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FOREWORD

Alhamdulillah, praised to Allah, Journal *Qanun Medika: Fakultas Kedokteran Universitas Muhammadiyah Surabaya* vol 05 no 02 has been published. It consists of 15 articles including 3 literature reviews, 3 case report 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

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Literature Review

The risk factors of diabetes mellitus towards Covid-19's outbreaks

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ABSTRACT

Covid-19 patients with Diabetes mellitus (DM) ranked third after hypertension and cardiovascular disease with an estimated 36% of all Covid-19 cases. These patients have a risk of experiencing a higher complication possibility since their metabolic disorder can cause hyperglycemia to the patient. It is showed that the number of deaths reached 7,3%, which is higher than non-diabetes. The increase of DM patients caused by stress factors may trigger the onset of glucose in blood sugar, and the glucose variability became abnormal. This circumstance may cause a glycemic increase that causes the predisposition intensification of susceptible affected by Covid-19. Good management is truly needed for DM patients affected by Covid-19. It is hoped to reduce the risk factor, such as preventing complications and increasing life quality by regular medical check to have a good prognosis. Some research showed that Covid-19 patients with DM are essential in ICU and need more treatment attention as they may experience Acute Respiratory Distress Syndrome (ARDS). Diabetes mellitus patients' treatment strategy is to manage the blood glucose level, especially in post-prandial glucose. This literature aims to know the degree of serious illness of Covid-19 patients by the comorbidity of DM in this pandemic event.

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INTRODUCTION

Coronavirus is the class of Coronaviridae that has layered by RNA's genome with a large strand secured by polyadenylated (Van Der Hoek et al., 2016). Coronavirus's shape could be a circle secured by the pleomorphic shape. It also comprises glycoprotein that encompassed the center, which comprises a protein lattice with the single structure of RNA interior. This structure is related to nucleoprotein, a glycoprotein that has the capability to connect to the have additionally as the most antigenic (Guo et al., 2020).

The clinical manifestation may appear in 2-14 days after infected the exposure sign and symptoms, for example, having a fever of more than 37°C, fatigue, and dry cough. In some cases, the patient may also experience an ache and pain, nasal congestion, cold, tightness, sore throat, or diarrhea. The risk factor of those who may be affected is in the age of 60 years above, male, have comorbidities disease, chronic pulmonary disease, kidney disease, and diabetes disease medical record (WHO, 2020). The incubation time of Coronavirus is described as the first phase of infection until the appearance of symptoms/disease. As mentioned from some studies in China, the incubation time average is five days, and the symptoms increase at 97,5% in 12 days (Hussain, Bhowmik, & do Vale Moreira, 2020). The prognosis of COVID-19 is some patients that have a mild infection is not necessary to do hospitalization. Meanwhile, patients who are hospitalized are 10%-20% in ICU, 3%-10% need intubation, and the rest 2%-5% died (Tinku, 2020).

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia due to the occurrence of insulin disorders (Goldenberg & Punthakee, 2013). Based on the International Diabetes Federation (IDF), the prevalence of Diabetes Mellitus in the world is 1.9% and ranked the seventh leading cause of death in the world. In 2013, the number of Mellitus cases in the world reached 382 million. The proportion of events Diabetes Mellitus type 2 is 95% of the world population and became prevalence Diabetes Mellitus type 2 in the number of 85%-90% (Saeedi et al., 2019). The signs and side effects of Diabetes Mellitus may show up as frequent urination, intemperate thirst, inconsequential weight loss, extraordinary starvation (polyphagia), shivering (paranesthesia) or deadness in hands or feet, weariness, exceptionally dry skin (xerosis), and on the off chance that there's a contamination, the bruises are moderate to recuperate (CDC, 2016) The prognosis of Diabetes Mellitus itself depends on the patient condition and their discipline to consume the prescribed medication (Hill, Mantzoros, & Sowers, 2020).

The COVID patient with Diabetes Mellitus disease showed a higher risk of complication or death. In the Intensive Care Unit of COVID, 22% of patients have Diabetes Mellitus medical records. The report summary from China showed that 72.314 cases of death increase to 7,3% to Diabetes Mellitus patients with the comorbidity Diabetes of death patients to 2,3% compared to the Cardiovascular and Hypertension (Hill et al., 2020).

Diabetes Mellitus also reported as one of the comorbidities to COVID-19 patients since it is found the worse number of mortality and significantly can make the patient's condition severe related to the age and the uncontrolled Diabetes Mellitus. The number of mortalities, in this case, is varied in each country and age group from the affected patient. In the case of diabetes patients, there is an increase of 7,3% of comorbidity comparing to the general people, which is only 2,3%. The Diabetes condition can make the patient's condition severe since the disorder of immune is experienced. The prognosis is diagnosed may be severe because of organ failure, acute respiratory disorders, and the last septic shock of the patient that

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experienced the disorder (Baidya et al., 2020)

Many theories have been proposed to explain the risk factor of diabetes mellitus toward Covid-19 outbreaks. Although the literature covers a wide variety of such theories, it is difficult to know the factor that aggravates DM in Covid-19 comorbidities. We conducted a systemic literature review of the risk factor of diabetes mellitus toward Covid-19 outbreaks to better understand the distribution of pathogenesis specific of Diabetes Mellitus in Covid-19 patients. To our knowledge, this is the systemic review designed for the data from multiple pathogens which might be applied to annual incidence.

RESEARCH METHODS

The method used is to collect and analyze research articles related to Covid-19 patients with Diabetes Mellitus morbidity. Articles were obtained through searches using Google Scholar, PubMed, and Elsevier electronic databases using the keywords Covid-19, Sars Cov-2, risk factor, and Diabetes Mellitus. The articles reviewed are all articles published from 2010-2020 that discuss Covid-19 in full-text format, where the specifications discuss Covid-19 patients with Diabetes Mellitus comorbidity.

Table 1. Research Summary on The Risk Factor of diabetes mellitus towards covid-19's outbreaks

Author; Years	Type of Literature	Conclusion According to PICO
Singh, Gupta, Ghosh, & Misra, 2020a	*Study Case*	Diabetes is associated with an increase in the incidence of severity of Covid-19. It is important to control blood glucose in patients infected with Covid-19.
Bornstein et al., 2020a	*Literature review*	Care management of Diabetes Mellitus patients with Covid-19 infection is certain. In patients with DM are expected to continue to regulate lifestyle and take primary prevention in order to avoid complications.
Orioli et al., 2020	*Clinical Research*	Patients with Diabetes Mellitus type 1 should often do checking blood glucose and ketone urine at the time of fever. Drug doses and corrective bolus are necessary to maintain normoglycemia.
Saeedi et al., 2019	*Experimental Study*	Patient with Diabetes Mellitus infected with Covid-19 must regulate stress levels related to the presence of self-isolation during the pandemic and regulate physical activities due to reduced physical activity to worsen the glycemic state and blood pressure, thus making patients vulnerable to Covid-19

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Continued from Table 1.

Author; Years	Type of Literature	Conclusion According to PICO
Hill et al., 2020a	*Study Case*	Diabetes Mellitus patients who are infected with Covid-19 but do outpatient required self-awareness to take drugs adequately and conduct glycemic examinations regularly and carry out routine controls
Jiang, 2020	*Article in Press*	The incubation period of Covid-19 is 1 to 14 days and generally 3 to 7 days. The treatment includes isolation, symptomatic, support, and close monitoring of condition change; the critical case should be admitted to the ICU as soon as possible
Shereen, Khan, Kazmi, Bashir, & Siddique, 2020	*Literature Review*	The novel coronavirus originated from the Hunan seafood market at Wuhan. DNA recombination was found to be involved at spike glycoprotein, which assorted SARS-COV with RBD of another Beta Cov.
Muniyappa & Gubbi, 2020	*Study Case*	In experiments using mice, ACE-2 aims to understand how hyperglycemia, hyperinsulinemia, and hypoglycemic agents affect
Di Gennaro et al., 2020	*Study Case*	efficacy of vaccines and antiviral investigation agencies. People with Covid-19 require self-isolation; among others, patients who are recommended to have follow-up examinations can be the main symptoms and have a history of traveling to cities exposed to covid-19
Katulanda et al., 2020	*Study Case*	Guidelines for the Treatment of Diabetes Mellitus with Covid-19 infection still do not get adequate drugs so until now conduct clinical trials while the safety of management needs to be considered safe with relative advantages

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LITERATURE REVIEW

EPIDEMIOLOGY

The Covid-19 pandemic was starting to spread widely at the beginning of December in Wuhan, the 7th most populous city in China. The first confirmed Covid-19 case outside China is on 13 January 2020 in Bangkok. On 2 March 2020, 67 areas outside China had been reported in 8565 confirmed cases with the number of deaths of 132 people. It was also found the significant spread of the virus in some countries, including Iran and Italia, which has been stated as a global pandemic by WHO on 11 March 2020. The number of confirmed cases is to keep increasing all over the world in Europe and Asia. By 31 March 2020, WHO reported there are 693.224 confirmed cases globally and found 33.106 deaths that are divided into some region, Western Pacific 103.775 cases with 3649 deaths, Europe 392.757 cases with 29.962 deaths, South-East Asia 4084 cases with 184 deaths, Eastern Mediterranean 46.329 cases with 2813 deaths, America 142.081 cases with 2457 deaths, and Africa 3486 cases with 60 deaths (Rothan & Byrareddy, 2020).

World Health Organization (WHO) predicts that the number of Diabetes Mellitus patients in Indonesia was 8.4 million in 2000, then becomes 21.3 million in 2030. The International Diabetes Federation (IDF) also predicts the increasing number of Diabetes Mellitus patients in Indonesia from 9.1 million in 2014 to 14.1 million in 2035. Based on IDF data in 2014, Indonesia ranked in the 5th position globally, which has increased two times in 2013, with 7.6 million Diabetes Mellitus patients (Rahmadi, 2019). The research conducted by Onder et al.,2020 in Italia showed that the Diabetes Mellitus patient with Covid-19 case reached 36%, meanwhile in the United States of America reported about the Covid-19 patient with Diabetes Mellitus reached 58%. The response team of Covid-19 from the Centre for Disease Control (CDC) reported that the prevalence is 11% of 7.162 COVID patient data (CDC, 2016) stated in his research that he found the Covid-19 patient with comorbidities, including Diabetes Mellitus, required to be in ICU. The patient with Diabetes Mellitus clinical record has a chance of Acute Respiratory Distress Syndrome (ARSDS) intricacy. The study in the Philippines had resulted that 55% of COVID-19 patients with Diabetes Mellitus got a bad prognosis and resulted in a worse number of deaths and complications (Singh et al., 2020).

PATHOPHYSIOLOGY

Pathophysiology of Covid-19

Coronavirus contains specific gen, which is ORF1, to do transmigration that works to give codes to protein so that there will happen a virus replication and nucleocapsid formation. The glycoprotein in the outer surface of the virus has a function to attach and enter the virus into the main cell and build Domain Receptor Binding (RBD) that can loosen up and attach to the virus. Some of the Coronavirus take back the aminopeptidase or carbohydrate as the key to enter the human body. The mechanism of Coronavirus entering the human body is based on the cellular protease that consists of Human Airway Trypsin Like Protease (HAT). The cathepsin and transmembrane protease serine 2 (TMPRSS2) will break the protein and form penetration. The Coronavirus has a typical structure with protein. The increment of protein in Coronavirus contains a 3D structure to maintain Van Der Waals (Shereen et al., 2020).

Pathophysiology of Diabetes Mellitus

The insulin resistance of muscle and liver and also pancreatic beta-cell failure has made the central pathophysiology failure in Diabetes Mellitus in the condition of beta-cell failure. Besides occurring in the muscles, liver, and

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beta cell, it also occurred in fat tissue (lipolysis increase), gastrointestinal (incretin deficiency), alpha pancreas cell (hyperglucagonemia), kidney (glucose absorption increase), and brain (insulin resistance) in diabetic organs that can cause the glucose tolerance disorder on Diabetes Mellitus (Soelistijo et al., 2015). The pancreatic beta cells cannot produce insulin secretion at high speed to balance the insulin resistance, insulin sensitivity disorder, and insulin secretion since it must occur altogether before glucose intolerance happens at the same time. This condition caused late insulin secretion that is enough to reduce the glucose level in peripheral tissue, fat tissue, and muscle tissue. The prandial glucose fluctuation is also considered as the determinant in setting the glucose fluctuation daily. The condition of high post-prandial glucose can cause long-term diabetic complications. The post-prandial glucose fluctuation can be the determiner to measure HbA1c level, especially after eating lunch. Otherwise, Hb1Ac becomes the determiner of progressive diabetic complications (Tjandrawinata, 2016).

Pathophysiology of Diabetes Mellitus with Covid-19

Uncontrolled Diabetes and glycemia are reported to be significant predictors with severity and mortality in patients affected by viral infections. The Covid-19 patient with Diabetes Mellitus record can experience higher stress level conditions that can trigger the hormone release, which causes hyperglycaemic, for example, glucocorticoid and catecholamines. Those conditions can increase glucose level and abnormal glucose variability (Hussain et al., 2020). They could also encounter a decrease of the immune response towards the infection related to the cytokines and the immune response change, including T-cell and macrophages. In China, several Diabetes Mellitus patient has an inadequate metabolic control which makes them susceptible to Covid-19 infection (Zhang et al., 2020).

Coronavirus uses ACE-2 as the receptor to enter the alveolar epithelial cells type I and II in the lungs and the heart, endothelium, epithelial of the kidney, digestive tract, and pancreas. The S-glycoprotein will connect to Coronavirus. The virus that enters the cell generates an inflammation response by using a T-helper that activates interferon γ, which will make the cytokines active. This condition can cause organ damage, and also the failure of related organs to the kidney will increase ACE-2 activity in the kidney's cortex, liver, and pancreas. The increase of urine production of the Diabetes Mellitus patient is obtained by the protease type-1 that is related to membrane cell and causes the Coronavirus replication faster. The T-cell function disorder can cause lymphocytopenia and will lead to a patient's prognosis. The increase of Interleukin-6 (IL-6) has a role as a destroyer of Covid-19 infection but still under research (Baidya et al., 2020). Angiotensin-Converting Enzyme 2 (ACE) is the surface receptor of Coronavirus's surface, which directly interacting with S-Glycoprotein (Protein S). The research mentioned that ACE has a role as the binder domain receptor of Coronavirus that later will be spread to certain organs and cause the patient of Covid-19 to die because of organ failure (Weina et al., 2020).

