rapid antigen test typically consists of a plastic cassette with a sample cavity and buffer and a nitrocellulose matrix strip with a test line with an antibody bound to the target conjugated antigen-antibody complex and a control line with an antibody bound to the conjugated antibody (World Health

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Organization, 2020c). The specimens used in this test are a swab nasopharynx or rub the oropharynx (swabs airways) (The Association of Indonesian Clinical Pathology and Laboratory Medicine Specialists (PDS PatKLIn), 2020). If the concentration of the target antigen in the sample is sufficient, the antigen will bind to the antibodies on the test strip. It will produce a visual signal, usually within 10 - 30 minutes (Koczuła & Gallotta, 2016). The detected antigen can only be expressed when the virus is actively replicating. Therefore, this test is best used to identify infection in the acute phase or early stage of infection.

METHODS

Study setting

The study was conducted using a retrospective method. Data was taken from the patient's medical record for the SARS-CoV-2 rapid antigen test at the Brata Medika Pare Clinical Laboratory for the period of February 2021, with complete data inclusion criteria including the examination carried out in February 2021, complete identity, analysis examination results, and the results of the rapid antigen test SARS-CoV-2. Data were analyzed in a tabular form containing frequency and percentage. This study has been ethically approved (The certificate number of ethical clearance is 893.3/022/438.6.7/2022).

The rapid antigen test typically consists of a plastic cassette with a sample cavity and buffer and a nitrocellulose matrix strip with a test line with an antibody bound to the target conjugated antigen-antibody complex and a control line with an antibody bound to the conjugated antibody (World Health Organization, 2020c). If the concentration of the target antigen in the sample is sufficient, the antigen will bind to the antibodies on the test strip and will produce a visual signal usually within 10 - 30 minutes (Koczula and Gallota, 2016). The detected antigen can only be expressed when the virus is actively replicating (Anita, 2020).

Sample size calculation

The number of samples taken is using the formula Slovin n = N / (1 + (N x e^2)), where N is the population: 1 0 0, e: margin of error 5% (0.05), with a degree of confidence of 95% obtained n the number of samples: 80. This study uses the Covid-19 brand test reagent (SARS-CoV-2) Antigen Test Kit (Colloidal Gold) from Anhui Deepblu Medical Technology Co. Ltd, with the Indonesian Ministry of Health license number AKL 20303028147.

RESULTS

Characteristics of Respondents

Table 1. Characteristics of respondents

Age (Year)	Frequency (n)	Percentage (%)
0-10	2	2.5
11-20	11	13.8
21-30	18	22.5
30-40	14	17.5
>40	35	43.7
Gender		
Men	39	48.8
Women	41	51.2
Total	80	100

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Table 2. Distribution of Respondents with and without Clinical Complaints/Symptoms.

Anamneses	Frequency (n)	Percentage (%)
With symptoms (fever, dry cough, fatigue, losing taste/smell)	34	42.5
No symptoms	46	57.5
Total	80	100

Figure 1. The process and final result of the rapid antigen test

Table 3. Distribution of SARS-CoV-2Antigen Rapid Test Results.

Checkup result	Frequency (n)	Percentage (%)
Positive (+)	18	22.5
Negative (-)	62	77.5
Total	80	100

Table 4. Distribution of Anamnese Results and Results of the SARS-CoV-2 Rapid Antigen Test.

Result	Results of the SARS-CoV-2 Rapid Antigen Test		Total
	Positive (+)	Negative (-)	
Anamnese	n (%)	n (%)	n (%)
With symptoms (fever, dry cough, fatigue, losing taste/smell)	16 (88.9)	18 (29.0)	34 (100)
No symptoms	2 (11.1)	44 (71.0)	46 (100)
Total n (%)	18 (100)	62 (100)	80 (100)

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The data in table 1 shows that the age range> 40 years is the largest age among respondents in this study with a total of 35 (43.7%) and the lowest is in the age range 0 - 10 years as much as 2 (2.5%).

Distribution of Respondents

Table 2 shows that 34 (42.5%) respondents in this study experienced clinical complaints/ symptoms when carrying out a rapid antigen test examination and 46 (57.5%) respondents experienced no clinical complaints/symptoms.

Figure 1 shows the process and final result of rapid antigen test examination. The former shows the initial result of rapid antigen test examination. The latter shows the final result of the rapid antigent test examination.

Table 3 illustrates that in this study, out of 80 respondents, it was found that 18 (22.5%) respondents had positive results on the SARS-CoV-2rapid antigen test, and 62 (77.5%) had negative results. 22.5% is a fairly high prevalence. For that, it is necessary to take further action in coordination with the tracing team from the nearest health center to carry out a confirmation check with RT-PCR, close contact tracing to prevent wider spread, and advice to do quarantine or independent isolation according to the criteria and apply PHBS (healthy lifestyle: washing hands, applying cough etiquette, using masks, maintaining stamina) and physical distancing.

Table 4 shows that in this study, 16 (88.9%) respondents from 18 who had positive SARS-CoV-2antigen rapid test results had clinical complaints/symptoms, and 2 (11.1%) had no complaints/symptoms. Meanwhile, the respondents with negative rapid test results were found to be 18 (29.0%) with clinical complaints/symptoms and 44 (71.0%) without clinical complaints/symptoms.

DISCUSSION

Immune status is indeed a factor that needs to be considered in the transmission/spread of Covid-19 infection, and age affects immunity status. According to experts from Imperial College, London, UK, the immune system will decrease with age due to reduced quality of the cells you have, for example, naive T-Cell, which is a group of immune cells. Usually, these cells will go around warning them when they find an infection. However, when cells age, less naive T-Cells are formed. This is because the small glands behind the breastbone (thymus) where they develop have shrunk (Budi et al, 2020).

Meanwhile, based on gender, there was no significant difference in numbers and percentages. Both men and women had the same risk of being infected with Covid-19. The immune system is not influenced by the sexual fetus but rather by the health status of the individual (Aspinall, 2005)

Clinical complaints/symptoms and contact with a confirmed patient with Covid-19 are the conditions recommended for the SARS-CoV-2 rapid antigen test. Symptoms commonly experienced by respondents in this study include weakness and fatigue (such as fainting), nasal congestion, hoarseness, fever, body aches, and dizziness. WHO mentioned these clinical complaints/symptoms as typical signs of Covid-19 infection (World Health Organization, 2020a).

Table 3 illustrates that in this study, out of 80 respondents, it was found that 18 (22.5%) respondents had positive results on the SARS-CoV-2rapid antigen test, and 62 (77.5%) had negative results. 22.5% is a fairly high prevalence. For that it is necessary to take further action in coordination with the tracing team from the nearest health center to carry out a confirmation check with RT-PCR, close contact tracing to prevent wider spread, and advice to do quarantine or independent isolation according

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to the criteria and apply PHBS (healthy lifestyle: washing hands, applying cough etiquette, using masks, maintaining stamina) and physical distancing. Whereas respondents with negative rapid antigen test results do not rule out the possibility of being infected with SARS-CoV-2so that they are still at risk of transmitting to others, it is recommended to do a repeat test or confirmatory test with NAAT (nucleic acid amplification test) if the pretest probability is relatively high, especially if the patient is are symptomatic or known to have had contact with a person confirmed to have Covid -19, and negative results can also occur when the quantity of antigen in the specimen is below the level of detection of the instrument (The Association of Indonesian Clinical Pathology and Laboratory Medicine Specialists (PDS PatKLIn), 2020).

Table 4 shows that in this study, 16 (88.9%) respondents from 18 respondents who had positive SARS-CoV-2antigen rapid test results had clinical complaints/symptoms, and 2 (11.1%) had no complaints/symptoms. Meanwhile, the respondents with negative rapid test results were found 18 (29.0%) with clinical complaints/symptoms and 44 (71.0%) without clinical complaints/symptoms. The high percentage of respondents with clinical complaints/symptoms with negative results of the rapid antigen test can be a suspicion of false-negative results. This is due to the data and the fact that the rapid antigen test can only detect components of the SARS-CoV-2virus in the early case detection. It is the phase where the viral load is still high. Therefore, the virus replication period is still ongoing and will decline as the disease progresses (Agustina & Fajrunni'mah, 2020). Besides that, the inability of the staff to collect specimens can also affect the results obtained. A low quantity of antigen below the test detection level can also be the cause of false-negative results. So that in cases like this, it is recommended to do an examination or confirmation test with a NAAT-based examination such as RT-PCR (The Association of Indonesian Clinical Pathology and Laboratory Medicine Specialists (PDS PatKLIn), 2020).

CONCLUSION

From this research, it can be concluded that from the 18 respondents with antigen rapid test results, SARS -CoV-2 positive get the 16 (89%) with complaints/symptoms and 2 (11%) without any complaints/symptoms. From 62 (77, 5 %) with negative SARS-CoV-2 rapid antigen test results, 18 (29.0%) were patients with complaints/symptoms and 44 (71.0%) were patients without complaints/symptoms. The high percentage of negative SARS-CoV-2 rapid antigen test results in patients with complaints/symptoms (29.0%) could be due to a decrease in viral load (old infection). Thus it is suspected of producing false negatives as a follow-up, and it is recommended to perform a confirmatory examination with the RT- PCR molecular test. Complaints/clinical symptoms experienced by patients who test positive for rapid antigen in this research include runny nose, weakness, fatigue (such as fainting), hoarseness, fever, body aches, cough, and dizziness.

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Research Articles

Correlation between exclusive breastfeeding and obesity among children at kindergartens in Una-Una Central Sulawesi

Dipta Tejo Nugroho[1*], Sepfrita Katerine Aftabuddin[2]

1) Hospital Management Student of Universitas Airlangga, Surabaya, Indonesia

2) Department of Pediatrics, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

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Correspondence:

dr.dipta.nugroho@gmail.com

ABSTRACT

Obesity has become a global health problem that strongly correlates with morbidity and mortality. Despite the importance of obesity, there remains a paucity of evidence on obesity among kindergarten children in Tonjouna, Central Sulawesi. Obesity in children is influenced by various factors, one of which is exclusive breastfeeding. This study aims to find the correlation between exclusive breastfeeding and obesity among children aged four to six years in three kindergartens in Una-Una. The study uses a cross-sectional design involving all children at this kindergarten. Anthropometric measurement was carried out in school before questionnaires were distributed to determine the number of breastfeeding given to the children. The data analysis revealed that 25% of children suffer from obesity. Five out of 68 children or 29.4% of those who get exclusive breast milk suffer from obesity. The statistical analysis using the Chi-square test shows a p-value of 0.002 ($p<0.05$), which means that exclusive breastfeeding correlates with obesity in children aged four to six years. This is rather disappointing that the percentage of obesity is relatively high. Hence, educating parents and schools about the causes, risks, and ways to prevent obesity is necessary.