Two specific mechanisms will play a role in the Covid-19 infection of Diabetes Mellitus patients. Firstly, the SARS Cov-2 virus starts to broke the endocrine track in charge of arranging blood pressure, metabolism, and inflammation. The Coronavirus will disturb ACE-2, which will induct cell failure, hyper inflammation, and respiratory failure (Bornstein et al., 2020b). Diabetes Mellitus patients with hyperglycemia will experience the ACE-2 increase that can facilitate the virus to enter. However, it will reduce the ACE-2 level in chronic hyperglycemia conditions and

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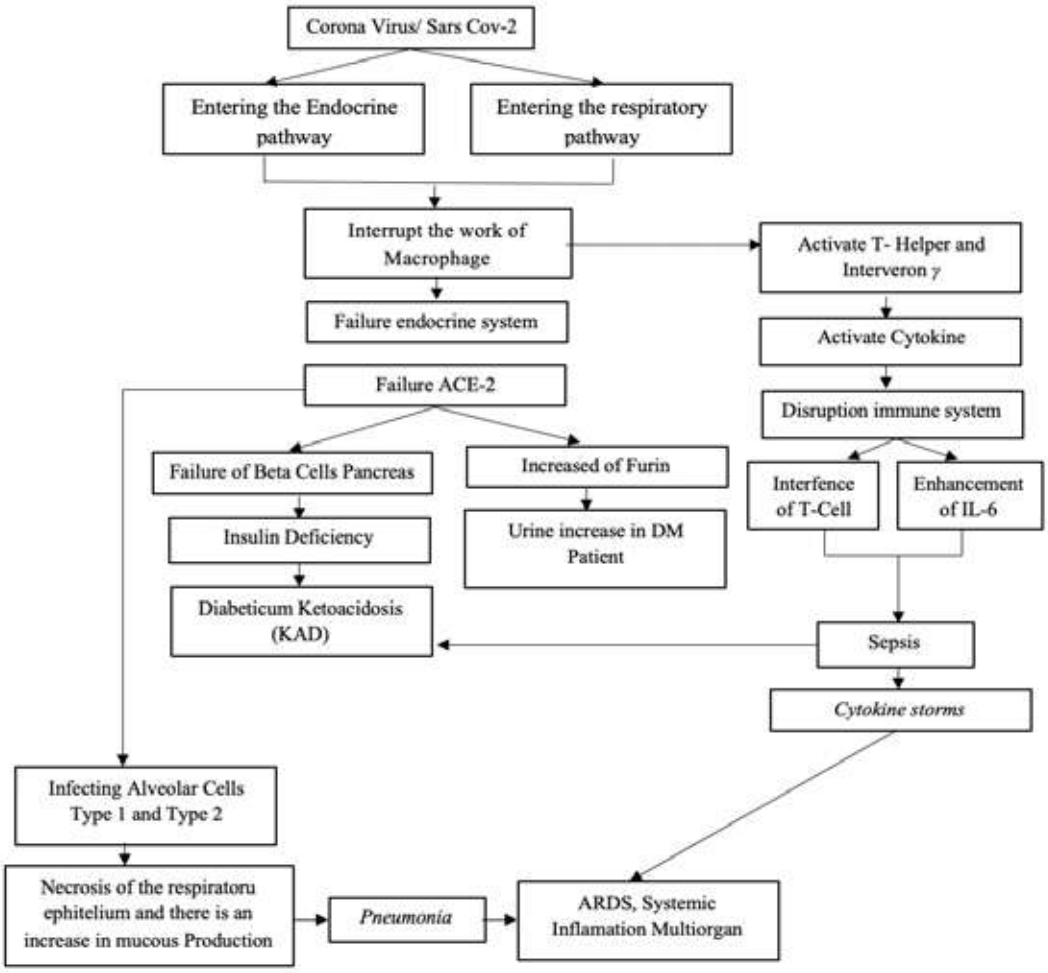
cause inflammation and virus failure. The β-cell failure can cause insulin deficiency, which may cause Diabetic Ketoacidosis (DKA) (Chen, Li, Chen, & Li, 2020). Secondly, it is related to the dipeptidyl peptidase-4 (DPP-4) enzyme. The DPP-4 has a function as a functional receptor for Human Coronavirus Erasmus Medical Center (hCov-EMC) tt is a glycoprotein transmembrane type II that has an important role in glucose metabolism and insulin and can increase the inflammation of Diabetes Mellitus type II inflammation (Van Der Hoek et al., 2016).

The DPP-4 is oligopeptide, a tissue that is involved as the activation of growth factor and as the activation T-cell peptide as the glucose metabolism controller (Shereen et al., 2020). The patient of Diabetes Mellitus, hyperglycemia, and insulinogenic can weaken proinflammation cytokine synthesis functionally by damaging the immune system and human host in long-term conditions. It can damage metabolic disorder, damage macrophage function, and lymphocytes that caused an individual more susceptible to complications (Lu, Gu, Zhang, Liu, & Ning, 2020)

Figure 1. The mechanism is expected to have a contribution to the susceptible increase of Coronavirus (COVID-19) disease in Diabetes Mellitus patient



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DIAGNOSIS

The COVID patient case is divided into three classifications. The first is patient under observation; which is a person that experiencing symptoms of fever (≥380°C) or having a fever medical record and symptoms like cough, cold, sore throat, mild to severe pneumonia, and also arrived from some affected countries in the last 14 days after experiencing the symptoms or patients with acute respiratory infections with mild severity as severe and have been in close contact with patients with confirmed or probable cases of Covid-19, worked or visited health care facilities with confirmed cases in areas/ countries affected by Covid-19, have a history of travel to countries affected by Covid-19 and have a fever. The second is persons under surveillance, which is a person that experienced a fever or the medical record of fever or upper respiratory tract infection (URI) without pneumonia and arrived from some affected countries in the last 14 days before experiencing the symptoms and does not have one or more exposure histories including a history of close contact with Covid-19 confirmed cases, Probable cases are patients under supervision who are examined for Covid-19 but are cannot be confirmed that a person with positive confirmation results of pan-coronavirus or beta-corona virus. The case can be categorized as positive if the patient infected by COVID-19 has been tested by the laboratory by using the PCR swab test twice, and both have resulted positive (Singh et al., 2020a). The incubation time of Coronavirus is described as the first phase of infection until the appearance of symptoms/ disease. As mentioned from some studies in China, the incubation time average is five days, and the symptoms increase at 97,5% in 12 days (Hussain et al., 2020).

The prognosis of COVID-19 is some patients that have a mild infection is not necessary to do hospitalization. M. The prognosis of Covid-19 is some patients that have a mild infection is not necessary to do hospitalization. Meanwhile, hospitalized patients are 10%-20% in ICU, 3%-10% need intubation, and the rest 2%-5% died (Hill, Mantzoros, & Sowers, 2020b).

The diagnosis of Covid-19 can be made by doing some tests, such as rapid test, PCR, radiology of thorax photo, CT-Scan, and thorax USG that have a result of bilateral opacity subsegmental consolidation, lobar or lungs collapse or nodule, and ground glass image. In the early stage, it shows a small plague with the interstitial change that shows in lungs peripheral and develops to multiple shadows of ground glass and also found the existence of infiltrate in both lungs. In the serious case, it is found the existence of “white-lung” (Shi et al., 2020). The radiographic image captured on Covid-19 patient from CT-scan is found that the compromised unilateral image (53%), ground-glass opacification (93%), the thickening of the interlobular septum and pleura, nodule exist, and bronchiectasis (Shi et al., 2020).

The antigen base examination has a function to detect protein virus (antigen) in the respiratory tract sample. The antigen will tie a certain antibody and will result in a visual sign. The duplicate antigen will react when the virus is active in doing duplication (WHO, 2020). Doing RT-PCR examination on the suspected patient of Covid-19 is essential, especially for those who feel pneumonia or serious illness and shortness of breath. If the RT-PCR is not available, it can be examined by doing a serology check. Besides, the Bronchoscopy check is also possible, along with the pleura function and blood test (Mardani et al., 2020). In the PCR test, those are needed to have a sensitivity level of 69% in IgM and 93.1% in IgG. Some PCR tests resulted in “true positive” which means the COVID patient still has not developed the specific virus antibody to have a more sensitive result of IgG. A further Immunosorbent assay

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enzyme (ELISA) test is needed since it has a higher sensitive test in 97.5% (Hoffman et al., 2020).

In Diabetes Mellitus suggested test is to check the glucose enzymatically by using vena blood plasm, which resulted in a specific symptom and also the plasma glucose random >200mg/dl., plasma glucose fasting >126mg/dl can prove the diagnose of Diabetes Mellitus, there are some methods in conducting tests for Diabetes Mellitus patients that have a certain purpose, for example, diagnostic tests and filter test. The diagnostic test is conducted for patients who have Diabetes Mellitus symptoms and filter tests for those who have no symptoms but are included in the risk factor of Diabetes Mellitus. The characteristics are more than 45 years old, obesity, hypertense, family history of Diabetes Mellitus patients, cholesterol HDL <=35mg/dL, or triglycerides >250mg/dL If the condition of blood sugar level 2 hours of TTGO > 200mg, it uses glucose load that is equal to 75 grams of glucose dissolved in water (Fatimah, 2015). The Diabetes Mellitus patient that is infected by Covid-19 at the examination will find the existence of lymphocytopenia, thrombopenia, and leukopenia. The next stage is found in the increase of pro-inflammatory cytokines, including IL-6 and C-reactive protein. After that, the result discovers the increase of insulin resentences with endothelial failure. The chronic patient will show the existence of vascular (Hussain et al., 2020).

The glucose level of Diabetes Mellitus tolerant turns into the free indicator factor that can build the likely contamination of Coronavirus it comprises of the decline of white blood cell work, and CVD positive which causes Diabetes Mellitus patient to have the chance of IFN cumulation and to diminish of TH1/TH17 reaction that adds to aggravation reaction so it can build the inconvenience hazard (Muniyappa & Gubbi, 2020). Patients with Covid-19 comorbidities Diabetes Mellitus can be a dangerous condition because of hyperglycemia, insulin tolerance, and obesity. The Coronavirus comorbidity with Diabetes Mellitus issue has an all the more clear depiction, for instance, the extension of exacerbation biomarker [C-responsive protein (CRP) and Interleukin 6 (IL-6) and (IL-1)], the addition of synthetic [Lactate Dehydrogenase (LDH)], and coagulation issue (D-dimer) and Tumor Necrosis Factor-alpha (TNF- α) (Huang, Lim, & Pranata, 2020). Those issues are related to certifiable multi-organ dissatisfaction and tend to thrombotic events in like manner “Cytokine Storm” will make the Coronavirus outrageous (Orioli et al., 2020).

THERAPY

The treatment in Diabetes Mellitus tolerant with Covid-19 has an intent to diminish the chance of hyperglycemia since the ordinary glucose level will lessen the microorganisms improvement danger in pneumonia conditions (Singh, Gupta, Ghosh, & Misra, 2020b). For this reason, there are some managements to do such as doing exercise (3-4 times a week for 30 minutes), implementing a Diabetic Diet by counting basal calorie as 25-30 calorie/kg of ideal weight for an obese patient, making calorie reduction 20-30% from basal calorie, Mediterranean Diet is a diet by doing a plant-based diet as a glycemic controller and reduce the risk factor (Rahmadi, 2019).

In type 2 Diabetes Mellitus (T2DM) patients, the Metformin and Inhibitor SGLT-2 dose is needed to be stopped since metformin has antiproliferative characteristics and immunomodulator works as AMP-activated protein kinase inhibitors. The metformin function also reduces the death risk of patients with chronic respiratory system symptoms. The dipeptidyl peptidase 4 (PDP-4) inhibitor and also linagliptin can be used so kidney disorder and hypoglycemia will not occur. The DMT2 patient needs to have insulin treatment.

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For those who already get treatment of insulin in basal, they need to have the bolus insulin treatment as well to reduce the risk factor of hyperglycemia (Jia et al., 2019). The patient with hyperglycemia condition can affect the lung's function so they can experience a state of pulmonary dysfunction which led the virus to do duplication easily (Hill et al., 2020a). Suppose the patient has a glucose metabolism disorder and is in critical condition. In that case, they need to be given intravenous insulin, which aims to fix water disorder, electrolyte, and pH balance (acid-base balance) which refers to Diabetes ketoacidosis. Diabetes Mellitus patients with fever can be given glucocorticoid and insulin therapy. If the patient in critical condition, there some suggested medications such as acetaminophen, atenolol, and lisinopril (Ma & Ran, 2020).

In type 1 Diabetes Mellitus (T1DM) patients, they need to have blood glucose and urinary ketones frequently test if they feel a fever with hyperglycemia. Therefore, dosage change is needed to maintain normoglycemia (Bornstein et al., 2020b). They also need insulin pump therapy with the insulin dosage given is by monitoring the glucose and ketones to avoid glycemia in patient's decrease food intake. This treatment also works effectively to avoid serious hyperglycemia and ketoacidosis (Baidya et al., 2020).

The mechanism of Coronavirus itself is by doing isolation for the patient, symptomatic treatment, monitoring the patient intensively, and doing oxygen saturation measurement through the respiratory tract or by the oximeter. The dosage usage of ribavirin becomes 500 mg for adults in two until three times a day through an intravenous (Jiang, 2020). Giving Lopinavir/ Ritonavir also can decrease by 50% of Coronavirus duplication. Ribavirin and Oseltamivir can also be given along with ACE-inhibitor such as interferon, Chloroquine, Tocilizumab (optional), corticosteroid, and also the anti-bacterial therapy if the patient of Covid-19 has suffered pneumonia. Chloroquine was accepted in 2014 as the additional medicine for diet by the Drugs Controller General of India (DCGI) as the medicine that can increase glycemic control in T2DM and also showed a significant effect for Covid-19 patients (Jia et al., 2019).