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INTRODUCTION

Obesity is an increasingly important issue in global public health. WHO reported that obesity in children has been increasing over the last decade (Skinner *et al.*, 2018). It is estimated that more than 100 million people are suffering from obesity. Patients with obesity have a higher possibility of experiencing morbidity and mortality than those with average weight. In a study from Liendsberg et al., obesity in childhood increases the risk of mortality in early adulthood compared to theeneral healthy population (Lindberg *et al.*, 2020). Therefore, this condition needs special attention. Rachmi and Baur had conducted a study examining the prevalence of obesity in children and adolescent in Indonesia. The prevalence of obesity in children was 5,1%, while in Central jawa province, the prevalence of obesity was higher in non-poor urban children compared to rural and poor urban children (Rachmi, Li and Alison Baur, 2017).

One of the risk factors for childhood obesity is a lack of exclusive breastfeeding (Wallby, Lagerberg and Magnusson, 2017). A prior systematic review study reported that infants exclusively breastfed for six months are less likely to suffer from obesity. Breastfeeding provides adequate physical growth and a lower risk of gastrointestinal infection (Frank *et al.*, 2019) Palaska's study shows that the percentage of children with normal weight was higher in those who were breastfed for over six months or received exclusive breastfeeding. While the percentage of underweight and overweight children was lower in those, who got exclusive breastfeeding (Palaska *et al.*, 2020). A meta-analysis study stated that out of 17 studies have reported significant protective factors against obesity in children (Yan *et al.*, 2014a).

There has been limited study of risk factors of obesity in children based on age groups, specifically in Indonesia. Most studies focused on modifiable determinants and the driving factors of obesity and overweight. However, most studies are not concerned with the effect of obesity on specific age groups of children. We aimed to fill this gap in the literature on the correlation between exclusive breastfeeding and obesity among children aged four to six in Indonesia. We hypothesized a correlation between a lack of exclusive breastfeeding and a higher risk of obesity in children aged four to six years in Tojo Una-Una, Central Sulawesi.

METHODS

This cross-sectional observational survey study was fielded from June to October 2017. We include the data from three kindergartens in Una-una, Central Sulawesi. Most of the people in this area are farmers, including mothers of childbearing age. It causes most women in this area not exclusively breastfeed their children. The Ethics Committee has approved this study with ethical clearance number 319/HRECC. FODM/VI/2022.

Population and research samples

This study's population was all Una-una Kindergarten students in Central Sulawesi. A simple random sampling method was used to select the research participants. Using the formula of large samples, we obtain that the minimum number of samples is 68 children. In addition, selected subjects' mothers are also involved in the study. The first inclusion criteria in this study were children aged four to six years who are students from Al-Ikhlas Una-una Kindergarten, Central Sulawesi. Furthermore, the other criteria were mothers and their children willing to participate in this study based on informed consent. Children and mothers who are unwilling to participate in this study and children who suffer from chronic diseases (tuberculosis, chronic diarrhea, diabetes mellitus, chronic liver disease, kidney disease,

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Chronic hypothyroidism, or hyperthyroidism based on a physician's diagnosis) are excluded from the study.

Research instruments

The instrument used in this study was a questionnaire distributed to the children and then collected for analysis. The questionnaires comprised the explanation of the study and informed consent. In addition, the questionnaires were used to document the patient's demographic data and exclusive breastfeeding records. Breastfeeding is considered exclusive if it is given for six whole months. When it is only given less than six months, it is categorized into non-exclusive breast milk. The study used a digital scale with a precision of 0.1 kg to measure a child's weight, a Microtoise with a precision level of 0.1 cm to measure their height, a calculator to calculate the body mass index as well as the growth curve of the CDC 2000 Body Mass Index -for- percentile (Kuczmarski *et al.*, 2000).

Variable measurement

To ensure accuracy, the researcher utilized a digital bathroom scale set on a flat platform. Before the weight measurement, children were asked to take off their shoes, hat, and all objects on their bodies that may influence the scale. The child's position was perpendicular with a straight look forward and feet stepping on the scale. Afterward, the researcher read the numbers that appeared on the scale. The height measurement utilized OneMed Microtoise placed on a flat, two-meter wall. The lowest point, 0 (zero), was located at the lowest position on the ground. Children were measured without shoes and head coverings (ribbons used by girls will be removed if it affects the measurement). Then, the children stood upright with straight legs, and their heels, back, buttocks, and back of the head should touch the wall with the eye should be straightforward. The researcher lowered the Microtoise precisely on the children's upper head while the elbow should be straight, touching the wall. The researcher read the scale numbers in the Microtoise, representing the students' height.

The child's age was calculated by subtracting the child's date of birth from the data collection date. If the number of days is less than 15, it is rounded down and rounded up if it is more than 15 days. Parents or school caregivers filled out the shared questionnaires. Children's obesity was determined using the 2000 CDC growth curve based on anthropometric measurements (Kuczmarski et al., 2000).

Statistical analysis

Data was presented in the form of categorical data scales. The collected data were processed by following the process of editing, verification, and number (coding) answer questions. Furthermore, the data were converted into numbers, input into SPSS 21.0 software, and tested using Chi-square tests. The p-value < 0.05 was considered statistically significant.

RESULTS

A total of 68 children met the study's inclusion criteria. There were 40 male children, which comprised 59% of the sample. Children who receive exclusive breastfeeding are 43 (63%). Afterward, there are 45 children (66.2%) with normal Body Mass Index (BMI), consisting of 26 boys (38.2%) and 19 girls (27.9%). Children with an overweight BMI are six (8.8%), consisting of two boys (2.9%) and four girls (5.9%). Children with BMI obesity grade I are 11 children (16.2%), consisting of nine males (13.2%) and two females children (2.9%). Nevertheless, children with BMI obesity grade II are as many as six children (8.8%), consisting of three males (4.4%) and three females (4.4%). Patient characteristics related to the measurement can be seen in **Table 1.**

Twenty-five out of the 68 children involved

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Table 1. Demographic and BMI characteristic of subjects in this study

Demographic Characteristic n (%)	Value	
Gender		
Male	40 (59%)	
Female	28 (41%)	
Breastfeed		
Exclusively breastfed	43 (63%)	
Non-exclusively breastfed	25 (37%)	
	Male n (%)	**Female n (%)**
Normal BMI	26 (38.2%)	19 (27.9%)
Overweight	2 (2.9%)	4 (5.9%)
Obesity grade I	9 (13.2%)	2 (2.9%)
Obesity Grade II	3 (4.4%)	3 (4.4%)

Table 2. Chi-square statistical analysis

Breastfed history	Abnormal BMI n (%)	Normal BMI n (%)	Total n (%)	p-value
Non-exclusively	12 (70.6)	13 (25.5)	25 (36.85)	0.002
Exclusively	5 (29.4)	38 (74.5)	43 (63.23)	
Total	17	51	68	

in the study were given non-exclusive breastfeeding. 11 of them (16.2%) had normal BMI, two (2.9%) were overweight, eight (11.8%) were categorized to obesity grade I, and four (5.9%) were categorized to obesity grade II. Meanwhile, 43 children who are exclusively breastfed show different BMI. Thirty-four children (50%) perform normal BMI, four of them (5.9%) have overweight BMI, three children (4.4%) with BMI obesity grade I, and two children (2.9%) with BMI obesity grade II.

The correlation analysis of exclusive breastfeeding with the incidence of obesity using the Chi-square test shows that $p = 0.002$ ($p<0.05$). This result means that a lack of exclusive breastfeeding leads to obesity in children aged four to six. Therefore, it concludes that non-exclusive breastfeeding affects the possibility of obesity in children.

DISCUSSION

This study's percentage of obesity incidence is 25%, much higher than the percentage of obesity results of the 1999 Indonesian National Health Survey, which is 4.58%. It can happen due to the significant differences in the samples used in this study. Here, the study subjects were taken in Una-Una area, an area with a majority of the booming population, while in the 1999 Indonesian National Health Survey, the subjects used came from all over Indonesia.

The percentage of obesity incidence also shows

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an increase in private elementary school, overweight (17%) and obesity by 30.75% in South Jakarta (Annisa and Sumartini, 2021). A study in Iran also showed the prevalence of overweight by 19.7%. In that study, exclusive breastfeeding were not correlated with childhood BMI (Vafa *et al.*, 2012). Overweight in children of elementary school might due to various nutritional problems Those studies were conducted in elementary school, while this study was conducted in kindergarten. Therefore, the subjects studied have different age characteristics. Elementary school children are exposed to various foods sold in school more than kindergarten children (Welker, Lott and Story, 2016). More than that, elementary school children spend longer time in school than kindergarten children.

Risk Factors of Breastfeeding

Based on research in developed countries, the relationship between obesity and breastfeeding is still controversial. Some studies show protective effects, while others have found no difference. The researchers calculate and use *odds ratios* and show that the more children are not given exclusive breastfeeding, the greater the incidence of obesity. The incidence of obesity in children with exclusive breastfeeding is 29.4% and increases to 70.6% in children with non-exclusive breastfeeding. We consider the confounding and bias in this study as we know that other risk factors contribute to obesity. We excluded children with chronic diseases to avoid bias and control the confounding factors.

Exclusively breastfed children have 7.015 times fewer obese risk factors than non-exclusively breastfed children. Exclusive breastfeeding prevents obesity 0.143 times compared to children who are not exclusively breastfed. In other words, exclusive breastfeeding can prevent obesity. Another meta-analysis study stated that breastfeeding is inversely correlated with the incidence of obesity in children aged from two to six years (Qiao *et al.*, 2020).