The Covid-19 patient with Diabetes Mellitus, which is in the Intensive Care Unit (ICU), needs to be monitored, especially the plasm glucose, electrolytes, pH, blood ketones, or beta-hydroxybutyrate, and insulin therapy intravenously. In the case of ARDS and hyper inflammation, for proper titration, high insulin management is given, and the subcutaneous insulin infusion can be an option and have some advantages (Bornstein et al., 2020b). The inpatients need to be given insulin therapy subcutaneously by giving once or twice a day along with the eat time bolus so the insulin will work faster or slower. This kind of strategy is one of the glycemic management. The metformin dosage must be stopped if lactic acidosis happened (Katulanda et al., 2020). It is necessary to do glycemic control since this is having an important role for the Diabetes Mellitus patient with Covid-19 since the control management can decrease complication risk and death numbers. For inpatient who suffers a mild infection, the therapy is given antihyperglycemic orally, yet it is also suggested inhibiting SGLT-2 because it has dehydration risk. The euglycemic ketosis and metformin dosage need to be stopped if the patient vomiting or have cannot have oral sulfonylurea intake and the dosage of insulin need to be changed based on the blood glucose, a special strategy for Covid-19 with Diabetes Mellitus patient is by managing the blood glucose especially the post-prandial. The patient must diet, and those who in quarantine are not allowed to exercise in a small room since they have a bad pulmonary

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function to overcome their anxiety that may lead to hyperglycemia. The patient also needs to consume medicine routinely since the pancreas is the potential target of the virus that can affect glucose metabolism (Jia et al., 2019).

CONCLUSION

Diabetes Mellitus patients have a higher risk of being infected by the Covid-19 virus. They also have a higher risk to experience a complication along with death. The patient's self-isolation must be carried out because this action can increase the stress level, which may lead the glycemia to increase and predispose the patient to be susceptible to be infected by Covid-19. The methods conducted to diagnose Covid-19 are Rapid Test, PCR Test, Radiology check of Thorax image, CT scan, and Thorax USG. The primary purpose of therapy for Covid-19 patients with Diabetes is to decrease the hyperglycemia occurrence so it will not increase the possibility of complications of the patient. The dosage of Metformin and SGLT-2 need to be stopped in the long term since it may cause a hypoglycemia effect to the patient.

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Literature Review

Understanding pacing-induced cardiomyopathy: a mini-review

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ABSTRACT

Patients with total atrioventricular block or sinus node dysfunction will need pacemaker implantation to improve the heart's physiologic function. It is known that chronic pacing such as right ventricular pacing could deteriorate cardiac function (decreased left ventricular ejection fraction) due to dyssynchrony. This condition is known as pacing-induced cardiomyopathy (PICM). The incidence of PICM could reach 19.5% during 3 years of follow-up. The right ventricle is one of the locations for implantation. Chronic right ventricular pacing may cause interventricular dyssynchrony and disrupt the contraction mechanism in the heart. These will lead to cardiac remodeling and eventually impair the left ventricular function. Therapy is needed in patients with PICM to improve the symptoms and maintain the cardiac function. We included 47 literatures in this review to further highlight the definition, mechanism, risk factor, treatment and preventive strategy for patients with PICM

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INTRODUCTION

The relationship between bradycardia and cardiovascular disease (CVD) or heart disease-related sudden death is not well emphasized. However, this might be an iceberg phenomenon because there is a lack of report or difficulty associating the symptoms with bradycardia condition. Many clinical trial studies demonstrate the relationship between heart rate (HR) and CVD outcome, but bradycardia still does not become appealing compared to tachycardia.(Cook et al., 2006; Fox et al., 2007) Whereas severe bradycardia might relate to prognostic of the CVD.(Diaz et al, 2005; Fox et al., 2007; Jouven et al., 2009). A large sample cohort study, HUNT-2, indicates bradycardia with CVD and all-cause mortality.(Nauman et al.,2011) Base on all the evidences, the bradycardia condition is much more essential than what we thought.(Makita et al., 2014).

Bradycardia defines as a HR <60bpm in adults other than well-trained athletes and visualized by electrocardiogram (ECG) (Kadish et al., 2001). There are some etiologies of bradycardia and conduction abnormalities such as abnormalities of the sinus node, atrial tissue, atrioventricular nodal tissue. Bradycardia more elaborate into two main categories; sick node dysfunction (SND) or formerly known as sick sinus syndrome (SSS) and atrioventricular block.(Kusumoto et al., 2019) There is a wide variety of clinical manifestations form bradycardia, from asymptomatic to abrupt syncope.

SND/SSS is an abnormal cardiac pace function caused by abnormal cardiac impulse formation and the sinoatrial node's alteration. As a consequence, the cardiac rate cannot fulfill body's physiologic need. The ECG manifestation also varies, including sinus bradycardia, sinus pauses/arrest, sinoatrial exit block, or alternating bradyarrhythmia and tachyarrhythmias.(Semelka et al., 2013). Clinical manifestation of the atrioventricular block (AV block) depends on the persistent or intermittent event, ventricular rate or duration of ventricular asystole correlated with AV block (Kusumoto et al., 2019). Bradycardia with or without symptoms alongside high-risk stratification becomes an indication for implantation of permanent pacemaker (PPM) (Kusumoto et al., 2019). Other absolute indications for PPM therapy are; tachycardia-bradycardia syndrome, atrial fibrillation with sinus node dysfunction, complete atrioventricular block (third-degree block), chronotropic incompetence, prolonged QT syndrome, and cardiac resynchronization therapy with biventricular pacing.(Kotsakou et al., 2015)

PPM could improve the quality of life of the patients who have the indication. Many individuals could tolerate the pacemaker implantation on the right ventricle (RV) for many years without adverse effects. Still, chronic RV pacing may lead to impaired left ventricle (LV) function and may result in symptoms of heart failure (HF), a syndrome known as pacing-induced cardiomyopathy (PICM) and significantly increases the incidence of hospitalization.(Dreger et al., 2012; Lu et al., 2018). The incidence of PICM is about 14.1% (Cho et al., 2019). In a study by Khurshid, the incidence of PICM is 19.5% at 3 years follow-up (Khurshid et al., 2014). However, the prevalence and study of PICM in Indonesia are still not available yet. It is important to understand the mechanism of PICM so the clinician can determine the management strategy for the patient. In this review, we included 47 literatures related to the topic. We aim to understand the mechanism of PICM and describe the clinical characteristics so the physician can give the proper management for patients.

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LITERATURE REVIEW

PACEMAKER

It is a small device powered by a battery to regulate a regular heartbeat. There are two primary components of the pacemaker; the generator and the wires/leads. The small generator may be implanted under the skin or a temporary external generator. The generator will send the impulse to the heart through the leads implanted in patient's heart (Kotsakou et al., 2015). Three types of permanent cardiac pacemakers are; (1) single-chamber pacemaker-VVI, (2) dual-chamber pacemaker-DDD, and (3) biventricular pacemaker-BiV.

Pacing Leads

Lead has two edge cable structures: terminal pins inserted to generator and electrode that implanted into cardiac structure act as sensing, pacing, or defibrillation. There are two types of pacemaker leads; unipolar and bipolar lead. In the unipolar lead, a single-implanted lead work as a sensing and pacing lead. Whereas, in the bipolar lead, there is a separate lead between sensing lead and pacing lead. Bipolar lead more superior in eliminating oversense noncardiac signal (Cornacchia et al., 2000). In the Unipolar lead system, the metal part of the pacemaker's generator serves as an anode (positive pole) and lead as a cathode (negative pole). Meanwhile, in a bipolar system, both anode and cathode are located on the same lead, as seen in **Figure 1** (Lazar et al., 2017). Bipolar lead overseeing of myopotentials might be caused by failure of the insulation in pacemaker pocket.

However, unipolar lead has simpler construction and much easier in locating of the pacing artifact. In few cases, the unipolar lead's sensing and capture thresholds might be superior to bipolar lead (Cornacchia et al., 2000). To overcome unipolar lead's problem in over-sense pectoral myopotential, protective coating on the device might contribute in this case.

Generator

The pacemaker generator contains several components: a battery, voltage supply, microprocessor, ROM and RAM memory, telemetry control, system controller, rate-adaptive sensor, filters, sensing amplifier, and pacing output circuit (Swerdlow, Wang, & Zipes, 2015). Batteries refer to total therapeutic energy for pacemakers, and its lifetime must be predicted in the beginning of the implantation. Lithium iodine batteries produce some amount of voltage that the output circuit should convert into the desire amount of voltage.

Sensing

Sensing is the capability of the pacemaker to identify intrinsic cardiac activity. Sensing mode make pacemaker feasible to stop sending impulse in a certain condition. It is easier for pacemaker to sense it in the larger amplitude of the cardiac signal in millivolts (mV). In sensitivity setting mode, the higher sensing value means a lower threshold of the pacemaker's sensitivity, vice versa (Lazar, Huang, & Wissner, 2017). Pacemakers need to analyze cardiac depolarization with time and signal morphology. Further, it also needs to filter out the cardiac signal and separate it from another noncardiac signal before analyzed it (Swerdlow, Wang, & Zipes, 2015) (**Figure 2**).

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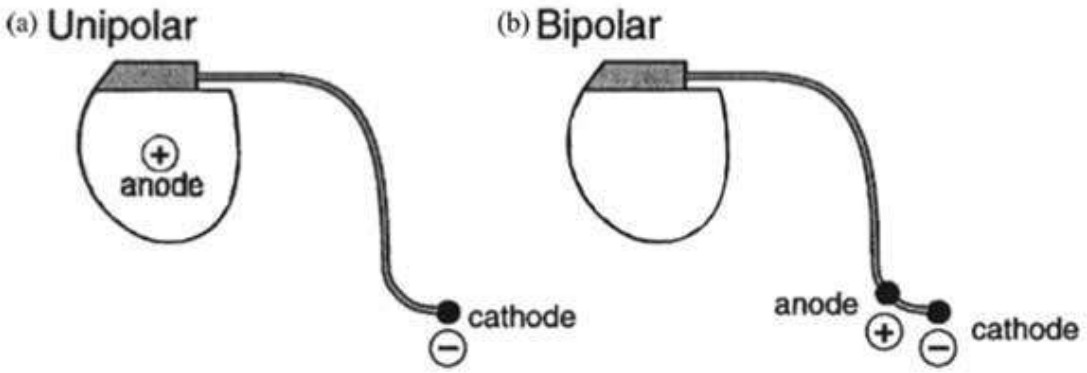

Figure 1. (left) unipolar pacemaker system, (right) bipolar pacemaker system (Lazar et al., 2017).

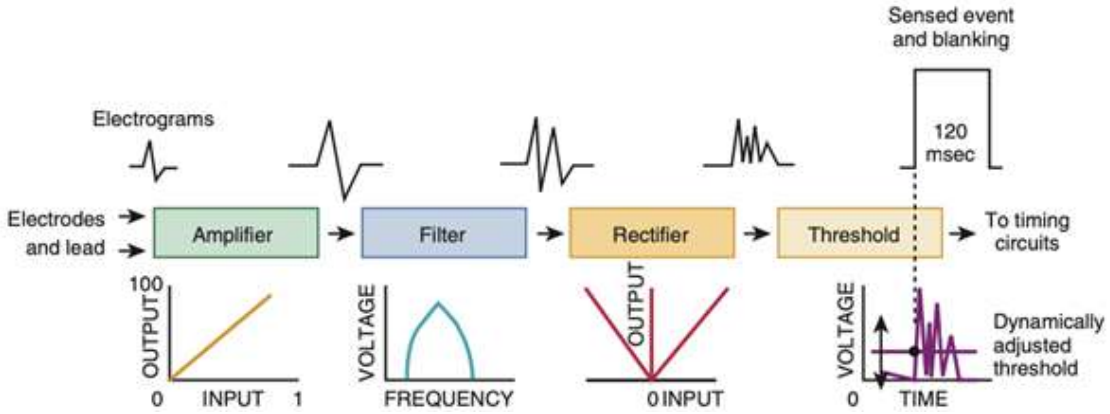

Figure 2. Functional block diagram for pacemaker (Swerdlow, Wang, & Zipes, 2015).

CARDIOMYOPATHY

Definition

Cardiomyopathy is a condition where there is a change in the anatomic of the heart. American Heart Association defines cardiomyopathy as a heterogeneous group of diseases of the myocardium associated with mechanical and/ or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders (Maron et al., 2006) Cardiomyopathy is classified into primary (the disease process is mainly in the heart) and secondary (cardiac involvement in systemic condition). (Table 1) (Maron et al., 2006). The 4 major types are dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and Arrhythmogenic right ventricular Cardiomyopathy.

Classification and Pathophysiology

Dilated cardiomyopathy (DCM) is defined as the dilatation of the left or both ventricles that is not explained by abnormal loading conditions

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Table 1. Classification of Cardiomyopathy

Classification of Cardiomyopathy	
Primary	**Secondary**
Acquired	Inflammatory/autoimmune
Genetic	Endocrine
Mixed	Infectious
	Infiltrative disorder
	Neuromuscular storage disorder
	Nutritional deficiencies
	Toxic

or coronary artery disease. In DCM, there is an enlargement of the cardiac, but the ventricular wall thickness remains normal, and the systolic function is impaired. Patients with DCM can develop heart failure with reduced ejection fraction. DCM is caused by several diseases such as hypertension, coronary artery disease, viral myocarditis, valvular disease, and genetic predisposition (Elliott et al., 2008).

Hypertrophic cardiomyopathy (HCM) is a clinically and genetic disorder. It is characterized by muscle hypertrophy without dilatation of the left ventricle, and there is no other systemic or cardiac disease that can cause hypertrophy of the heart muscle, such as hypertension. HCM is a common genetic heart disease with a prevalence of 1 in 500 people (Semsarian et al., 2015). The etiology of HCM is usually from genetic factors. HCM is caused by 11 mutant genes with more than 500 individual transmutations which; the most common variation involves the beta-myosin heavy chain and myosin-binding protein.

The prevalence of arrhythmogenic right ventricular hypertrophy (ARCV) is lesser than DCM and HCM. It is estimated at 1/2000 to 5000 (Marcus et al., 2010). ARCV occurs when there is a progressive loss of myocytes and replaced by fatty tissue, resulting in functional and morphological right ventricular abnormalities. It involves the right ventricle at the beginning, but the pathologic process can also affect the left ventricle. ARVC is caused by autosomal dominantly inherited mutations in genes encoding plakophilin 2 and other proteins of the desmosome of cardiomyocytes, inherited disorder of the muscle of the right ventricle (Buja et al., 2008; Elliott et al., 2008).