Weight gain occurs more precisely in babies who are given instant milk because of the tendency of parents to force their babies to drink milk in a bottle at once. Parents tend not to decrease the quantity of milk given even though the baby has consumed other foods than milk. Infants exclusively breastfed can control input energy, and exclusive breastfeeding does not contain sugar or additional fat (*trans-fat*). Cheshmeh stated that some genes increase body weight, including FTO, CPT1A, and PPAR-α genes. Expression of these genes was found to be lower in those who got exclusively breastfeeding compared to formula-fed and mix-fed children. In addition, infant's formula milk contains high levels of branched-chain amino acids (BCAAs) and glutamine that increase gene expression (Cheshmeh *et al.*, 2020).

The results of this study correspond with Sulanto (2012) in Indonesia, and Wang (2017) in the United States. The studies, as mentioned earlier, show that breast milk has a protective effect on the incidence of obesity and *overweight* (Sulanto, Wandita and Julia, 2012; Wang *et al.*, 2017). Similar with a study by Yan in 2017, an American study finds an inconsistent relationship between breastfeeding, duration, and risk factors for *overweight* children (Yan *et al.*, 2014b). However, unlike research conducted by Li in 2003 that shows a tendency to increase the risk of obesity incidence, these results do not have a significant statistical percentage (Li, 2003).

The results of research conducted both abroad and domestically showed different results. It may happen because the research subjects used as comparisons by researchers have different characteristics, namely subjects from developing and developed countries. Therefore, it is important for mothers during pregnancy to study the identification of the development of

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newborn risks in place early action to prevent childhood obesity in the future (Thibault *et al.*, 2022).

This study uses *a cross-sectional* design, so it becomes the study's limitation. This design cannot analyze the causal relationship between the two variables. In addition, there is no Validity Test and Reliability Test in this study because it does not use questionnaires on the Likert scale (Joshi *et al.*, 2015).

CONCLUSION

There is a correlation between exclusive breastfeeding and obesity in children aged four to six years. Children given exclusive breast milk have a seven times lower risk of obesity than those given non-exclusive breast milk. Further research is needed with a larger sample. We hope that the upcoming research can determine how much the percentage of obesity increases and detect excessive weight gain early.

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Research Articles

Informed consent management guidance model of regional anesthesia: Education of young doctors in Teaching Hospitals

Titin Setyowati*, Aisyah Ladji

1,2) Faculty of Medicine, Universitas Muhammadiyah Semarang, Semarang

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****Correspondence:***

Titinsetyowati113@gmail.com

ABSTRACT

Informed consent is not necessarily a guarantee for a hospital or health service to avoid disputes between the health provider and the recipient of the health service. This can be caused by the disruption of communication that is less effective and efficient where an Anesthesia Co-Assistant is less clear in delivering the informed consent problem so that the patient has another understanding of what the Anesthesia Co-Assistant is saying. So it takes guidance for Co-Assistant Anesthesia to have comprehensive abilities about a) understanding of regional anesthesia, b) understanding of regional anesthetic techniques, c) understanding of indications and contraindications, d) understanding of drug pharmacology, e) understanding of how to deal with complications, f) understanding of effective communication with patients.

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INTRODUCTION

Guidance is an assistance service for each student, whether carried out independently or individually, whether carried out in groups or groups, to increase independence and develop personal life, social life, skills in learning, skills in planning further careers, with many kinds of services and supporting activities following applicable regulations (Hikmawati, 2016). With directed and measurable guidance, it is hoped that students will be able to achieve the targets or achievements that have been set or formulated previously.

Guidance on Regional Anesthesia Inform Consent is intended for Anesthesia Co-Assistant Students to improve and condense the basic abilities of a prospective Anesthesiologist on a matter that will be in their field. In practice, problems that occur cannot be resolved with informed consent. This means that even though a doctor has provided information and approval, the potential for a dispute will still happen (Looqman, 2000). Regarding this, it can be concluded that the element of delivery is one of the most critical things in increasing the understanding of the patient and the patient's family and avoiding disputes about things that are not expected.

Informed consent is two words that have independent meanings: Informed, which means obtaining information, and consent, which means agreeing or giving permission. So we can conclude that informed consent is an agreement made after obtaining information (Karbala, 2000). The consent given by both the patient and the patient's family must be based on a comprehensive or comprehensive understanding so that the patient and the patient's family can determine whether or not to agree or reject the policies that have been conveyed to the patient and the patient's family either through a doctor or a medical officer on duty.

The level of effectiveness in communicating depends on what method is used. An approach is needed to strengthen communication, namely an ontological approach (the definition of communication), but also axiologically (the process of effective communication) and epistemologically (the function of implementing a communication). Important things in communication that are used in a mentoring, include: (1) the content of what you want to convey as an outcome, (2) the experience and thinking power of students, (3) having a curiosity that makes it active, (4) the response from students. students or guidance participants, and (5) practice rooms for students (Miftah, 2017).

One of the keys to building relationships and improving skills is communication. So that someone can send messages properly and be able to be received according to the content of the message to be conveyed, accuracy and effectiveness in communication are needed. Proper delivery is expected to reduce the risk of disputes that occur due to failure to understand the message intended by the sender of the message. Skills in sending and receiving messages are highly dependent on individual skills. (Sari, 2016) Competence in communicating, of course, makes it important and determines success in health problems experienced by a patient. Effective communication can be a solution to reduce patient doubts, and increase the value of patient compliance (Setyowati, 2021) Because Anesthesia Co-Assistants have various stressors and can be analogized as "novice" workers in the health sector who are prone to make mistakes accidentally because of lack of experience (Putra & Aryani, 2015).

With the ability of an Anesthesia Co-Assistant who is not yet shrewd in processing messages in conveying information that is so important and must be understood by the patient and the patient's family, who will later determine whether or not to agree or not through informed

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consent, it is feared that it will become an event that triggers a dispute between medical staff and patients and their families who will receive medical treatment (Abdu Rauf, 2019).

Co-Assistant and patient can act as a receiver or as a message senders. The patient will convey all the complaints he feels, and the doctor will respond according to his knowledge, and the doctor is obliged and responsible to ensure that the patient understands what the doctor on duty is saying (Ali et al., 2006). Communication does not always end well in the context of solving health problems experienced by patients, one of the most important things in increasing the level of patient compliance with a doctor or co-assistant is an effective communication network because with the realization of effective communication between both parties are expected to be able to be a solution to resolve (Fourianalistyawati, 2012).

Co-Assistants must be able to provide complete and appropriate services; of course, this is not something that is easy to do, especially regarding the healthy lifestyle that has been carried out by patients, because the level of patient compliance can be influenced by cultural factors (Larasati, 2019). The level of compliance and patient anxiety can be increased by an effective communication method to explore the extent to which a doctor can actually explore the relationship or bonding between a patient and Co-Assistant Regional Anesthesia (Pratita et al., 2014). This problem is hampered by communication between the two parties, which often causes the problem to have more opinions to show or raise problems than to choose an opinion to find solutions to the issues at hand (Sari, 2016). An Anesthesiologist's guidance is also needed to regulate and control a good, clear and smooth delivery method. Because by mastering this ability, it is likely that the patient will understand everything that is done by a health worker attached to the informed consent will become easier for the patient (Setyowati et al., 2020).

METHOD

This study uses a qualitative method with interview techniques, which has been approved by the ethics section. In-depth, formal, and open interviews are the main points in qualitative nursing. A formal qualitative interview is a conversation that does not have a structure and usually aims to prioritize verbatim (word for word) data transcripts. A rigid question structure is not an option in making interview guidelines. The interview guide was prepared using a set of general questions. The general rule in qualitative interviews is to allow time and flexibility for participants to capture as much information as possible from a fairly broad data source. The purpose of doing this is to capture the participants' perspectives (Robinson, 2000), followed by a discussion about using informed consent for the maximum of 15 Anesthesia Medical Students practicing at Roemani Muhammadiyah Hospital Semarang. Each interview session is carried out for approximately 60 minutes with a discussion of informed consent relating to a) understanding of regional anesthesia, b) understanding of regional anesthetic techniques, c) understanding of indications and contraindications, d) understanding of drug pharmacology, e) understanding of how to handle complications, f) understanding of effective communication with patients.

RESULT

From discussions and interviews conducted with 15 medical students conducted at the Roemani Muhammadiyah Hospital in Semarang, the following results were found :

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Table 1. Understanding of informed consent

Understanding of informed consent items	Yes (%)	No (%)
Able to convey about regional anesthesia	27	73
Able to convey regional anesthetic techniques	13	87
Able to convey indications and contraindications	20	80
Able to convey about drug pharmacology	47	53
Able to convey how to handle complications	33	67
Able to convey effective communication with patients.	13	87
Average ability to convey material	26	74

Students who are practicing are less able to communicate effectively and efficiently in delivering general anesthesia to anesthesia patients at Roemani Muhammadiyah Hospital Semarang. The language conveyed tends to use complicated diction choices that potentially reduce the patient's sense of trust in medical personnel (Co-Assistant Anesthesia).

DISCUSSION

In this study, the 15 students who participated in the interview session still had difficulty communicating effectively and efficiently with patients. One of the most common reasons found in this interview is the feeling of nervousness when meeting directly with patients and their families. What has been learned from the learning period while at the Faculty is sometimes simply forgotten and causes what is conveyed to patients becomes convoluted, more complicated and difficult to understand.

The factor regarding mastery of the material has also become the focus of researchers in making assessments of Anesthesia Medical Students who are practicing at Roemani Hospital. With poor knowledge of the material, they cannot carry out proper communication analysis and provide answers as desired by the patient or the patient's family.

In these discussions and interviews, the researcher also provided full guidance and gave examples of cases that an anesthesiologist would often face in the actual work field. As an Anesthesiologist, the delivery of General Anesthesia must be conveyed simply so that there is no failure to understand the patient. The way it works and the schema of the nervous system is quite complex; it must be able to reach the patient clearly in simple word choices, considering that the patients at Roemani Hospital are quite diverse.