Restrictive Cardiomyopathy is the type of cardiomyopathy that occurs when the ventricles become stiff and rigid without wall thickening which causes an increased chamber pressure in response to relatively small increases in volume. This results in the dysfunction of blood filling. The ventricle does not relax and fill the normal blood volume. This type is the most uncommon type of cardiomyopathy. This process results from several diseases such as sarcoidosis, hemochromatosis, amyloidosis, and abnormalities related to desmin. Desmin is a protein marker found in sarcomeres (Wexler et al., 2009).

Sign and symptoms

These four types of cardiomyopathy present in several sign and symptoms. DCM presents with shortness of breath, fatigue, cough, orthopnea, paroxysmal nocturnal dyspnea, and edema. Clinical presentation of HCM includes chest pain, congestive heart failure symptoms, syncope or pre-syncope, palpitations, and sudden cardiac death. Restrictive cardiomyopathy can

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present with pulmonary congestion, dyspnea on exertion, decreased cardiac output, and syncope. ARCV presents with syncope, atypical chest pain, initial episode of ventricular tachycardia, recurrent ventricular tachycardia. (Wexler et al., 2009)

Diagnostic evaluation

Cardiomyopathy usually presents with signs and symptoms of heart failure, and some diagnostic tools are beneficial to diagnose cardiomyopathy. The diagnostic tools include B-type natriuretic peptide (BNP), echocardiography, electrocardiography, and chest radiography. The rise in volume and filling pressure on ventricle will induce BNP secretion into the bloodstream as a response to ventricular stretching or wall tension (Doust et al., 2006). Imaging modality using echocardiography is also a beneficial diagnostic tool for cardiomyopathy. In DCM patients, th echocardiography will show enlargement of the ventricular chamber with normal or decreased wall thickness and systolic dysfunction. In HCM patient, the echocardiography will show left ventricular hypertrophy with a decreased ventricular volume. Patient with restrictive cardiomyopathy will show biatrial enlargement with a normal or reduced ventricular volume, normal left ventricular wall thickness with normal systolic function, and impaired ventricular filling in echocardiography. The echocardiography in ARVC will show global or segmental wall abnormalities with or without motion abnormalities. Electrocardiography (ECG) can also be used to diagnose cardiomyopathy. In DCM and HCM, the ECG will show left ventricular hypertrophy. ECG in a patient with RCM will show a decreased voltage without signs of left ventricular hypertrophy, and in ARVC patient the ECG will show abnormal repolarization and small-amplitude potentials at the end of the QRS complex.(Maron et al., 2006).

PACING-INDUCED CARDIOMYOPATHY

Definition and Diagnostic Criteria

Pacing-induced cardiomyopathy is a condition which a new onset of left ventricular systolic dysfunction occur due to chronic pacing, with a deterioration of left ventricular ejection fraction (LVEF) ≥10% or regional wall motion abnormality with no other causes can be explained (Khurshid et al., 2014; Sarvari et al., 2017). There are no specific criteria to make a diagnosis of PICM. However, several aspects can be measured that help the physician to diagnose. Decreased LVEF more than 10% after the pacemaker implantation is the common and established criteria to diagnose a PICM. Other than LVEF, the paced beats should be involved > 20% of the whole QRS complex. (Khurshid et al., 2016).

Mechanism of PICM

Chronic RV pacing has been associated with electrical and then mechanical dyssynchrony of the ventricles, leading to ventricular remodeling and causing heart failure (Gebauer et al., 2009). Physiologically, the conduction mechanism will go through the His-purkinje system. In RV pacing, the conduction will go directly to the myocardium and not going through the His-purkinje system (Bank et al., 2012). The abnormality in the conduction system may cause intraventricular. Interventricular, and atrioventricular dyssynchrony. Intraventricular dyssynchrony is associated with prolonged isovolumic contraction and isovolumic relaxation, thus delaying the mitral valve opening. The longitudinal intraventricular dyssynchrony in RV pacing-induced heart failure is even greater than in patients with other causes of heart failure (Bank et al., 2010). Interventricular dyssynchrony causes the septum to be pushed toward the left ventricle during RV ejection. The left ventricular diastolic filling period is impaired due to atrioventricular dyssynchrony (Bank, Gage, & Burns, 2012;

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Mollazadeh et al., 2012; Tops, Schalij, & Bax, 2009). All these mechanisms also lead to abnormal metabolic changes in cardiac tissue level, causing different myocardial blood flow, glucose uptake, and altered regional perfusion (Cicchitti et al., 2016). Other than mechanical dyssynchrony, left ventricular torsion abnormalities may occur. The abnormalities consist of lower basal and apical peak rotation and lower peak systolic torsion (Burns et al., 2011).

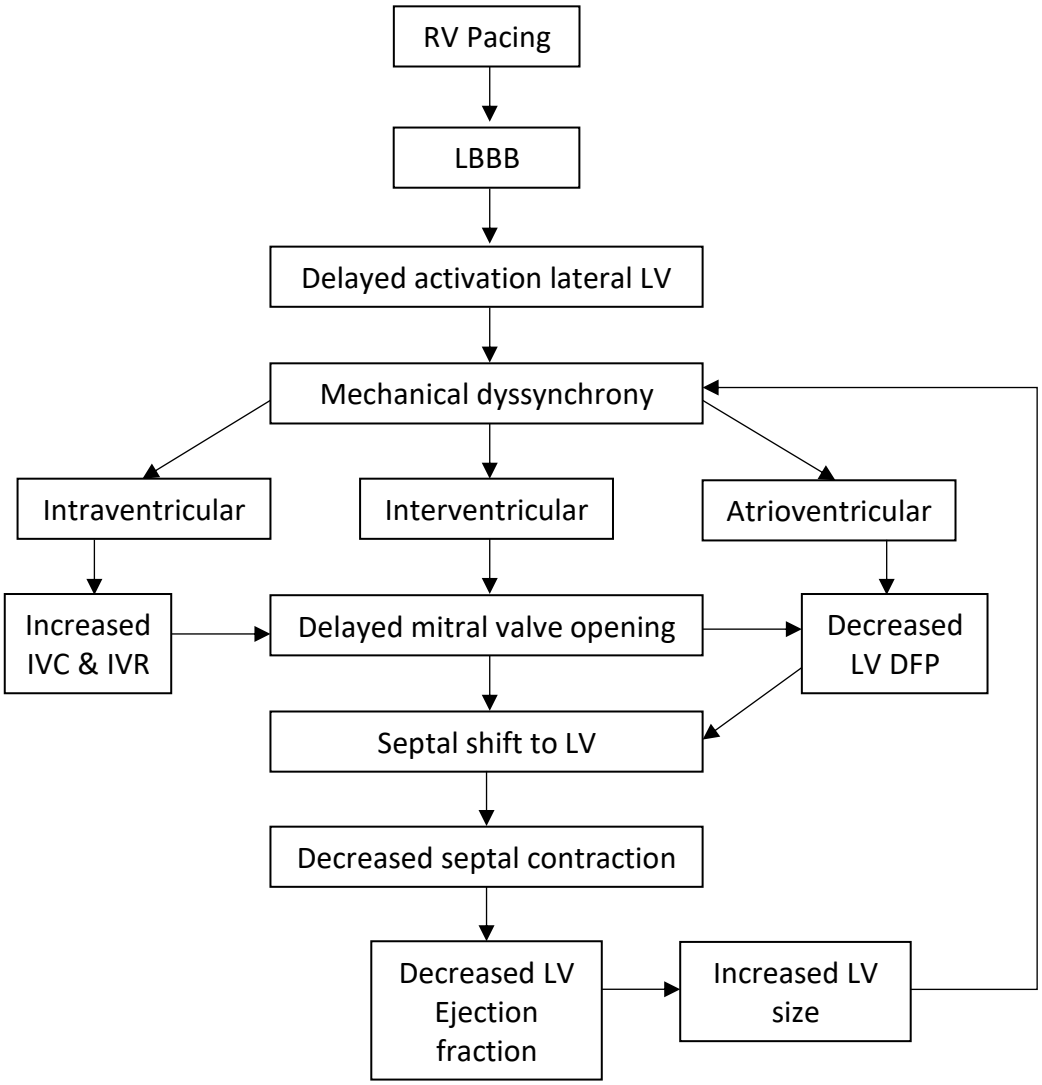

Figure 3. Mechanism of PICM (Bank, Gage, & Burns, 2012) RV: right ventricle; LV: left ventricle; LBBB: left bundle branch block; IVC: isovolumic contraction; IVR: isovolumic relaxation; DFP: diastolic filling pressure.

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Risk factor for developing PICM

Understanding the risk factors for someone to develop PICM will help the clinician to prevent the event. Several risk factors have been related to the likelihood of experiencing PICM, such as older age, male, wider intrinsic QRS, history of atrial fibrillation, and baseline left ventricular dysfunction (impaired left ventricular ejection fraction) (Curtis et al., 2016; Kim et al., 2018; Lee et al., 2016; Merchant et al., 2017; Merchant & Mittal, 2020). Several risk factors could also be evaluated after the pacemaker implantation. Those are the increased RV pacing burden (> 20%) and wider paced QRS duration (Kiehl et al., 2016; Kim et al., 2018). Lead location as another risk factor is still not clear. While several studies showed no association between RV apical (RVA) pacing and non-RVA pacing, a greater deterioration of LVEF might occur in RVA pacing group (Hussain et al., 2015; Kaye et al., 2019; Khurshid et al., 2014; Riahi et al., 2012).

Clinical manifestation

PICM shares similar clinical signs and symptoms with heart failure in general, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema of the extremity, and fatigue. The difference is only at the fact that PICM occurs in patients with pacemaker, and no other etiology of heart failure is identified. The diagnosis of PICM can also be made in the absence of heart failure signs and symptoms (Kim et al., 2018).

Treatment and preventive strategy for PICM

For individuals with PICM, cardiac resynchronization therapy (CRT) is one of the treatment strategies. A study by Khurshid et al showed that 85.5% of the patients with severe PICM responded with a rise of LVEF ≥5% within the first 3 months of treatment (Khurshid et al., 2018). The implantation of CRT in PICM patients also showed a better electromechanical reverse remodelling than other indications for CRT implantation (Gwag et al., 2017).

Another treatment for PICM is an implantation of His-bundle pacemaker (HBP) system. This strategy's benefit is that it plays role as a dual-chamber pacemaker, whereby the ventricular lead is placed on the His bundle and does not cause a dyssynchrony (Shan et al., 2018). A study reported that HBP implantation successfully reversed the electrical and structural changes due to previous chronic RV pacing in 79 (93%) patients, increasing the ejection fraction in 60 patients with reduced ejection fraction due to RV pacing (Vijayaraman et al., 2019).

The patient who needs ventricular pacemaker can be given biventricular pacing instead of RV pacing as a preventive strategy of PICM. It is showed that biventricular pacing patients would have a less mortality, hospital visits, and also an increase ≥15% in LV end-systolic volume index (Curtis et al., 2013).

CONCLUSION

Permanent pacemaker implantation is a definitive therapy for a condition such as total heart block. The pacemaker is usually located on the right ventricle. Chronic RV pacing can lead to pacing-induced cardiomyopathy. Patients with PICM will present with signs and symptoms of heart failure. Risk factors identification is also important to make the right diagnosis. PICM can be treated and prevented with a biventricular pacemaker, cardiac resynchronization therapy which can improve the systolic function, and implantation of the pacemaker on the His-bundle system to avoid dyssynchrony. This review could give the physician more insight about PICM diagnosis and management and could also be used as a basis or reference to conduct a further study related to PICM.

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Literature Review

Brain-derived neurotrophic factor after long term stress exposure of depressed mice: systematic literature review

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ABSTRACT

BDNF plays an important role in the management of chronic depression. Adequate levels of BDNF trigger the formation of new synapses in the brain, thereby improving symptoms of depression, which is a mechanism known as neuroplasticity. BDNF has a central role in brain cell development due to its ability to protect brain cells from a wide variety of pathological conditions. BDNF also affects the number of glial cells and indicates a good nerve synapse function. At some point, long-term exposure to stress, which causes chronic depression, actually stops BDNF from working itself, resulting in decreased neuroplasticity of the brain. This paper aims to analyze long-term stress exposure on BDNF levels in depressed mice. This *systematic literature review* uses the PubMed and Google Scholar databases for the period 2015-2020. A total of 322 articles at the beginning of identification, and those that met the inclusion criteria in this study were six articles. Data extraction results showed that the depression condition caused by various stressors resulted in BDNF levels in the hippocampus decreased significantly by $p \leq 0.005$. Based on the literature study, the BDFN levels in the brain in depressive conditions

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INTRODUCTION

Depression is a mental condition that causes individuals to experience cognitive deficits, both temporary and permanent (Jeon and Kim, 2016). Short exposure to stress can lead to acute depression where there is a reversible cognitive deficit, while long-term stress exposure can lead to chronic depression characterized by permanent cognitive deficits. Despite being declared remission from depression, some individuals still show sequelae in the form of anhedonia, and this anhedonia is closely related to permanent cognitive deficits to suicidal ideation (Winer *et al.*, 2014; Hawes *et al.*, 2018).

Several theories regarding the pathogenesis of depression are the monoamine hypothesis, neuroendocrine mechanisms, neuroimmunity, cytokines, and neuroplasticity (Jeon and Kim, 2016; Yang *et al.*, 2020). The monoamine hypothesis states that low serotonin (5-HT2) neurotransmitters cause depression in the postsynaptic cleft**.** This condition is reversible, but in chronic stress, there is the pruning of nerve cell dendrites so that the depression condition becomes irreversible. Recent findings in experimental animals show that serotonergic preparations are needed to increase serotonin levels in the synaptic cleft so that it triggers the formation of new dendrites to make depression conditions reversible (Massart, Mongeau, and Lanfumey, 2012). The results differ when these preparations cause resistance in cases of chronic depression (Diaz *et al.*, 2016) and increase the risk of uncomfortable and even fatal side effects in long-term use.

Continuously low levels of serotonin (5-HT2) in the long run can activate the HPA (Hypothalamic Pituitary Adrenal) axis, which increases glucocorticoid (cortisol) then causes Ca2+ influx to increase. This activation of Ca2+ influx stimulates the N-methyl D-aspartate (NMDA) receptor from glutamate through the 5-HT2 receptor so that the Brain-Derived Neurotropic Factor (BDNF) levels will decrease (Tunisya, Maria Maramis, and Kusuma, 2010). Decreased BDNF will contribute to the pruning of nerve cell dendrites which makes depression irreversible even with extensive treatment.