The Anesthesia Medical student has the same obstacles in delivering, namely the lack of experience directly dealing with patients so that it creates a sense of nervousness, public speaking skills that have not been sufficiently trained and an incomplete understanding of regional anesthesia, regional anesthetic techniques, indications and contraindications, drug pharmacology, how to handle complications, effective communication with patients. The

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researcher also provides tips that can help the Anesthesia Medical Student when he later becomes an Anesthesiologist who practices at the hospital. And also the delivery of 6 (six) ways to overcome communication comprehension, namely by preparing and practicing, putting communication comprehension from a different point of view, trying to stay relaxed, focusing on success, improving skills and experience in communicating, and getting used to being in situations to communicate (DeVito, 2007).

The theories that the Anesthesiologist Co-Assistant has accepted during his studies at the Faculty of Medicine cannot be directly used to answer or educate every question posed by the patient. The ability to process words verbally certainly requires experience in the field to ensure the patient and the patient's family convey any theories that are in accordance with the conditions in the field. With a theoretical basis that is not strong and is not sure, of course, it cannot convince the patient's family. The delivery method is stammering; body movements that look doubtful can reduce the level of confidence of the patient and the patient's family towards a doctor or Anesthesiologist Co-Assistant.

It takes guidance through flowing discussions and providing examples of cases in the field to increase the confidence of the Anesthesia Co-Assistant in conveying the appropriate informed consent, which must be approved or rejected by the patient without hesitation. So that it minimizes the potential for patient misunderstanding and minimizes the occurrence of disputes that can arise during health care at the hospital.

CONCLUSION

Discussions and interviews conducted between researchers and 15 Anesthesia Medical Students for 2 weeks showed that the communication method between Anesthesia Medical Students and patients and their families was not effective and efficient due to the lack of a comprehensive understanding of regional anesthesia, regional anesthetic techniques, indications and contraindications, pharmacology of drugs, how to deal with complications, effective communication with patients, so it is necessary to provide general and specific guidance to deal with situations that may be faced by an anesthesiologist during practice.

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Case Report

DUTCH (Dried Urine Test for Comprehensive Hormones) as a method for detecting disease-related to hormone function

Asti Widuri[1], Rizka Fakhriani[2*], Qorry Agustin[3], Astika Cahyarani[4]

1) Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine and Health Science, Universitas Muhammadiyah Yogyakarta
2) Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine and Health Science, Universitas Muhammadiyah Yogyakarta
3) Kucala Medical Centre, Yogyakarta, Indonesia
4) Kucala Medical Centre, Yogyakarta, Indonesia

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Correspondence:

rizkafakhriani@umy.ac.id

ABSTRACT

Hormones released and absorbed by the human body in a balanced state will affect the balance and health, while a change in hormone levels can cause various severe and chronic health problems. Hormone testing is a method of measuring hormone levels in the body that can be used to diagnose and treat disease, monitor a patient's overall health, or prevent the development of specific health problems. This study may provide information about the functional hormone test (DUTCH). This study presents the case of a 47-year-old woman with a history of chronic dysmenorrhea. Functional hormone testing was performed on days 19-22 of the menstrual cycle in women with regular 28-day periods. The results of the DUTCH test in this patient are 2-OH dominant, so they are safe from symptoms of estrogen dominance and low 4-OH production. The methylation process is smooth, reducing the risk of cancer-related to estrogen dominance syndrome. Hormone examination through urine is intended to see metabolites (metabolic wastes) of hormones released through urine. How dangerous it is for a person to have Estrogen Domination Syndrome can be determined by looking at estrogen and progesterone metabolites.

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INTRODUCTION

Hormonal tests are mainly performed for disease epidemiology, clinical research, and patient care. Hormone tests can be assessed by their levels in serum or plasma. It can also be seen from the saliva or metabolites found in the urine. The testing technique is carried out using serum samples (Direito et al., 2013). Although serum samples are universally accepted, they have limitations, which are not available in all regions. In addition, a type of cortisol hormone cannot be checked throughout the day. Thus, urine sampling was developed to facilitate the sampling process and shorten the process (Roos et al., 2015).

DUTCH is a functional hormone test performed by taking a dry urine specimen. It was carried out by the Precision Analytical (USA) laboratory. Hormone tests through urine are intended to see metabolites (metabolic wastes) of hormones released through urine. Looking at the metabolites of estrogen & progesterone can help determine how much a person is at risk of developing Estrogen Dominant Syndrome (Rezvanpour & Don-Wauchope, 2017). The NETHERLANDS can check sex hormones (estrogen, progesterone), adrenal hormones (cortisol), and androgen hormones (DHEA, Testosterone) (Newman et al., 2019).

Analysis of dry urine samples on filter paper by gas chromatography with tandem mass spectrometry (GC-MS/MS) gave similar results to serum analyzed by radioimmunoassay (Stanczyk & Clarke, 2010). Likewise, a collection of four samples during the day (4-place method) can be substituted for a 24-hour collection. Urine analysis from a dry sample is equivalent to a liquid urine sample (Newman & Curran, 2021). Urine sample testing is superior to saliva because it loses a significant portion of the patient's HPA Axis function with saliva testing when measuring cortisol metabolites (Shackleton, 2010). To properly view a patient's cortisol status, free and metabolized cortisol should be measured to avoid misleading results when cortisol clearance is abnormally high or low as in the sex hormones. Measuring estrogen and androgen hormones can provide a complete picture of a more precise clinical diagnosis of hormonal imbalance and HRT monitoring (Krone et al., 2010)

Sex steroid hormone production can be assessed by levels in serum or plasma as well as from metabolites in urine. This makes it easier to take samples, especially for hormones that have daily, circadian, and monthly cycles that need to be checked regularly (Bédard et al., 2000). In Indonesia, the treatment of diseases related to hormonal imbalances such as endometriosis, irregular menstrual cycles, premenstrual syndrome, polycystic ovary syndrome, fibroids, fertility problems, osteoporosis, and hormone-sensitive cancers with medication or surgery. The use of prevention methods with a complete picture of hormonal health, the balance of estrogen metabolism, the balance of androgen metabolism, stress hormones cortisol, DHEA, and other markers with DUTCH examination is still rarely used. The Netherlands also analyzed its importance for reproductive health, bone health, reproductive function, cancer prevention, mood and motivation, and antioxidant defense with free radicals. This report presents the result of the active hormone on a 47-year-old woman with a history of chronic dysmenorrhea and a regular period of 28 days.

CASE REPORT

We report the case of a 47-year-old woman with a history of chronic dysmenorrhea, a health condition associated with hormonal imbalance. Functional hormone testing was performed on days 19-22 of the menstrual cycle in women with regular 28-day periods. The test is carried out by dipping a special paper into

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a urine specimen and drying it. Sampling was done by collecting the urine at certain times, namely at 17.00, before going to bed at 10.00, when waking up, and 2 hours after waking up. All specialty papers that have been soaked in urine are dried and plasticized and sent for analysis by the Precision Analytical (US) Lab. The hormones assessed and analyzed in this DUTCH are as follows: Estrogen hormone, in three important forms, namely: 2-OH Estrone, 4-OH Estrone & 16-OH Estrone, as shown in the table below.

Table 1. Results of the estrogen hormone test

No	Estrogen Hormone Test	Result	Patient's Percentage	Expected Percentage
1	2-OH Estrone	The patient's body produces enough 2-OH during the initial phase of metabolism, which protects her from EDS symptoms.	84%	60-80%
2	4-OH Estrone	Estrogen positively influences the patient's body since it shields the patient from the symptoms of Estrogen Dominance Syndrome (EDS). The patient's body creates enough 2-OH during the first phase of metabolism to keep EDS symptoms at bay.	7%	7.5-11%
3	16-OH Estrone	The patient's body produces very little 16-OH. It provides an overview that the risk of EDS symptoms is relatively low due to the much higher level of 2-OH.	9%	13-30%

Table 2. Results of the testosterone hormone test

No	Testosterone Hormone test	Result	Normal Range
1	Testosterone	4.7 ng/mg	2.3 – 14 ng/mg
2	5a-DHT	3.3 ng/mg	0 - 6.6 ng/mg
3	5a-Androstanediol	18.4 ng/mg	12 – 30 ng/mg
4	5b-Androstanediol	58.0 ng/mg	20 – 75 ng/mg
5	Epi-Testosterone	9.6 ng/mg	2.3 – 14 ng/mg

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Another hormone analyzed was progesterone. The sample results show that the production of progesterone is very high. High progesterone can occur naturally but also due to stress or synthetic progesterone hormones such as those found in hormonal birth control drugs.

Testosterone was also tested. Women and men both produce testosterone, but normal testosterone levels in women are generally lower than in men. It can be seen that the testosterone levels produced by the sample are still within normal limits, and the levels of testosterone metabolites (5a/5b-androstenediol) are also within the normal range.

A hormone that was tested was androgen. It seems that the results of normal DHEA hormone production. This indicates that the function of the adrenal glands produces sufficient DHEA. In addition, free cortisol (cortisol circulating in the arteries) and cortisol metabolites (the product of cortisol metabolism) were still within normal limits. This indicates the optimal function of the HPA (Hypothalamus-Pituitary-Adrenal Axis) axis.

Another marker that was analyzed was the Organic Acid Test (OATs). The following are some of the organic acid markers assessed in the Netherlands: Methylmalonate Acid (MMA), Xanthurenate & Kynurenate, Pyroglutamate, Homovanillate (HVA), Venilmandelate (VMA), melatonin, 8-OHdG, which act as markers of DNA damage.

Table 3. Results of the DHEA, Cortisol test

No	Total of DHEA Production	
	Age	**Range**
1	20 - 39	1300 – 3000
2	40 - 60	750 - 2000
3	>60	500 - 1200
4	20 - 39	1300 – 3000

Table 4. Result of some organic acid markers that were assessed in the DUTCH.

No	Organic Acid Markers	Result	Normal range
1	Methylmalonate (MMA)	0.8 ug/mg	0-2.2 ug/mg
2	Xanthurenate	0.4 ug/mg	0-1.4 ug/mg
3	Kynurenate	2.6 ug/mg	0-7.3 ug/mg
4	Pyroglutamate	56.3 ug/mg	32-60 ug/mg

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DISCUSSION

Hormone or metabolite analysis is useful for dealing with patients with many nonspecific symptoms to diagnose and screen for various diseases (Sansone et al., 2019). Steroid hormones measured from urine samples are essential in diagnosing hormone-related diseases (de Jong et al., 2017). The hormones assessed and analyzed at DUTCH are as follows: Estrogen, in three essential forms: 2-OH Estrone, 4-OH Estrone, and 16-OH Estrone. These three hormones have their respective functions and can describe abnormalities in estrogen metabolism (Newman & Curran, 2021).

The first type of estrogen hormone is 2-OH, which can be categorized as a type of estrogen with a very positive effect on our bodies; it protects us from the symptoms of diseases caused by Estrogen Domination Syndrome (EDS). The production of 2-OH in the first phase of metabolism from the samples taken was relatively high. Thus, protecting them from EDS symptoms (Newman & Curran, 2021).

The second estrogen hormone is 4-OH, which can damage cell DNA and undergo mutations, making it very susceptible to developing into cancer. If the level of 4-OH is excessive, and in phase II, it cannot be metabolized entirely through the methylation process, the risk of cancer will increase significantly. The production of 4-OH in this sample was not high, and the methylation process was smooth. The cancer risk associated with estrogen dominance syndrome is low because it is still protected by optimal metabolism. This condition can be maintained by consuming vegetables from the cabbage group such as cabbage, cauliflower, broccoli, broccoli sprouts, Brussel sprouts, broccoli sprouts every day (Sampson et al., 2017).

The third estrogen hormone is 16-OH, a type of proliferative estrogen (supports tissue growth) but rarely causes DNA damage in cancer. The production of 16-OH in the sample body is low, indicating that the risk of having EDS symptoms is relatively low because 2-OH is much higher (Newman et al., 2019).

The sample results showed very high progesterone production. High progesterone can occur naturally but also due to stress and synthetic progesterone hormones such as those found in hormonal birth control drugs. On the plus side, high progesterone protects against the deleterious effects of estrogen that cause cancer due to EDS. High progesterone can cause symptoms such as bloating or flatulence, fatigue & food cravings, or an urge to eat, especially high-calorie foods. On the other hand, optimal progesterone is an excellent condition if the sample plans to become pregnant. We know that samples produce eggs at ovulation with high progesterone, ready to be fertilized (Groenewoud et al., 2017).

Another hormone analyzed is testosterone. Both women and men produce testosterone, but the normal female testosterone range is generally lower than men's. We can see that the testosterone levels produced by the samples are still within the normal range; testosterone metabolite levels (5a/5b-androstenediol) were also within the normal range (Savkovic et al., 2018). Normal testosterone can prevent symptoms: fatigue (low energy), decreased libido, and lack of motivation. Androgen hormone is the result of average DHEA hormone production, which indicates the function of the adrenal gland to produce sufficient DHEA (Klein et al., 2019).

Free cortisol (cortisol in blood vessels) and metabolites of cortisol (the product of cortisol metabolism) were still within normal limits. This indicates optimal functioning of the HPA (Hypothalamus-Pituitary-Adrenal Axis) (Marcos et al., 2014). Another marker analyzed was Organic Acid tests (OATs). Some of the organic acid markers assessed at DUTCH are as follows.

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Methylmalonate Acid (MMA), the sample's MMA levels were still in the normal range of 0.8 ug/mg. This shows that the intake of B12 is sufficient but can be further increased so that its function can be more optimal. Xanthurenate & Kynurenate levels of Xanthurenate & Kynurenate, which are metabolites of vitamin B6, also appeared to be within the normal range. It should be increased a little more, maybe up to 0.8 for Xanthurenate and up to 4 for Kynurenate, so the function can be more optimal (McCann et al., 1996).

Pyroglutamate, Pyroglutamate released in urine samples is at the upper threshold. Pyroglutamate is a metabolite of glutathione, the most vital antioxidant that protects our body. Low levels of glutathione can be caused by the use of drugs (fever reducers, pain medications) and exposure to toxins (e.g., alcohol). This is in line with the history that the sample often used analgesics as pain relievers during dysmenorrhea (Newman & Curran, 2021).

Homovanillate (HVA) is a metabolite of the neurotransmitter Dopamine (nerve hormone). The sample's HVA level was at a lower threshold, indicating little dopamine production or low dopamine levels that can be converted to HVA (Black et al., 2015). Low levels of dopamine, which can be converted to HVA, can be caused by a deficiency of several nutrients. Conversely, low dopamine production can be caused by BH4 deficiency, iron, and tyrosine. Some of the symptoms of low dopamine are addiction (to food or other substances), food cravings, pleasure-seeking, sleepiness, impulsivity, tremors, low motivation, fatigue & flat affect (Blasco et al., 2010).

Venilmandelate (VMA), the sample VMA test results were in the upper threshold; An increase in the threshold can be caused by physical or psychological stress. Melatonin, the sample's melatonin level, was also on the upper threshold. No studies show that high levels of melatonin can be a problem. However, the problem can be found in chronic fatigue syndrome or depression conditions. Increased melatonin levels can be caused by consuming foods/supplements containing melatonin (Schiffer et al., 2019). The last marker is 8-OHdG, which serves as a marker of DNA damage. The higher the level, the more severe the oxidative stress condition in the body. The sample's 8-OHdG level is still within the normal range.

CONCLUSION

We report a 47-year-old woman with 28-day regular menstruation who underwent the DUTCH test. The results of the DUTCH test in this patient are 2-OH dominant, so they are safe from symptoms of estrogen dominance and low 4-OH production. The methylation process is smooth so that the risk of cancer related to estrogen dominance syndrome is low.

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Case Report

Prominent bradycardia in a COVID-19 patient receiving Remdesivir

Sidhi Laksono[1], Grace Trifena Hosea[2]

1) Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Muhammadiyah Prof Dr. Hamka, Indonesia
2) Faculty of Medicine, Universitas Pelita Harapan, Indonesia

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Correspondence:

sidhilaksono@uhamka.ac.id

ABSTRACT

Remdesivir is a commonly used antiviral drug to treat COVID-19. Remdesivir has some side effects; however, whether it has any effect on cardiac is rarely reported. A 44-year-old woman with symptomatic confirmed COVID-19 was treated with intravenous remdesivir 200 mg on day one and followed with 100 mg remdesivir until day five. Three days after the treatment, she had significant bradycardia shown on the electrocardiography; however, the patient had no complaint or symptom regarding the bradycardia. Based on the discussion with the cardiology team, it was decided to cease remdesivir and replace it with oseltamivir, and the ECG showed some improvement. Remdesivir is a drug that should be used safely and cannot be taken at home, as there may be side effects left unaware.

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INTRODUCTION

In this pandemic era of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease (COVID-19), many countries have entered the second wave, including Indonesia. The treatment is given according to the severity of the disease, one of which is antiviral drugs such as remdesivir. Remdesivir is an antiviral commonly used to treat COVID-19 and has some adverse effects. Cardiac adverse events (including supraventricular arrhythmias, atrial fibrillation, and other arrhythmias) are rare in patients treated with this drug. It occurred on 2.6% adverse events in remdesivir administration. Although very few, some have reported that remdesivir also causes bradycardia, a slow or irregular heart rhythm, usually fewer than 60 beats per minute. This case report aims to raise awareness of bradycardia as an adverse event in remdesivir administration (Attena et al., 2021; Hafeez & Grossman, 2021).

CASE REPORT

A 44-year-old woman was referred with confirmed COVID-19. She had been hospitalized two days before. The Computed Tomography scan (CT-scan) showed a normal result. She had a medical history of uncontrolled hypertension. Previously, the patient had received methylprednisolone 4 mg bid, ivermectin protocol, vitamin D od, oseltamivir 75 mg bid, vitamin B and C od, azithromycin 500 mg od, lansoprazole 30 mg od, rivaroxaban 10 mg bid, acetylcysteine bid, and doxycycline 100 mg bid. During the admission, she complained of having fever, cough, and flu, fully alert. The blood pressure was 154/94 mmHg, heart rate 83 bpm, the temperature of 38°C, oxygen saturation of 98%, and other physical examinations were otherwise normal. The chest x-ray showed cardiomegaly and some infiltrate on the left and right lower lobe of the lung, compared to the previous x-ray (**Figure 1**).

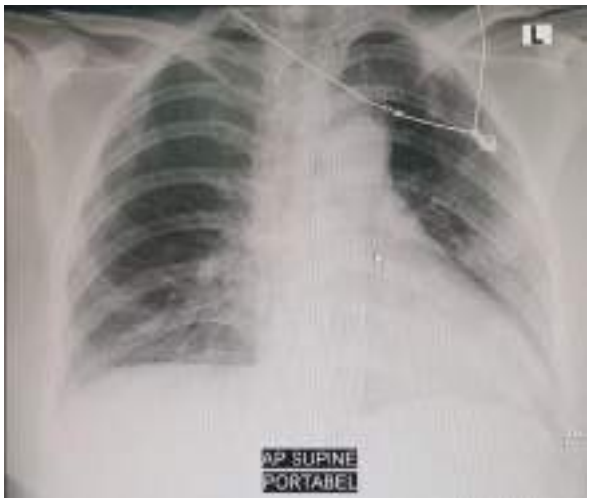

Figure 1. The chest x-ray after admission showed infiltrate on the right and left lower lobe lung