BDNF is a linking variable between clinical depression and serotonin levels in the brain. BDNF has a central role in brain cell development due to its ability to protect brain cells from a wide variety of pathological conditions, including depression (Stadelmann *et al.*, 2002). In addition to nerve cells, BDNF affects the number of glial cells (Sanyal *et al.*, 2013), while the increase in the number of glial cells indicates a good nerve synapse function (Verkhratsky, 2010).

METHODS

This study used a review method with the PRISMA method. A literature search was using PubMed and Google Scholar in English. According to PICO, the search criteria are based on the inclusion criteria; namely, the population is experimental animals with intervention in the form of all methods that can make the animals become depressed, the comparison is control animals, and the desired result is BDNF.

The search results with keywords (Brain-Derived Neurotropic Factor OR BDNF) AND Stress AND Chronic Depression AND Experimental Study found 322 articles. After conducting a review that met the inclusion criteria, there were six articles.

DATA EXTRACTION

Several data were extracted from the six articles included in the inclusion criteria, including research title, researcher, year, research design, research sample, intervention, random, parameters studied, and research results.

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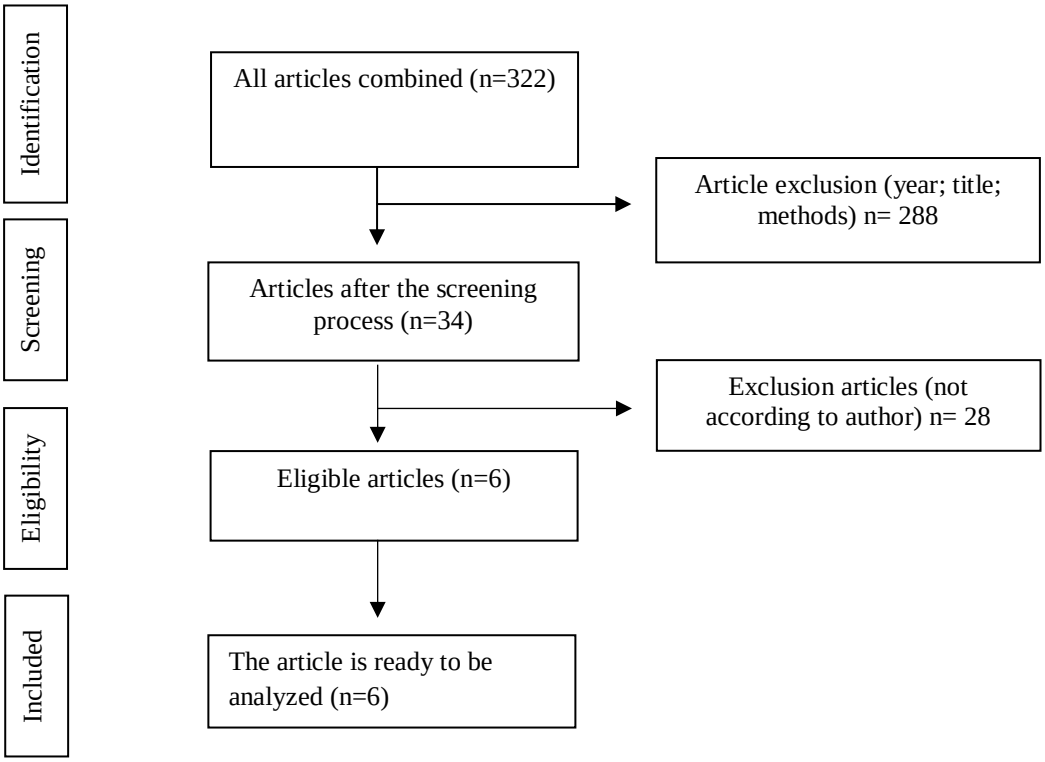

Figure 1. PRISMA *Flowchart*

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Table 1 . Data Extraction

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
1.	Effect of combined chronic predictable and unpredictable stress on depression-like symptoms in mice	(Qiao *et al.*, 2020)	Experimental study	Male mice 8 weeks old	- Mice were placed in cages with wood shavings, temperature 22 ± 1 °C and artificial lighting from 7.00 am to 7.00 pm, fed laboratory standard chow, and distilled water ad libitum. - one week of mice were randomly divided into 4 groups (n = 10) = (I) normal, (II) CRS, (III) CUMS, and (IV) combined stress (CRS + CUMS) - The CRS group was placed in a tube of 8.30 until 14.30 for three weeks - CUMS mice were exposed to 7 different stressors for three weeks - 5 minutes of heat stress at 45 - 2 minutes cold stress at 10 - 2 minutes shaking back and forth - 24 hours 45 ° inclined cage and humid environment, - 24 hours of the shortage of food, - 24 hours of water shortages - 24 hours of reversal of day and night.	Yes	- Stress stimulation with bodyweight - Stress stimulation with the level of glucocorticoid receptors (GR) - Stress stimulation with the neurotransmitter monoamine, BDNF, neuroendocrine in HPA. - Stress stimulation by oxidative stress. - Stress stimulation with gut microbiota.	BDNF intervention in hippocampus <control (p <0.05)

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					- Each stimulation is arranged and carried out randomly three times per day. - Mice in the combined stress group were exposed to daily confinement for 6 hours (8.30-14.30) combined with unexpected mild stress from 7 different stressors for three weeks.			
2.	Decreased BDNF in female but not male rats after exposure to stress: a sex-sensitive rat model of stress?	(Weisbrod *et al.*, 2019)	Experimental study	Eighty male and female rats aged 51-55 days	- Mice are placed in cages with hardwood plinths, - Rodent food is available (Harlan Teklad 4% Mouse / Rat Diet 7001), and water - Temperature is maintained at 23 ° C with 40% relative humidity with a 12-hour reverse light cycle (05.00-17.00 dark) - Male and female rats separated - Divided into three groups (no stress, CUMS, and SS) - CUMS, bright, fluorescent, and overhead lighting maintained for 20 minutes every day for 14 days. - On the first day, a stressor in the form of a cotton ball soaked in 10 mL of urine is placed in each rat cage in clear plastic (29x 18x12cm) for 20 minutes. - The next day the first 10 minutes of the cotton ball stressor, then the additional stressors vary (e.g.,	Yes	- Weight of male, female mice and treatment - BDNF control, CUMS, and SS	BDNF SS intervention in hippocampus <control (p <0.001)

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					whistle blast, coin wobble, flashing light, and rocking cage) at 20-minute intervals First stress on days 6 to 12 (seven consecutive days) and started again on day 14 to day 20 - SS was performed by restraining the head and immobilized rats in a ventilated Plexiglas tube. Forty electric shocks (2mA, duration 3 seconds, Floor Shocker Animal Test Case Box, Coulbourn Instruments, Holliston, MA) were delivered to the tail at random intervals of 150-210 seconds for three consecutive days on days 18 to 20 at CUMS days 12-14 - The first day the animals arrived were taken randomly and put in a cage - The second day was numbered On the fourth day, five were allowed to move and evaluated the condition of the mice - On the 22nd day was euthanized with carbon monoxide and decapitated. Blood from the brain stem was immediately taken The blood was then centrifuged at 4 ° and 3,600rpm for 10 min; the serum aliquots were put into an Eppendorf			

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					tube (200 IL each) and stored in the 80 C freezer. - Results checked ELISA			
3.	BDNF prevents central oxidative damage in a chronic unpredictable mild stress model: the possible role of PRDX-1 in anhedonic behavior	(Scotton *et al.*, 2019)	Experimental study	Thirty-five male Wistar mice (45 days old, 220-250g).	- Rats were housed alone in standard polycarbonate rat cages under standard environmental conditions, a 12 hour light / dark cycle (lights on between 7.00 am and 19.00 am), controlled temperature (22 ± 1°C), and food and water available. - SPT After two weeks of exposure to water and 1% sucrose solution in eight basic tests, which are carried out twice a week. - After 12 hours of lack of food and water, two bottles, one with a 1% sucrose solution and the other with water for animals for 1 hour. The bottles are weighed before and after the test to evaluate sucrose intake. All analyzes were performed half an hour after the start of the dark cycle. Based on the preference level of sucrose in the final baseline test, animals with an unstable and/or low basal sucrose preference (below 60%) were excluded. The remaining animals were divided into paired control (n = 7) and the CUMS group (n = 16).	No data	- Oxidative damage - Total antioxidant capacity - BDNF Level	BDNF Intervention in hippocampus> control (p = 0.001)

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					whistle blast, coin wobble, flashing light, and rocking cage) at 20-minute intervals First stress on days 6 to 12 (seven consecutive days) and started again on day 14 to day 20 - SS was performed by restraining the head and immobilized rats in a ventilated Plexiglas tube. Forty electric shocks (2mA, duration 3 seconds, Floor Shocker Animal Test Case Box, Coulbourn Instruments, Holliston, MA) were delivered to the tail at random intervals of 150-210 seconds for three consecutive days on days 18 to 20 at CUMS days 12-14 - The first day the animals arrived were taken randomly and put in a cage - The second day was numbered On the fourth day, five were allowed to move and evaluated the condition of the mice - On the 22nd day was euthanized with carbon monoxide and decapitated. Blood from the brain stem was immediately taken The blood was then centrifuged at 4 ° and 3,600rpm for 10 min; the serum aliquots were put into an Eppendorf			

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					tube (200 IL each) and stored in the 80 C freezer. - Results checked ELISA			
3.	BDNF prevents central oxidative damage in a chronic unpredictable mild stress model: the possible role of PRDX-1 in anhedonic behavior	(Scotton *et al.*, 2019)	Experimental study	Thirty-five male Wistar mice (45 days old, 220-250g).	- Rats were housed alone in standard polycarbonate rat cages under standard environmental conditions, a 12 hour light / dark cycle (lights on between 7.00 am and 19.00 am), controlled temperature (22 ± 1°C), and food and water available. - SPT After two weeks of exposure to water and 1% sucrose solution in eight basic tests, which are carried out twice a week. - After 12 hours of lack of food and water, two bottles, one with a 1% sucrose solution and the other with water for animals for 1 hour. The bottles are weighed before and after the test to evaluate sucrose intake. All analyzes were performed half an hour after the start of the dark cycle. Based on the preference level of sucrose in the final baseline test, animals with an unstable and/or low basal sucrose preference (below 60%) were excluded. The remaining animals were divided into paired control (n = 7) and the CUMS group (n = 16).	No data	- Oxidative damage - Total antioxidant capacity - BDNF Level	BDNF Intervention in hippocampus> control (p = 0.001)

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					phosphate buffer then 4% paraformaldehyde. - The brain is removed, saturated with 30% sucrose, and frozen in isopentane. Sixteen µm thick sections were cut using a cryostat. This section evaluates BDNF and TPH proteins in ventral DRN both throughout the structure and in 5-HT cells located within the DRN (30 cells/part) using conventional immunofluorescence methods.			
5.	The effects of chronic and acute physical and psychological Stress on Brain-Derived Neurotropic Factor in Rats	(Ghooshchi and Jahromi, 2018)	Experimental study	Ninety 3-month-old male Wistar rats weigh 200 ± 40 gram	- Indoor rats with temperature 22 ± 1°C), light (from 07.00 to 19.00). - Divided into six groups (each group of 8 rats): exercise (EX), emotional (ES), physical stress (PS), exercise combined with emotional stress (EXES), exercise combined with physical stress (EXPS), and control. - EX mice with a treadmill for 1-2 sessions for acute and two weeks for chronic. In the first week, all rats were on the treadmill for 10 min. Each mouse ran for 23 minutes on the treadmill at low speed, then increased it to 5 m / min every 3 minutes until the rats were exhausted (unable to continue running).	Yes	- Shows BDNF - exercise - emotional stress - physical stress - exercise and emotional stress - exercise and physical stress	BDNF chronic emotional stress intervention in hippocampus <control (p = 0.002)

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
					- The second day, all rats were given EX 50 minutes/day 5 days/week with an intensity of 60-75% maximum oxygen uptake. Each EX session begins with a warm-up for 10 minutes (gradual increase in speed) followed by 30 minutes of EX with 60-75% maximum oxygen intensity and 10 min speed reduced for cooling. - EX at 09.00 - 12.00 - The physical stress group of mice received 0.5 mA, 1-second leg sting every 30 seconds for 10 minutes, five times a week for one minute. - Emotional stress rats only looked at physical stress rats. - A blood sample (2 ml) was taken from the ventral caudal artery of light etherized mice immediately after the first treatment and 12 hours after the last treatment (after two weeks). Blood samples were centrifuged for 10 minutes (3500 rounds) and stored at -20 C. - BDNF levels were determined using ELISA			
6.	Chronic stress associated with a	(Macedo *et al.*, 2015)	Experimental study	Thirty-two male Wistar rats, 60	- Rats were placed in cages made of polypropylene and measuring 49 × 34 × 16 cm. on a 12 hour light / dark cycle (lights turn on at 7.00	Yes	- Calorie Intake - Weight Loss - SPT - BDNF	BDNF chronic stress intervention in hippocampus

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Next Table 1

No	Title	Researcher, year	Design	Sample	Intervention	Random	Parameters studied	Results
	hypercaloric diet changes the hippocampal BDNF levels in male Wistar rats			days old and weighing 200–250 g	a.m. and turn off at 19.00), with a controlled temperature of 22 ± 2 ° C - In 1 cage, there are four rats, after one week divided into four groups, namely control (C), hypercaloric diet (HD), a standard diet with restraint stress (S), a hypercaloric diet with restraint stress (SHD). - Restraint stress using a plastic tube measuring 25 × 7 cm with adhesive tape outside one end of the open tube. The mice were exposed to stress for 1 hour each day in the morning (between 9 am and 12 pm), then returned to their cages. They performed 5 days a week for 12 weeks. - Animals are weighed weekly, and their food intake is recorded every day. - At 24 hours after the end of the stress session and after 12 hours of fasting, the rats were decapitated, and tissue samples were taken, frozen at -70 ° C. - BDNF analysis by ELISA			<control (p = 0,05)

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RESULTS AND DISCUSSION

Based on the six selected articles, all of them used experimental designs. The samples were mice whose ages were not the same; two articles showed the mice were three months old, while the others were eight weeks, 51-55 days, 45 days, and 60 days. In the division of the treatment and control groups in four articles using random and two articles, there is no information about how the groups are divided.