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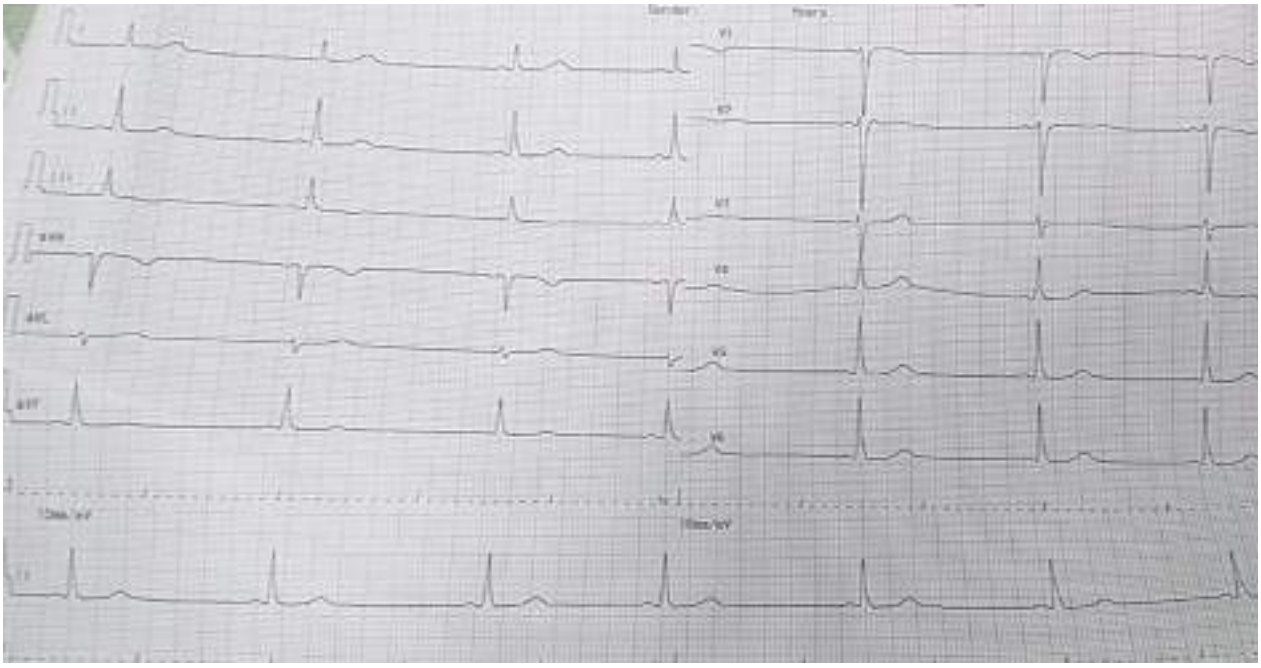

Figure 2. ECG 3 days after receiving remdesivir treatment

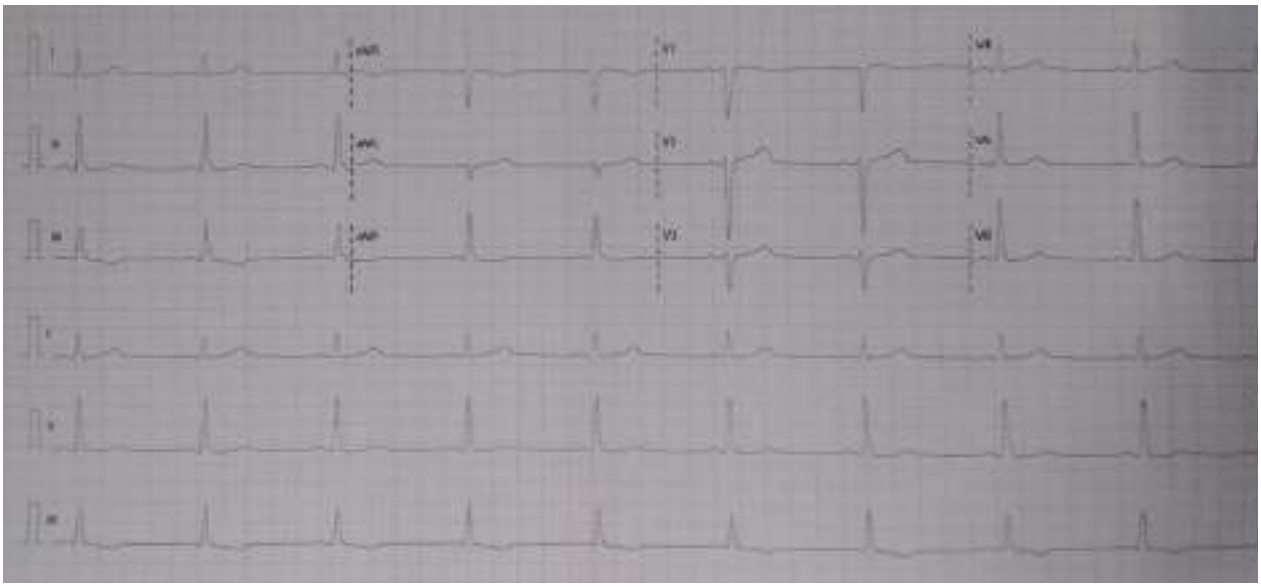

Figure 3. ECG after remdesivir was stopped

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Laboratory investigations were significant for the following: leukopenia (4.72 x 103 UL), lymphopenia (18%), monocytosis (11%), and slightly increased D-dimer (0,61 mg/L). Then the patients started the following treatment: intravenous loading dose remdesivir 200 mg on day one and intravenous remdesivir 100 mg on day two to day five, subcutaneous enoxaparin 2.5 mg, oral ivermectin 24 mg, and oral doxycycline 100 mg. On day 3 of the treatment, the ECG showed bradyarrhythmia with a heart rate of approximately 40 bpm and PR interval of 0,12 s (shown in **Figure 2**); the patient was in a stable condition (no symptoms related to bradycardia). High sensitivity troponin T (hs-TropT) was within normal limits (6.88 ng/L). Based on a discussion with the pulmonologist and cardiologist, we decided to stop Remdesivir, and the ECG showed an improvement in the heart rate of 56 bpm (**Figure 3**). Oseltamivir was given the following day.

DISCUSSION

The patient had already been hospitalized at another hospital for two days. On admission, there were no remarkable physical or examination findings except for her chest x-ray showing an infiltrate on both lungs' lower lobe compared to her previous CT scan. A normal hs-TropT rules out acute myocardial infarction. The patient then was started on COVID-19 treatment, and the antiviral of choice was Remdesivir. Remdesivir was the first antiviral drug approved by the Food and Drug Administration (FDA) for COVID-19 treatment. It was a nucleotide prodrug developed on the early Ebola epidemic in 2013. (Brown et al., 2019; Commissioner, 2020). Remdesivir is indicated for adults and children at least 12-year-old with COVID-19 that are hospitalized with a body weight not less than 40 kg (Commissioner, 2020). As bradycardia occurred in this patient, remdesivir, a guideline-recommended antiviral drug, has to be stopped and substituted with other drugs.

The reported remdesivir side effects were gastrointestinal symptoms, hepatotoxicity, and nephrotoxicity (Fan et al., 2020). In studies done on 53 patients receiving remdesivir, 32 reported increased hepatic enzyme, diarrhea, rash, renal impairment, and hypotension. Those side effects are commonly found in those on mechanical ventilation (Grein et al., 2020). Very few studies reported cardiac side effects. Those cardiac side effects are hypertension, atrial fibrillations, and cardiac arrest, which are not confirmed in a placebo-controlled trial (Grein et al., 2020; Wang et al., 2020). Some case reports describe patients with COVID-19 receiving remdesivir developed bradycardia within three days like the patient in this case (Day et al., 2021; Gubitosa et al., 2020; Gupta et al., 2020; Sanchez-Codez et al., 2021). Another medication known that can cause bradycardia in this patient is enoxaparin, although exceedingly rare (Alquwaizani et al., 2013). The patient did not have comorbidities other than uncontrolled hypertension that can cause sudden bradycardia. Enoxaparin causing bradycardia can be excluded because after the remdesivir was stopped, the patient's heartbeat improved, so it can be said that remdesivir is the cause of the patient's bradycardia.

Some of the most extensive randomized controlled trials (RCT) about remdesivir on COVID-19 are Adaptive COVID-19 Treatment Trial (ACTT-1) and Solidarity Trials by World Health Organization (WHO), has shown varying results. The ACTT-1 compares placebo with remdesivir on hospitalized patients. No significant benefit is demonstrated in patients with mild to moderate disease with a respiratory rate of more than 24x/min or oxygen saturation of more than 94% or without oxygen supplementation. However, the patients receiving remdesivir show faster improvement than the placebo group (Beigel et al., 2020).

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The solidarity trials suggest that the mortality rate is similar to those on standard care (WHO Solidarity Trial Consortium, 2021). According to WHO guidelines, they no longer recommend Remdesivir as COVID-19 treatment, and the National Institute of Health (NIH) COVID-19 treatment guideline also recommends giving remdesivir to the hospitalized patient in need of oxygen supplementation (National Institutes of Health, 2021; World Health Organization, 2020).

The mechanisms for cardiac adverse effects with remdesivir are still limited. The possible mechanisms are that remdesivir active metabolite is similar to adenosine triphosphate, which can reduce sinus node automaticity through vagal stimulation and sinus bradycardia (Pelleg & Belhassen, 2010). Remdesivir has a markedly high binding affinity for viral polymerases; cross-reactivity with human mitochondrial RNA polymerase could lead to mitochondrial dysfunction due to drug-induced cardiotoxicity (Gupta et al., 2020; Sanchez-Codez et al., 2021). Choi and colleagues showed that the cytotoxic effects of remdesivir on cardiomyocytes increased over time, such that a longer duration of treatment (48 h compared to 24 h) was associated with reduced cell viability. Also, Remdesivir, as an adenosine analog, could affect atrioventricular nodal conduction, which could explain the QRS prolongation. (Gubitosa et al., 2020; Gupta et al., 2020; Sanchez-Codez et al., 2021)

In our patient, the bradycardia occurred on day 3 after starting the medication and improved within 24 hours of discontinuing it. She was on no other medications that would otherwise account for the bradyarrhythmia seen, and there were no clinical features suggestive of increased−vagal tone. Although case reports cannot establish causality, this time course raises suspicion that remdesivir was a causative factor. Additionally, although bradycardia has been reported on a few patients with severe COVID-19, our patient did not present with severe COVID-19 and bradycardia before, and the bradycardia occurred after starting remdesivir when he was improving clinically. This case is aligned with the study by Brunetti et al., where the result of a multivariate analysis includes age, gender, cardiovascular risk factors, presence of ischemic heart disease, atrial fibrillation, baseline heart rate, troponin, renal function values, cardiovascular therapy (beta-blockers, amiodarone), and need for ventilation, showed that the only factor significantly related to lower heart rate levels observed after remdesivir administration was a less severe clinical presentation of COVID-19 (Brunetti et al., 2021). This study also aligned with Attena et al.'s study, where the univariable regression for the male sex (relative risk, 0.28 [95% CI, 0.85–0.93]; P=0.038) was associated with a reduced risk of incident sinus bradycardia (Attena et al., 2021). Findings regarding risk factors of bradycardia after administration of remdesivir in COVID-19 patients remain inconsistent. Better evidence is needed to conclude risk factors of bradycardia in COVID-19 patients receiving remdesivir.

CONCLUSION

Remdesivir is a drug often used for COVID-19 treatment, and some cases have already reported its adverse cardiac effect, one of which is bradycardia. This case report was also added to the literature as evidence. The patient, in this case, did not have any medical comorbidities and was not on any medication that could cause bradycardia. The bradycardia improves once Remdesivir is stopped; it suggests that remdesivir is the cause. Patients with less severe COVID-19 symptoms receiving remdesivir should be monitored carefully as there may be missed side effects, so it should never be taken at home. In a patient with less severe COVID-19 symptoms, other antiviral must be considered to be given instead.

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Case Report

Severe anemia on the treatment of a Lepra patient with a history of long-term steroid consumption suspect of Cushing syndrome

Gede Padmawajiya[1], Andi Ridwan Jalal[2], Zakaria Mustari[3]

1,2) General Practitioner, Syekh Yusuf Hospital, Indonesia

3) Department of Internal Medicine, Syekh Yusuf Hospital, Indonesia

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Correspondence:

gedepadmawijaya@yahoo.com

ABSTRACT

Anemia is a clinical symptom caused by the disruption of erythrocyte formation, bleeding, and premature blood hemolysis. Severe anemia can occur in patients taking dapsone for the treatment of leprosy. Long-term use of steroids is also a predisposing factor for the occurrence of hematological changes and raises the suspicion of Cushing's syndrome. Reportedly a 20-year-old woman with the main complaint of sudden shortness of breath, accompanied by a cough with phlegm. The patient has had a history of multibacillary type leprosy since a month ago. There was a history of steroid consumption for about two years and only stopped a couple of months ago. Physical examination showed the oxygen saturation was 93%, conjunctival anemia, hyperpigmented plaques, tenderness in the abdominal, meteorism, and pitting edema in the upper and lower extremities. Laboratory examination revealed hemoglobin (Hb) level 2.4 mg/dl, erythrocytes $0.8x10^6$/ul, and albumin 3.2g/dl. Peripheral blood smear results suggest refractory anemia and myelodysplasia syndrome. After being treated for seven days, the patient was re-evaluated and controlled at the Internal Medicine outpatient clinic, Syekh Yusuf Hospital. Complex symptoms and limited investigations make it difficult to establish the exact cause. Immediate blood transfusion and management of the underlying disease causing anemia, such as discontinuation of dapsone, are the primary management of this case.

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INTRODUCTION

Anemia is a clinical finding often found in leprosy, especially in patients who have not received adequate treatment. In leprosy, two types of anemia can occur hemolytic anemia due to dapsone and anemia of chronic disease, anemia due to impaired iron utilization in the formation of erythrocytes (Wiryo, 2018). Dapsone is a multiple drug therapy (MDT) drug that is bacteriostatic by inhibiting the enzyme dihydrofolate synthetase. This main hydroxylation pathway is responsible for hematological disorders (Muhaira, Darmi, & Lubis, 2018).

Morbus Hansen is a chronic infectious disease caused by *Mycobacterium leprae*, an obligate intracellular rod-shaped bacteria (Gupta et al., 2020; Tamara et al., 2018). Mycobacterium requires iron that is obtained from its host. The iron will be used in various metabolic processes and as an energy co-factor in mitochondrial respiration and the proliferation of B lymphocytes and T lymphocytes, and the activation of both lymphocytes (Amalia, Tabri, Vitayani, & Petellongi, 2017; Tamara et al., 2018). In 1981, the World Health Organization (WHO) established a treatment regimen with multiple drug therapy, a combination of two or more anti-leprosy drugs known as MDT-WHO. The MDT includes rifampin, clofazimine, and dapsone in the treatment of leprosy (Palimbong & Kandou, 2019). However, there have been side effects from the dapsone (Deviana, 2019).

Cushing syndrome is a clinical syndrome caused by a chronic excess of glucocorticoids as a result of long-term exposure to exogenous glucocorticoids (Cushingoid phenotype) or adrenocorticotropic hormone (ACTH), or endogenously due to hypersecretion of cortisol, ACTH, or *corticotropin-releasing hormone* (CRH) (Tarigan, 2014). This article provides insight into the rare case of severe anemia in leprosy treatment, which is suspected to be caused by Cushing syndrome due to long-term steroid consumption within a limited setting. An adjunct examination area could also be done to achieve patient recovery.

CASE REPORT

A 20-year-old female patient was brought to the Emergency Room with a chief complaint of shortness of breath. Shortness of breath suddenly appeared a day before and worsened in the morning. It was the first time this had happened.

The patient has had a cough since three days ago. Cough with whitish sputum, slightly thick, odorless, and did not appear bloody. Complaints of abdominal pain were also felt in the upper abdomen, in the solar plexus to the upper left. The pain was felt for two days before admission, and the pain worsened. The patient also complained of muscle pain throughout the body, nausea, vomiting, dizziness, weakness, and fever since the day before she was admitted to the hospital. The patient complained of edema on the face (Figure 1) and hands and feet that had been felt two months ago.

The patient has had a history of multibacillary type leprosy since a month ago and is currently being treated. The patient also had a history of gastric disease, asthma, diabetes, and hypertension. The patient had a history of Methylprednisolone 3x8 mg for ± 2 years post tympanomastoidectomy and septoplasty surgery and stopped since 2 months ago when she complaint of face edema. Currently, the patient is taking multiple drug therapy (Rifampicin, Dapsone, Clofazimine) as a treatment regimen for multibacillary type leprosy.

The general condition was severe on physical examination but still compos mentis with GCS E4V5M6. The patient vital signs were as follows: blood pressure 110/70 mmHg, pulse 109 beats/min, respiration rate 33 breaths/

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min, temperature 37.2°C, O_2 saturation 93% in room air, and 99% saturation when given O_2 with nasal cannula 3 liters per minute (lpm). The conjunctivas were anemic. The abdomen was round and soefl, and there was tenderness in the epigastric region and right hypochondria region, tympani, and meteorism, with increased peristalsis. There were generalized hyperpigmented and well-demarcated plaques (Figure 2) and pitting edema in the upper and lower extremities (Figure 3).

Figure 1. Moon face after prolonged steroid use

Figure 2. Generalized hyperpigmentation of the extremities

Figure 3. Pitting edema in lower extremities

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Table 1. Laboratory results

Day	Day 1	Day 3	Day 5	Day 7
Leukocytes (x103/ul)	13.1		5.5	5.7
Erythrocytes (x106/ul)	0.87		2.12	2.96
Hemoglobin (g/dl)	2.4		6.2	8.5
Hematocrit (%)	8.8		19.3	26.3
MCV (fl)	90		91.0	88.9
MCH (pg)	27.6		29.2	28.7
MCHC (g/dl)	27.3		32.1	32.3
PLT (x103/ul)	210		179	174
Lymph %	7.1		11.4	13.4
Mxd %				3.7
net %				82.9
Lymph # (x103/ul)	0.9		0.6	0.8
Mxd # (x103/ul)				0.2
Neut # (x103/ul)				4.7
RDW (fl)	92.4		57.9	54.3
PDW(fl)	11.0		11.6	11.2
MPV (fl)	9.3		9.9	9.7
P-LCR (%)	20.7		24.5	23.8
Ureum (mg/dl)	34			
Creatinine (mg/dl)	0.2			
SGOT (µ/L)		30		
SGPT (µ/L)		22		
RBG (mg/dl)	141	244	228	
FBG (mg/dl)			108	
Serum albumin (gr/dl)	3.2			
Total Cholesterol (mg/dl)	92			
Triglycerides (mg/dl)	153			

Table 2. Evaluation of Peripheral Blood Smear

Peripheral Blood Smear	Result
Erythrocytes	
Distribution	Normal
Size	Normocytic + Normocytic dominant microcytic
Color	Normochrome
Morphology	Normoblast (+), Bilobed normoblast (+) , inclusion objects (-)
Normoblast	Found
Leukocytes	
Amount	Enough
Count Type	PMN > Lymphocytes, young cells (-)
Morphology	Normal
Platelets	
Amount	Enough
Morphology	Normal + Megaplatelet (+)
Conclusion	Suspect Refractory Anemia Myelodysplasia Syndrome

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Table 3. Urinalysis

Urinalysis	Result
Leukocytes (cell/ul)	15
Ketones (mg/dl)	-
Nitrate (mg/dl)	-
Urobilinogen (mg/dl)	0.2
Bilirubin (mg/dl)	-
Protein (mg/dl)	-
Glucose (mg/dl)	-
Erythrocytes (cell/µl)	1.020
Specific gravity	-
pH	7.0
Clarity (mg/dl)	10

The laboratory examination showed some abnormal results. It revealed severe anemia with Hb 2.4 mg/dl, erythrocytes 0.8 $x10^6$/ ul, and albumin 3.2 g/dl. Peripheral blood smear results suggested refractory anemia and myelodysplasia syndrome.

The patient was diagnosed with severe anemia on leprosy treatment due to suspect Cushing syndrome caused by long-term steroid consumption.

Pharmacologically therapy, in this case, was given oxygen via nasal cannula at 3 lpm, ringer's lactate infusion fluid 28 drops per minute, evaluation of fluid balance every 24 hours, pantoprazole 40 mg/12 hours/IV for six days to reduce nausea and vomiting, spironolactone 100 mg/24 hourly/IV for two days, furosemide 40 mg/24 hours/IV for five days, transfusion of packed red cell 250 cc/ day for four days, premedication of transfusion with dexamethasone 5 mg/24 hours/IV for four days, and consult to Dermato-Venerology Department giving blood supplement tablets (ferrous fumarate - folic acid) 1 tablet for three times a day at the time of outpatient. The patient continued leprosy treatment with clofazimine and rifampicin, 2 caps MDT once daily without dapsone. As a result, the patient's hemoglobin has increased, and the patient's anemia symptoms have improved. Non-pharmacological therapy gave in the form of a high-calorie diet and protein.