Almost all of the lighting obtained in the study used artificial light. Only the study of Shishkina *et al.* (2018) uses natural lighting. Lighting is made from 07.00 to 19.00, but in the research of Weisbrod *et al.* (2019), lighting applies 12 hours backward, which is dark at 05.00-17.00. The lighting in this study is almost all the same, namely bright conditions in the morning. The intervention was given in the morning, where the time in the morning is the time to rest the mice because they are nocturnal animals. This condition creates stressors for mice in addition to the stressors given. In the study of Weisbrod *et al*. (2019), the lighting is given a different time, namely, at night; this is to show the disruption of circadian rhythms as well as being a stressor.

Various kinds of intervention methods were used to get stressed mice. Some studies have the same form of treatment and are added to other forms of treatment. The intervention method is that rats are placed in a tube, given stress stimuli in the form of heat stress, cold stress, shaken back and forth, tilted cage and humid environment, lack of food and water, hypercaloric diet, day and night reversal, giving cotton balls soaked in urine are placed in the cage, the whistle blew, the lights blinked, the rats restrain their heads and bodies immobilized in the tube, electric shocks, pinching the tails, giving sucrose solutions, swimming, treadmill, and only seeing the group of mice that were treated. The intervention method used in each study was different; there was a single intervention or a combination of other interventions. This can represent a picture of stressors that occur both mild, moderate, and severe (Weisbrod *et al.*, 2019). Mental stress can lead to depression (Qiao *et al.*, 2020).

The duration of treatment in each study was almost the same, namely for two weeks except in Scotton *et al*. (2019) in mice with CUMS for six weeks, and in the Ghooshchi and Jahromi (2018) study, there was an EX (exercise) group who received 1-2 sessions of recording to show acute conditions and two weeks for chronic. The duration of the intervention showed the duration of the stressor given to the mice, and almost all studies lasted two weeks which could indicate chronic conditions. A meta-analysis showed that the sensitivity of mice varied between species, with the Wistar mouse species showing a more optimal distress response at exposure at the third week, while at exposure beyond that time, these mice tended to be non-responsive, which would have been expected there is an adaptation or even fatigue (Antoniuk *et al.*, 2019).

In this study, besides measuring the ratio of BDNF levels in stressed mice to control mice, it also measured stress by weight, stress with receptor levels glucocorticoids (GR), and stress with monoamine neurotransmitters, neuroendocrine in HPA, stress with oxidative stress, stress with gut macrobiotic, antioxidant capacity, tryptophan hydroxylase levels, and calorie intake.

From the study results, five studies were showing a significant reduction in BDNF levels in stressed mice compared to controls, and one study showed an increase in BDNF in stressed mice, namely Scotton *et al.* (2019) ($p = 0.001$). Research by Weisbrod *et al.* (2019) showed that the BDNF results in male and female rats with CUMS stressors were higher than controls, but with SS stress, BDNF levels in female rats decreased significantly ($p < 0.001$).

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The study examined in this article demonstrated decreased BDNF levels in stressed mice, although not all studies have shown decreased BDNF results. In chronically stressed mice, there was a decrease in BDNF levels because chronic stress would affect the HPA axis, so that high glucocorticoid levels caused Ca2+ influx to increase. This activation Ca2+ influx stimulates the NMDA receptor from glutamate through the 5-HT2 receptor to decrease the BDNF levels (Tunisya, Maria Maramis, and Kusuma, 2010). The research of Scotton et al. (2019) obtained hypertrophy of the adrenal glands due to stress which should have increased glucocorticoid levels and decreased BDNF, but in fact, there was an increase in BDNF, which was probably a compensatory response to maintaining hippocampal homeostasis.

CONCLUSION

Chronic stressors persistently affect the HPA axis which can lead to decreased BDNF levels in the hippocampus.

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Research Article

Comparison of central vein pressure between distal, medial, and proximal lumens with water manometer method

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ABSTRACT

Catheter Vein Pressure in ward-cared patients is rarely measured and considered invalid. The two catheter vein pressure postulates contradict, making confusion among health workers. Dr Russo said the distal-medial-proximal Catheter Vein Pressure has no difference but were denied by Susan S. Scott. Proof of postulate is needed as a solution to inward care. Therefore, this study aimed to compare the central vein pressure between distal, medial, and proximal lumens with the water manometer method. Forty-nine samples retrospective study were taken from the distal - medial - proximal Catheter Vein Pressure of the "zero" until fifth days. The differences are analyzed with Statistical Paired t Test with p-Value < 0.05 from SPSS ver. 26 to prove the right postulate. 49 samples were concluded to represent of population. Catheter Vein Pressure from day "zero" becomes zero difference, the fifth day 91.8% are no difference while the rest have difference of 0.2 - 1.0 cm H2O and the conclusion are no significant difference with 95% CI. The correlation scale of 0.998 and 0.999 proves that the three lumens tend to produce no differences. In conclusion, the distal - medial - proximal Catheter Vein Pressure values in this study have no significant differences and consistent from "zero" until fifth days. This is formulated as P distal = P medial = P proximal (cm H2O).

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INTRODUCTION

Central Vein Catheter in the collaborative and intensive care space (Sanjiv J.Shah and Carolyn S. Calfee, 1998; Chen et al., 2000; Wolf Scott W., 2006) measurements are still useful in confined spaces (Magder, 2005; Miryam M Reems, DVM, and Marcel Aumann, Dr. Med Vet., DACVECC, 2012; Stephen M.Rupp, 2012), although this has only recently begun to doubt (Magder, 2012). In practice, Dr. Russo in his postulate said Central Vein Catheter pressure on the distal - medial - proximal lumen would be the same value based on the laws of physics, while according to Susan S Scott higher values in each lumen and buying every equalization (Susan S Scott et al., 1998).

This problem has an impact when working in the ward treatment room and the need for a road based on evidence from measurement practices that are then discussed in scientific form. From the explanation, it can be seen that the problem flow that must be proven is really needed for the equalization in the central vein catheter lumen.

The focus of attention from this research was the smooth operation of these three lumens from the time they were installed until the next five days, and that requires routine and thorough maintenance techniques (Stephen M.Rupp, 2012; Wolf et al., 2015; Anne Rose et al., 2017). When the lumen is not smooth, the measurement considered invalid also has a bias that determines clinical decisions (Magder, 2005, 2006, 2012). Therefore, this study aimed to seek a proof of the accuracy, difference and deviation of catheter vein pressure distal - medial - proximal lumens from patients with central vein catheter with the water manometer method.

METHODS

This study was cross-sectional in a descriptive retrospective observational design. This study aimed to compare the accuracy, difference, and deviation of catheter vein pressure distal - medial - proximal lumens from patients with central vein catheters. Measurements were taken when newly installed and compared with 5x24 hours afterward for the approved and independent variables.

The study population was patients with demographic characteristics of 17-80 years old samples, central vein catheter with three French 7 size lumens, catheter vein pressure measurements on Day-0, Day-3, and Day-5. Patients had to complete administration and had been evaluated by radiological studies after insertion as indicated. The central vein catheter was not pulled out or replaced before Day-5. According to statistics, the large samples were a minimum of 31 patients to take samples in the medical records room Dr. Soetomo Hospital Surabaya. This study has been ethically approved by the ethical committee of Dr. Soetomo Hospital Surabaya (certificate number: 1995 / KEPK / V / 2020)

The data was processed to obtain the difference and accuracy by comparing the distal catheter lumens. The data has been analyzed using a paired t-conformity test (statistical paired t-Test with p-Value < 0.05 from SPSS ver. 26).

RESULTS

Demographic characteristics data in this study diverged in normally distributed. Demographic data descriptions summarized are listed in the following table.

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Table 1. Demographic and Clinical Characteristic of Patients Sample

Variable	Means ± SD or Frequency (%)	Range
Age (yr)	50 ± 15,542	17 – 80
Gender		
Male (♂)	25 (51%)	
Female (♀)	24 (49%)	
Height (cm)	158,898 ± 7,570	143 – 170
Weight (kg)	60,082 ± 13,441	35 – 100
Body Mass Index (kg/m^2)	23,751 ± 4,835	16,647 - 40,058
Body Surface Area (m^2)	1,408 ± 0,152	0,919 - 1,623

* SD = Standard Deviation

Table 2. Difference Comparison of Catheter Vein Pressure (ΔP) Distal – Medial.

Difference Pressure (ΔP)	Interval Class frequency(F)	Percentage (%)
1.00	1	2.0
0.70	1	2.0
0.50	2	4.1
0.00	45	91.8
Population (N)	**49**	**100.0**

*N = Population; F = Interval Class frequency; ΔP = Difference Pressure.

Table 3. Difference Comparison of Catheter Vein Pressure (ΔP) Distal – Proximal.

Difference Pressure (ΔP)	Interval Class frequency (F)	Percentage (%)
2.00	1	2.0
1.40	1	2.0
1.20	1	2.0
0.90	1	2.0
0.00	45	91.8
Population (N)	**49**	**100.0**

*N = Population; F = Interval Class frequency; ΔP = Difference Pressure.

Table 4. Difference Comparison of Catheter Vein Pressure (ΔP) Medial - Proximal

Difference Pressure (ΔP)	Interval Class frequency (F)	Percentage (%)
1.00	1	2.0
0.90	1	2.0
0.70	1	2.0
0.20	1	2.0
0.00	45	91.8
Population (N)	**49**	**100.0**

*N = Population; F = Interval Class frequency; ΔP = Difference Pressure.

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Table 5. Difference Comparison Distal, Medial, Proximal Catheter Vein Pressure.

Paired Samples Test 95% CI		Mean ± SD	t	df	p Value**
Pair 1	Distal Medial	-0,055 ± 0,196	-1.969	48	0,055
Pair 2	Distal Proximal	-0,112 ± 0,398	-1.976	48	0,054
Pair 3	Medial Proximal	-0,057 ± 0,213	-1,877	48	0,067

*CI = Confidence Interval; df = *Degree of freedom*, t = Pair Test; SD = Standard Deviation
** Student t Paired Test with p Value < 0.05

The catheter vein pressure value of the first measurement day does not produce a difference. The paired t-test cannot be done, and the value is considered to be the baseline value of the central vein catheter test before it is marketed. The fifth-day measurement for the catheter vein pressure value difference values are obtained and shown in the following tables.

There was 91.8% distal and medial catheter vein pressure difference in is zero, while the rest is 0.5-1, and it is concluded that there is no significant difference.

From this data, 91.8% Distal and proximal catheter vein pressure differences in is zero, while the rest is 0.9 - 2.0 cm H2O and it is concluded that there is no significant difference.

Also, from this data, 91.8% Distal and proximal catheter vein pressure difference is zero, while the rest is 0.2 - 1.0 cm H2O, and it is concluded that there is no significant difference.

The difference in pressure from the three lumens does not significantly differ with a 95% confidence interval. It concludes the first measurement until the fifth-day catheter vein pressure values remain not disputed.

DISCUSSION

The study took data on several patients who had completed intensive care or resuscitation treatment with a central vein catheter device that was inserted to measure catheter vein pressure. Care for smooth lumen should be carried out if the lumen is used for total parenteral nutrition administration (Magder, 2005, 2006, 2012), or suspected to have formed fibrin fibers due to never being used (John Santilli, 2002; Miert, Hill and Jones, 2012; Wolf et al., 2015)

Many medical practitioners have assumed that if the lumen is used for total parenteral nutrition, catheter vein pressure measurements cannot be carried out (Blot and Laplanche, 2000; Magder, 2005; Barke et al., 2008; Malinoski et al., 2013). The Catheter Vein Pressures that are performed other than distal lumens produce invalid values and need to be synchronized (Susan S Scott et al., 1998).

On the first measurement day, the distal-medial-proximal lumen catheter vein pressure was proven to be no different using a water manometer, as well as proving the quality of production according to standards manufacturer (Arrow International, 2001; Marsha Halfman, RN and Sandra Reiner, RN, BSN, 2002; Davidovits, 2008; Ishikawa, 2010). This is in accordance with Dr. Russo's postulate in 1991 which was not published (Susan S Scott et al., 1998). In vitro similar studies not living

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things but resembling a human body have been conducted and prove the same result (Jonuarti, 2013).

All the data collected analyzed for its distribution and variance first. Levene's and Shapiro-Wilk tests proved that the study data within normal limit distribution and normal variance to represent all the statistical characteristics of the demographics of age, sex, height, weight, body mass index, and body surface area. This study's sample got different data of measurement from its previous study of Susan S Scott, which is 8 patients experiencing significant catheter vein pressure differences in the three distal-medial-proximal lumens (Susan S Scott et al., 1998). For both measurement techniques, Susan S Scott measures once using a modern transducer and is only done in the ICU room (Susan S Scott et al., 1998) but this study measured three times using a water manometer as a primary gauge and only once compared in a modern transducer for the first time and carried out in various ward treatments.

On the fifth day, as much as 91.8% of the catheter vein pressure value resulted in a zero difference, and the rest produced differences ranging from 0.2 to 1.0 cm H2O. From the t-test comparison between the differences in the three lumens, it was concluded that there was no significant difference between the distal-medial-proximal lumen catheter vein pressure from the day "zero" to fifth. The correlation scale results prove the distal-medial-proximal lumens catheter vein pressure tends to be the same value without a difference. This research also proved that there was no difference in distal - medial - proximal lumens catheter vein pressure both days from "zero" to fifth. The equation can be written as P distal = P medial = P proximal.

This study also found a technique to keep the distal-medial-proximal lumen so that it remained smooth to exchange the infusion lumen every 12-24 hours on each central vein catheter lumen. Although in some compendium the use of alteplase is included as a drug to prevent or destroy blood clots in the central vein catheter lumens (Barke et al., 2008; Miert, Hill and Jones, 2012; Miryam M. Reems, DVM and Marcel Aumann, Dr. Med. Vet. , DACVECC, 2012; Wolf et al., 2015; Anne Rose et al., 2017), but this technique is the safest, simplest and most economical way to be used during the care of patients in the care ward.

The researchers also found that if the pressure difference still occurs on the fifth day even though the lumens maintenance has been carried out. It must be wary of the surface's quality in the distal-medial-proximal central vein catheter lumens are not good and do not have the resistance according to standards production.