DISCUSSION

Shortness of breath is one of the many common symptoms that can arise due to anemia in which the hemoglobin level in the patient has decreased far below the normal value (2.4 mg/dl). Other symptoms that can arise due to a lack of hemoglobin in the body can be classified according to the organ affected. The cardiovascular system gives symptoms of lethargy, fatigue, palpitations, tachycardia, shortness of breath, on exertion, and heart failure. The nervous system gives symptoms of headache, dizziness, ringing in the ears, dizzy eyes, muscle weakness, irritability, and lethargy. The epithelium gives signs of pale skin and mucosa and decreased skin elasticity (Supandiman, Iman, & Fadjari, 2014). This is consistent with what was found in patients where the patient complained of shortness of breath with a respiratory rate of 33 breaths/ min, tachycardia with a heart rate of 109 beats/ min, accompanied by complaints of dizziness, difficulty walking due to feeling weak muscle strength, and pale skin and conjunctiva.

Shortness of breath due to lack of hemoglobin can be caused by various types of anemia depending on the type of anemia from the underlying disease. Morphologically, anemia can be classified according to the size of the cells and the hemoglobin they contain, such as macrocytic, microcytic, and normocytic anemia. It should be noted that there are various forms of normocytic anemia, namely anemia due to bleeding, anemia of chronic disease, anemia due to impaired iron absorption, and anemia due to parasitic infection (Manchanda, 2016). One of the most prominent symptoms of the patients, based on a history of leprosy suffered and history of dapsone treatment, was anemia of chronic disease and the patient's MCV and MCH levels were normal on laboratory examination. Anemia due to chronic disease is a decrease in Hb levels secondary to an underlying chronic disease (chronic

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inflammation, infection, or malignancy). It is the most common comorbidity in chronic disease. The pathogenesis of anemia in chronic disease involves various immune systems, namely cytokines and the reticuloendothelial system (Hawkins et al., 2013).

In anemia of chronic disease, uptake and retention of iron in reticuloendothelial cells increase which then causes the available iron to be limited for use by progenitor cells and erythropoiesis. This condition results in iron being easily stored in cells and not circulating freely (Yiannikourides & Latunde-Dada, 2019). Disruption of iron plays a significant role in the pathogenesis of anemia in chronic disease due to the effects of pro-inflammatory cytokines, TNF-a, IL-1, and IL-6, causing increased hypoferremia accompanied by increased ferritin synthesis (Tamara et al., 2018; Yacoub, Ferwiz, & Said, 2020). Heptidine, which is an acute-phase protein, will be produced by the liver, which plays a role in inhibiting the absorption of iron in the duodenum and inhibiting the release of iron by macrophages by inhibiting ferroportin. In anemia of chronic disease, low reticulocyte count indicates a failure of reticulocyte production to compensate for the decreased erythrocyte count (Hawkins et al., 2013; Oliveira et al., 2017; Yacoub et al., 2020). In this case, the patient was not tested for serum iron and reticulocyte levels in the blood because of the limited ability of the laboratory to carry out these tests.

The shortness of breath experienced by the patient is a sign of oxygen deficiency in the tissues and also an effort by the lungs to increase the respiratory rate so that oxygen in the tissues can be met (Muhaira et al., 2018; Supandiman et al., 2014). Anemia that occurs in the patient is also related to the patient's history of treatment using Dapsone (Muhaira et al., 2018; Pante, Coelho, Carelli, Avancini, & Trindade, 2018). Dapsone (4, 4-diamino-diphenyl sulfone) is a sulfonamide group that is slowly but almost completely absorbed from the gastrointestinal tract, and its central metabolism occurs in the liver (Vinod, Arun, & Dutta, 2013). Methemoglobinemia generally occurs when dapsone is administered at a dose of 200-300 mg/day, and severe methemoglobinemia results from a genetic disorder with deficiency of the enzyme NADH-dependent methemoglobin reductase (Kusumastanto, 2015; Muhaira et al., 2018; Tang et al., 2021). On laboratory examination, it was found that the Hb level was very low when the patient came with shortness of breath in the emergency room. The patient also had a history of leprosy and was currently on leprosy treatment.

Complaints of edema in the face and extremities can be caused by long-term steroid use, causing symptoms of Cushing syndrome in patients. Cushing syndrome is a collection of clinical signs and symptoms due to elevated glucocorticoids (cortisol) levels in the blood. Hyperglucocorticoid state in chusing syndrome causes excessive protein catabolism, which means the body lacks protein. The skin and subcutaneous tissue become thin, and blood vessels become fragile so that they appear as purple striae in the abdomen, thighs, buttocks, and upper arms. Muscles become weak and difficult to develop, bruise easily; wounds are difficult to heal, and thin and dry hair (Dow, Yu, & Carmichael, 2013; Nieman, 2015). On examination, not all can be found symptoms of Cushing syndrome in the patient. On examination, only found edema on the face and both extremities, hyperpigmentation of the skin, thin skin, weakness, and muscle pain when pressed. However, on physical examination, purple striae were not found, and there were no signs of bleeding. On laboratory examination, low albumin levels were found in the patient. The decrease in serum albumin is not proportional to the clinical symptoms of edema in the patient. Therefore, it is necessary

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to think about other causes that cause edema, such as a long history of steroid consumption in the patient.

Hyperglucocorticoid state in the liver will increase gluconeogenesis and aminotransferase enzymes. Amino acids resulting from protein catabolism are converted into glucose and cause hyperglycemia and decreased peripheral glucose utilization, leading to insulin-resistant diabetes. In Cushing syndrome, there is a characteristic redistribution of fat. Symptoms that can be found are obesity with redistribution of centripetal fat. Fat accumulates in the abdominal wall, upper back which forms a buffalo hump, and the face so that it looks round like a moon with a double chin (Dow et al., 2013; Nieman, 2015). On the third and fourth days, random blood sugar was found to be high but fasting blood sugar was still normal. This can occur due to the administration of dexamethasone as a premedication for transfusion or an increase in gluconeogenesis due to hyperglucocorticoids. However, in this case, the HbA1c test was not carried out because, at that time, the examination could not be carried out in the laboratory.

Standard adjuctional examination to determine the cause of the symptoms of suspect Cushing syndrome is laboratory examination (reticulocytes, ferritin, *Total Iron-Binding Capacity* (TIBC), serum Fe, liver function, and renal function) to determine the cause of anemia in patients. In addition, we also have to check the cortisol levels in the blood by performing the overnight 1-mg dexamethasone suppression test (DST) or late-night salivary cortisol test on the patient. A bone marrow puncture examination is also needed to confirm further the results obtained on the peripheral blood smear examination and assess the bone marrow's condition (Supandiman et al., 2014; Tarigan, 2014). In this case, the examination was not carried out due to the absence of standard examination facilities. As a result, it is difficult to diagnose Cushing syndrome and the specific cause of anemia.

General therapy when it is proven that the patient is anemic due to dapsone, in the form of discontinuation of dapsone as a suspected trigger drug, systemic steroids prednisone oral 1 mg/kg/day or equivalent dose of methylprednisolone, and supportive therapy while minimizing the use of other drugs (Kusumastanto, 2015). The administration of dapsone is started with a low dose of 25 mg twice daily for a week; if the hemolysis does not get worse, the dose can be increased at 3-4 weeks to 5-10 mg/day (Muhaira et al., 2018). In this patient, leprosy therapy was continued using only two drugs, rifampin and clofazimine. The use of steroids will also be minimized in the treatment selection in this case.

Treatment of anemia has different approaches in its treatment based on the cause of anemia. In anemia of chronic disease, namely treatment of underlying disease, high calorie-high protein diet, giving blood transfusion-packed red blood cell if hemoglobin <7 g/dl (125 cc packed red blood cell will increase hemoglobin in adults by an average of 1 g/dl), if accompanied by iron deficiency anemia, ferrous sulfate 300 mg twice daily can be added. In hemolytic anemia due to dapsone, if the hemoglobin is <7 g/dl, dapsone administration is discontinued. The patient had received a packed red cell transfusion of 250 cc/day or 2 bags/day for four days and was continued with blood supplement tablets (ferrous sulfate-folic acid) 3x1 at the time and consulted to Dermato-Venereology Department about leprosy treatment. As seen in the laboratory results (Table 1), the follow-up laboratory examination was carried out on day 5 after receiving a red blood cell transfusion of 500 cc/4 bags. There was an increase in hemoglobin to 6.2 g/dl.

The prognosis is generally better, although there have been reports of death in patients

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with dapsone syndrome. In this case, the patient's prognosis is good because of the early diagnosis and treatment, and there were improvements in the patient's condition. Therefore, the patient can be discharged, and the treatment could be continued at the Internal Medicine outpatient clinic.

CONCLUSION

We report a case of severe anemia in a 20-year-old woman being treated for leprosy using this regimen of multiple drugs therapy with complaints of shortness of breath, cough with phlegm, edema of the face and both extremities, and abdominal pain. The patient has a history of prolonged steroid consumption, which has been discontinued two months ago. The patient was treated in the hospital for seven days and improved after being given therapy. Furthermore, the patient was evaluated by undergoing outpatient and control at clinical of internal medicine Syekh Yusuf Hospital.

The complexity of the symptoms and limited investigations makes it challenging to establish the exact cause of diagnosis in patients. Examining the condition of the bone marrow with bone marrow puncture is essential to see the response of the bone marrow. In addition, it is necessary to examine cortisol levels to help direct the association of symptoms with a patient's history of prolonged steroid consumption.

Prompt blood transfusion and management of the underlying disease-causing anemia, such as discontinuation of Dapsone, are the primary management of this case. Iron supplementation to prevent hypochromic microcytic anemia due to chronic disease and consuming foods high in iron are also essential.

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