CONCLUSION

The distal - medial - proximal lumens catheter vein pressure of the first until the fifth day has proven to be consistent based on measurements and statistical tests. The important practical conclusion from this result is that catheter vein pressure can be measured from any of its lumens. Infusion fluid that flow through central vein catheter lumens every 12-24 hours maintains lumen patent. There is no limitation for the measurement from clinical patient's condition, it can be done for all patients with central vein catheters.

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Research Article

The effect of *Thespesia populnea* against *Plasmodium falciparum* enoyl acyl carrier protein reductase receptor by study in silico

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ABSTRACT

Indonesia is a country that has abundant natural resources; one of them is the *Baru laut* plant which is the latest breakthrough because it has an active substance that can be used as an anti-malaria medicine. It is very beneficial because there has been a case of resistance of artemisinin derivatives in Indonesia. The purpose of this study was to determine the potential of active compounds in *Baru laut* plants (*Thespesia populnea (L.) Soland ex. Correa*) against the *Plasmodium falciparum enoyl acyl carrier protein reductase* receptor in *P. falciparum* through in silico studies. This research is purely experimental using the One-Shot Experimental Study research design method. Observations were only made once between the variables studied through three analyzes, namely prediction analysis of active compound content, prediction analysis of the mechanism of action of active compound content, and prediction analysis of ADME active compound. The study results show that there are three active compounds in *Baru laut* plants that have antimalarial potential. The three compounds include gossypol, linoleic acid, and beta-sitosterol, have their respective potential in becoming a malaria drug. This study concludes that *Baru laut* plants have potential as anti-malaria drugs.

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INTRODUCTION

Based on WHO research in 2019, malaria in the world population showed a figure of 57.4 out of 1000 population while for Africa, the highest-ranking was 229.3 out of 1000 population (World Health Organization, 2019). According to the Indonesian Ministry of Health, the Annual Parasite Incidence (API) in 2015 showed 0.85 of the 1000 population. The distribution within the province from 2015, the provinces with the highest API, is Papua with a value of 31.93, followed by West Papua with a value of 31.29 and NTT 7.04. However, five provinces in Indonesia have reached the value of 0 out of 1000 population, which means they are free from malaria, namely North Kalimantan, West Java, Banten, East Java, Jakarta, and Bali. Nevertheless, with transportation progress, the risk of malaria transmission from populations originating from endemic areas to non-endemic populations can occur (Kementerian Kesehatan RI, 2016). Furthermore, based on WHO research, in 2018, people at risk of contracting malaria in Indonesia reached 263,991,376 people, and the death rate in Indonesia reached 5110 people in 2017 (World Health Organization, 2018).

The cause of malaria is the *Plasmodium* parasite transmitted through the bite of a female *Anopheles* mosquito. *Plasmodium* parasites that infect humans are divided into five species: Plasmodium *falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium knowlesi*, *Plasmodium ovale*. *Plasmodium falciparum* is a species of *Plasmodium* that causes severe clinical manifestations and can cause death if inadequate handling (Putra, 2018). Malaria parasites enter the human body through the bite of female *Anopheles* mosquitoes; in the circulation of these parasites enter the red blood cells, causing changes in the structure of red blood cells and cause red blood cell rupture (Yunita et al., 2019).

The characteristics of the pathogenesis and pathophysiology between malaria species are different, and this causes different clinical manifestations (Fitriany & Sabiq, 2015). *Plasmodium falciparum* has common clinical manifestations such as flu-like symptoms. However, in certain conditions, clinical manifestations of *Plasmodium falciparum* can develop into fatal complications such as cerebral malaria, severe anemia, acute kidney failure, pulmonary edema, hypoglycemia, shock, spontaneous bleeding, acidosis, and hemoglobinuria. This is because this parasite can infect all red blood cells, both young and old, so that damage to red blood cells or hemolysis occurs more severely than other *Plasmodium* species (Sutrimah, 2017).

Indonesia is a country that has abundant natural resources, so the consumption of herbal medicines has become a culture for the people of Indonesia. One of them is a *Baru laut* plant or *Thespesia populnea (L.) Soland ex. Correa.* The plant has many benefits; one of the properties of the plant is an anti-malaria drug (Yani et al., 2014). The emergence of *Plasmodium falciparum* resistance to various antimalarial drugs, especially artemisinin, is related to genetic mutations from the parasitic receptor protein (Suwandi, 2015).

Plasmodium falciparum has an enzyme called *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase*, or *PfENR*, located in the apicoplast is an organelle that regulates various metabolic processes in parasitic cells. The enzyme plays a role in the biosynthesis of type II fatty acids which are very much needed in the manufacture of membranes and as a source of energy reserves. The PfENR enzyme's role for *P. falciparum* is crucial because if there is a disruption to the work of the enzyme, the

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biological membrane is not formed, and there is a lack of energy reserves (Zuchrian, 2010).

This in silico test is a test carried out by docking molecules by predicting the activity of compounds in the selected target cell, which will later show results in the form of the amount of energy used from the compound to be docking to the receptors, which will display the bond energy value or Rerank Score (RS). The more negative or smaller the energy needed, the more stable the bonds formed, which means the greater the compound's activity (Kesuma et al., 2018).

Based on this phenomenon, researchers want to explore the effect of active substances in *Baru laut* plants (*Thespesia populnea (L.) Soland ex. Correa*) with *PfENR* receptor on *Plasmodium falciparum* by a study in silico.

METHODS

This study uses a One-Shot Experimental Study design to test the potential of active compounds in *Baru laut* plants (*Thespesia populnea (L.) Soland ex. Correa*) against the *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase receptor in Plasmodium falciparum*. Observations were only made once between the variables examined in this study. This research began in March 2020 until August 2020, which was carried out at the INBIO Lowokwaru Malang Indonesia Biomolecular and Bioinformatics Laboratory with ethical clearance numbers I/003/UHT.KEPK.03/III/2020.

This research method is in silico which consists of the following steps: preparation of ingredients, prediction of potential compounds, pathway prediction, molecular docking, visualization of docking results, visualization of amino acid interactions, prediction of ADME (absorption, distribution, metabolism, and excretion), and the last prediction of toxicity.

Preparation of ingredients

Downloading compounds inactive plants were obtained from Dr.Duke PhytoChemical data (https://phytochem.nal.usda.gov/phytochem/search/list) and the structure of the *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase* (*PfENR*) from the Indonesian INBIO Laboratory database.

Prediction of potential compounds

The compound that has been obtained will then be analyzed for its potential using WAY2DRUG PASS prediction original version (http://pharmaexpert.ru/PASSonline/index.php) as an antimalarial. The results of the search were measured using the Probability To Be Active value (the Pa value is a value that illustrates the potential of a compound being tested) to assess the activity related to the potential of the herb as a *Plasmodium* inhibitor. Determination of this value is done by comparing the structure of herbal compounds inputted with compounds that have been proven to be antimalarial. Pa values have two criteria (Filimonov et al., 2014), that is:

- If the Pa value is more than 0.7, it indicates that the compound is predicted to have high potential as an antiprotozoal (*Plasmodium*) because it has a high similarity with a compound that has been proven to be an antiprotozoal (*Plasmodium*).
- Whereas if the Pa value is more than 0.3 but less than 0.7, the compound has potential as an antiprotozoal (*Plasmodium*) but a low similarity with a compound that has been proven to be an antiprotozoal (*Plasmodiu*m).

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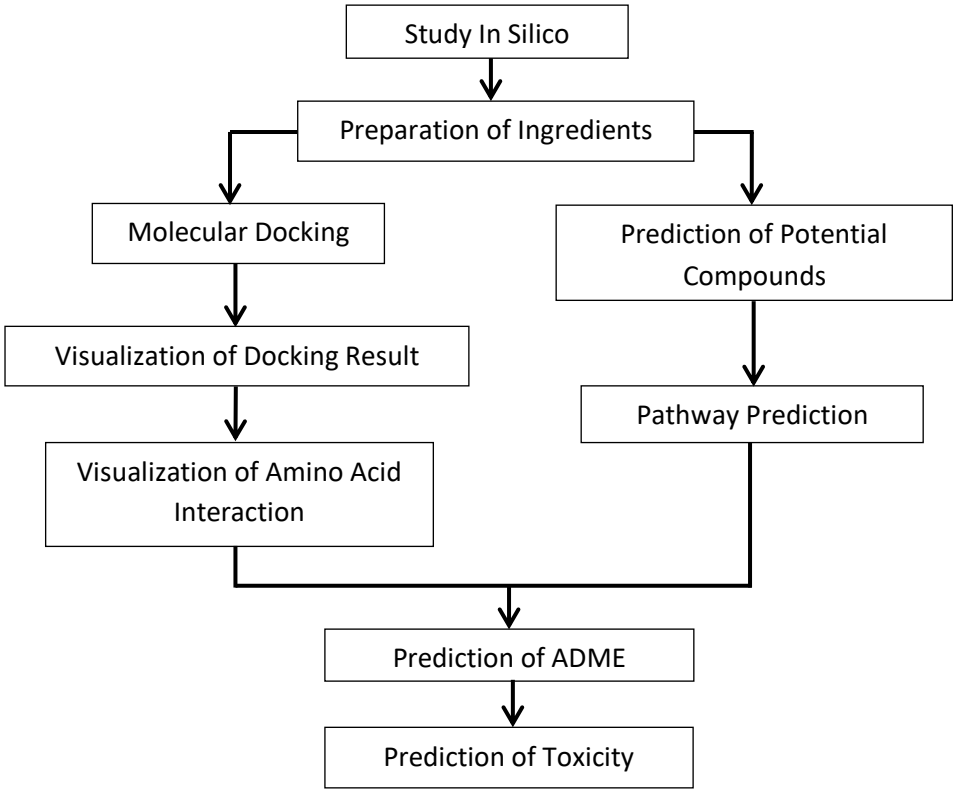

Figure 1. Research work scheme

Pathway prediction

After searching for bioactivity from herbs, then a pathway prediction is performed using the STITCH DB original version with a maximum prediction of 50 interactions. All herbal compounds were analyzed for their interaction with the target protein using the STITCH DB Version 5.0 original version (http://stitch.embl.de/) webserver with the *Plasmodium falciparum* organism model and secure medium (Szklarczyk et al., 2016).

Molecular docking

Molecular docking is done using Autodock Vina's original version in the PyRx 9.5 program. The target protein used is the Crystal structure of Plasmodium falciparum FabI complexed with NAD and inhibitors 7-(4-Chloro-2-hydroxyphenoxy)-4-methyl-2H-chromen-2-one (PDB 4IGE Chain B). While the ligands used are Beta-Sitosterol, Linonelic Acid, Artemisinin, Gossypol, and ligand control is **7-(4-chloro-2-hydroxyphenoxy)-4-methyl-2H-chromen-2-one**. Docking is a specific docking by mimicking the binding bond between the *PfENR* protein with inhibitor control to predict the strength of the interaction between the receptor and the ligand, based on the value of the binding affinity. The more negative the value, the stronger the interaction that occurs between receptors and ligands. If the bioactive tested has a score close to the control score, it can be predicted that the bioactive can have antagonistic activity against the target protein (Seeliger & De Groot, 2010). By using the following grid box :

- receptor = t1.pdbqt
- exhaustiveness = 8
- num_modes = 9
- center_x = 10.8213932702
- center_y = 99.3895537702

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- center_z = 25.471763746
- size_x = 11.709918201
- size_y = 13.7239389014
- size_z = 13.6149749039
- CPU = 7

Visualization of docking results

Visualization of docking result using the PyMol 2.3.1 original version program.

Visualization of amino acid interactions

Visualization of amino acid interactions using the LigPlot 2.1 original version program.

Prediction of ADME (absorption, distribution, metabolism, and excretion)

Prediction of ADME using the SWISS ADME webserver original version (http://www.swissadme.ch/index.php). The results of this prediction can be reviewed using the Lipinski parameter. Lipinski's rule of 5 has the following criteria (Ramadhan, 2019):

- Not more than 5 hydrogen bond donors (total bond of nitrogen-hydrogen or oxygen-hydrogen).
- Not more than 10 hydrogen bond receptors (all nitrogen or oxygen atoms).
- Molecular weight less than 500 Dalton

Then do a Blood-brain barrier (BBB) analysis to predict whether the compound can penetrate the blood-brain barrier. Moreover, the analysis of HIA (Human Intestinal Absorption) is a prediction to estimate the number of compounds that can be absorbed by the gastrointestinal (GI). The higher the value of HIA, the more is absorbed (Daina et al., 2017)

Prediction of toxicity

Prediction of toxicity using Pro-Tox original version (http://tox.charite.de/protox_II/) using the toxic dose or LD50 parameters with values in mg/kg body weight. LD50 is the mean lethal dose which means the dose at which 50% of test subjects die after exposure to the compound. The toxicity class is defined according to the chemical labeling classification system that is the globally harmonized system (GHS). GHS can be classified into (Fallis, 2013).

- Class I : fatal if swallowed (LD50 ≤ 5).
- Class II : fatal if swallowed (5 <LD50 ≤ 50).
- Class III : toxic if swallowed (50 <LD50 ≤ 300).
- Class IV : dangerous if swallowed (300 <LD50 ≤ 2000).
- Class V : may be dangerous if swallowed (2000 <LD50 ≤ 5000).
- Class VI : non-toxic (LD50> 5000).

RESULTS

1. The Content of Active Substances In *Baru laut* Plants and Prediction of Potential Antiparasitic

The prediction of potential compounds using WAY2DRUG PASS prediction (http://pharmaexpert.ru/PASSonline/index.php) is performed. The results of the analysis can be seen in the Table 1.

Table 1 states that *Baru laut* plants have several active substances, namely beta-sitosterol, gossypol, and linoleic acid. The potential of *Baru laut* plant active ingredients as antiparasitic shows that gossypol has no potential as an antiprotozoal, but beta-sitosterol and linoleic acid have antiparasitic activity. Based on the analysis using Pa values, it is known that there are two other compounds in *Thespesia populnea* (beta-sitosterol and linoleic-acid) that have an antiprotozoal role (Pa value <0.3), but the value is not as high as artemisinin (Pa value = 0.954).

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Table 1. Result of prediction of potential compounds.

No	Substances	Antiprotozoal (*Plasmodium*)	Antiparasitic
1	Beta-sitosterol	0.159	Not found
2	Gossypol	Not found	0.382
3	Linoleic-acid	0.172	0.388
4	Artemisinin	0.954	0.857

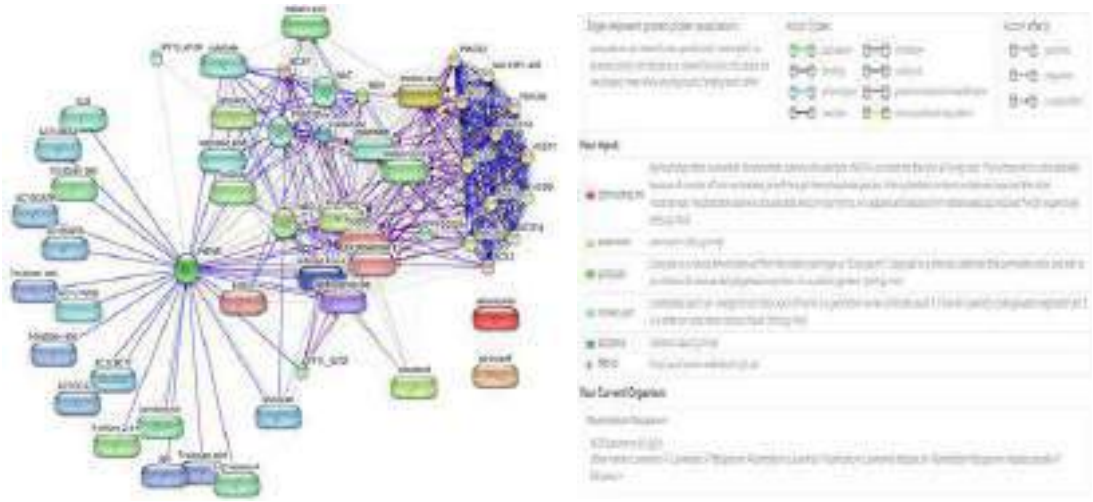

Figure 2. Pathway Prediction active compounds of *Baru laut* plant against *PfENR*

2. Prediction of the Mechanism of Action of Active Compounds Against *Pfenr*

Analysis of the prediction of active substances' mechanism of action using the STITCH DB program with a maximum prediction of 50 interactions. The prediction results are in the Figure 2, where it shows no direct interaction between the active compounds of *Baru laut* plants and artemisinin against *PfENR*.

The interaction between the active substances of *Baru laut* plants with *PfENR* can be seen in the Figure 3. There appears to be an indirect interaction between the active compounds of *Baru laut* plants, beta-sitosterol, and linoleic-acid in diphosphopyridine nucleotide, or another name, nicotinamide adenine dinucleotide (NAD) in *PfENR*. Furthermore, the active ingredients gossypol and artemisinin have no direct or indirect interaction with *PfENR*.

Analysis of the prediction of the mechanism of action of active *Baru laut* substances against *PfENR* using the molecular docking approach was also carried out in this study. Molecular docking results and visualization images can be seen in the Table 2 and Figure 4.

Binding affinity describes the ability of an active compound as a ligand to bind to its receptors. If the binding value of affinity is getting smaller (the more negative), the affinity between the receptor and the ligand is greater. Hydrogen bonds significantly influence the affinity of ligands and receptors because they have higher energy than hydrophobic bonds (1-7 times greater) (Fitriah, 2017). Based on the results of docking of several active compounds compared to the artemisinin derivate above, it can be said that beta-sitosterol has the greatest affinity bond compared to controls and other compounds. The active linoleic-acid compound has the weakest affinity for *PfENR*. The results of two-dimensional ligplot visualization to determine the hydrogen and hydrophobic bonds of active

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compounds with receptors and compared with controls can be seen in the Table 3.

The above results show that the active compound beta-sitosterol forms nine hydrophobic bonds at the same amino acid residue with comparison controls. Gossypol forms one hydrogen bond and five hydrophobic bonds, and linoleic acid forms seven hydrophobic bonds without forming hydrogen bonds. If the data analysis of ligplot visualization combined with the prediction of binding affinity of active compounds of *Baru laut* plants to *PfENR* shows that beta-sitosterol forms the strongest bond with *PfENR* compared to the other two compounds, the bond strength is similar to that of artemisinin derivatives. Gossypol forms a stronger bond than linoleic acid but is weaker than beta-sitosterol and artemisinin derivates.

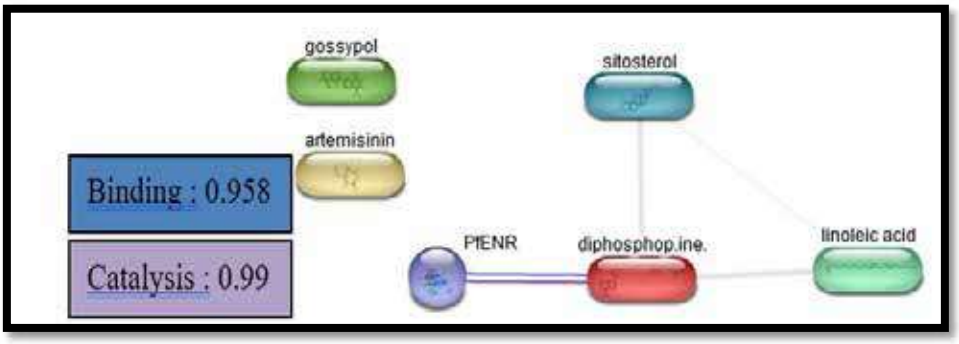

Figure 3. Pathway prediction active compounds of *Baru laut* plant against *PfENR*

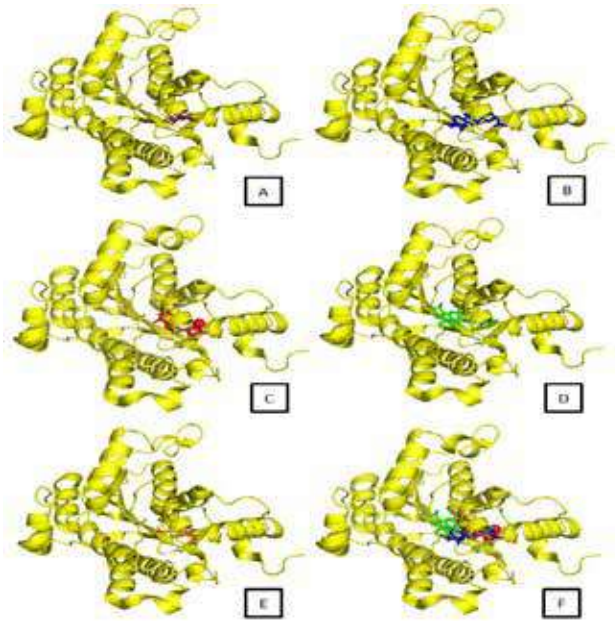

Figure 4. Visualization of molecular docking result between *PfENR* with a ligand. A is an Artemisinin bond, B is Beta-sitosterol, C is Control, D is Gossypol, E is Linoleic acid, and F is the overall result of molecular docking.

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Table 2. Molecular docking results between *PfENR* and ligand

No	Substances	Score Binding Affinity (kcal/mol)	Color visualization
1	Beta-sitosterol	-9.9	Blue
2	Gossypol	-6.9	Green
3	Linoleic-acid	-6.3	Orange
4	Artemisinin	-9.9	Purple
5	Control	-8.8	Red

Table 3. Visualization of LigPlot results between *PfENR* and ligand. Thickened data is the same amino acid residue between Control and Comparative Ligands.

Substance	Hydrophobic Bond	Hydrogen Bond
Control	GLY110 SER317 ALA312 PRO314 TYR277 TYR267 PHE368 ILE369 ALA217 ALA319	TYR111 GLY313
Beta-sitosterol	ALA320 **GLY313** LYS285 **TYR111** THR266 **ALA217** MET281 ASN218 **ALA319** ILE323 VAL222 **TYR277 ILE369 PHE368 TYR267 PRO314** LEU315	
Gossypol	**ALA217 PRO314** ALA320 **TYR267 ILE369** TYR 111 THR266 LYS285 LEU265 LEU216 **ALA319** SER215 TRP131	ASN 218 **SER317** LEU315 **GLY313** ALA312
Artemisinin	**ILE369** ALA320 **PRO314 GLY313 TYR267** ALA312 LEU265 **TYR111** THR266 ILE323	**TYR277** LYS285
Linoleic-acid	ALA312 THR266 SER215 **SER317 GLY313 TYR111** ILE323 **PHE368 TYR277** ALA320 **ILE369 TYR267**	LEU265 LEU216 LYS285

3. Prediction of Absorption, Distribution, Metabolism, Excretion (ADME) and Toxicity.

The prediction of ADME using the ADME SWISS web server (http://www.swissadme.ch/index.php) is reviewed using the Lipinski parameter. The prediction of toxicity using Pro-Tox (http://tox.charite.de/protox_II/) by using toxic dose or LD50 parameters with values in mg/kg body weight and toxicity class according to the chemical labeling classification system that is globally harmonized system (GHS). The results of these predictions can be seen in the Table 4.

Based on the results of ADME predictions made, it can be seen that beta-sitosterol, linoleic acid, and artemisinin have passed the Lipinski parameter. At the same time, gossypol does not pass because it has violated 2 of the three provisions, namely the weight exceeds 500 Dalton and also hydrogen bond donors that exceed 5. Among the compounds from *Baru laut* plants tested, linoleic-acid is the best compound because it has sufficient water solubility, high GI absorption, and high bioavailability. It indicates that linoleic acid is the closest to artemisinin derivatives. Then the results of the toxicity prediction can be seen in the Table 5.

Based on the results of the prediction of toxicity that has been done, it can be seen that linoleic acid has the highest Lethal Dose (LD50) value that exceeds artemisinin which is 10,000 mg/kg BW, which is included in class 6 (this class is the safest class for consumption).

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Table 4. Prediction of ADME results between *PfENR* with ligands

Explanation	Beta-sitosterol	Gossypol	Linoleic-acid	Artemisinin
Molecular Weight	414.71 g/mol	518.55 g/mol	280.45 g/mol	282.33 g/mol
Number of Atom	30	38	20	20
Hydrogen Bond Acceptors	1	8	2	5
Hydrogen Bond Donors	1	6	1	0
Air solubility	Low	Low	adequately	High
GI Absorption	Low	Low	High	High
Blood-Brain Barrier	-	-	+	+
Bioavailability	0.55	0.17	0.56	0.55

Table 5. Prediction of Toxicity results.

Explanation	Beta-sitosterol	Gossypol	Linoleic-acid	Artemisinin
Prediction of LD50 (mg/kg BW)	890	325	10.000	4.228
Prediction of Toxicity (class)	4	4	6	5

DISCUSSION

Prediction of potential compounds *Baru laut* as antimalarial

Baru laut plants have various active substances including flavonoids, alkaloids, saponins, tannins, terpenoids, phenolics, gossypol, beta-sitosterol, and linoleic-acid. The results of the prediction of potentially active compounds that have antimalarial effects indicate that there are 3 active compounds in baru laut plants that have antimalarial potential. The three compounds include gossypol, linoleic acid, and beta-sitosterol. The prediction of beta-sitosterol's potential test shows that the compound has no antiparasitic activity but has potential as an antimalarial. It is likely due to the active compound does not work as an antiparasitic against protozoa other than *Plasmodium* and helminths but has the potential as an antimalarial. This is related to a study conducted by Bo Zhai showing that the *Bixa Orelanna L* plant contains beta-sitosterol, which has the potential to be an antimalarial in linoleic acid shows that the compound has activity as an antiparasitic and as an antimalarial (Zhai et al., 2014). This proves that linoleic-acid can work on *Plasmodium* as an antimalarial and be an antiparasitic addition to *Plasmodium* such as worms and other protozoa. This is related to a study conducted by Paula Melariri showing that linoleic-acid compounds have potential as an antimalarial (Melariri et al., 2012). Furthermore, the last prediction of potential is gossypol which shows that the compound has no antimalarial activity but has potential as an antiparasitic. This is probably due to the active compound does not work as an antiparasitic to *Plasmodium* (antimalarial) but only works against other parasites such as worms or can be said to have potential antiparasitic but not as an antimalarial. However, a study conducted by Hoda Keshmiri-Neghab showed that the plant *Thespesia populnea (L) Soland ex Correa* contains gossypol, which has the potential to be an antimalarial (Keshmiri-Neghab & Goliaei, 2014). Overall results on the prediction of potential were obtained that *Thespesia populnea (L.) Soland ex. Correa* has a role as an antiparasitic, especially *Plasmodium* but the value is not as high as the prediction of artemisinin derivates.

Prediction of the mechanism of action of active compounds against *PfENR*

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The results of the prediction of the mechanism of action of the active compounds against *PfENR* indicate there is an indirect interaction between the active compounds of *Baru laut* plants, beta-sitosterol, and linoleic acid in diphosphopyridine nucleotide in *PfENR*. Diphosphopyridine nucleotide or nicotinamide adenine dinucleotide (NAD) components are cofactors that result from crotonoyl-CoA catalysis with NADH cofactors being butyryl-CoA and NAD and are alternating reactions (Zuchrian, 2010). In this experiment, beta-sitosterol was proven that the compound was able to bind indirectly to *PfENR* through inhibition of the diphosphopyridine nucleotide component of *PfENR*. Then linoleic acid is also shown to have an antimalarial effect and even affects an insecticide through diphosphopyridine nucleotide, which is similar to the mechanism of beta-sitosterol (Jansen et al., 2017). Then gossypol and artemisinin, there is no direct or indirect interaction with *PfENR*. This is because gossypol has a more precise target at *PfLDH* (Razakantoanina et al., 2000). Whereas artemisinin targets *Plasmodium falciparum SERCA-type ATPase 6 receptors*(Suwandi, 2015).

After that, the molecular docking method will be continued, with the results of gossypol (-6.9), beta-sitosterol (-9.9), artemisinin (-9.9), and linoleic-acid (-6.3) with control (-8 8). In this experiment, beta-sitosterol has the highest potential compared to other compounds and has the same value as artemisinin. The residue of beta-sitosterol has many similarities with control, even with artemisinin almost entirely the same. Because of this, the binding value of beta-sitosterol is not different from artemisinin and not much different from control (Bintari, 2018).

Prediction of ADME and toxicity

The next step is predicting absorption, distribution, metabolism, and excretion or ADME of all compounds. Among all the compounds tested, linoleic acid was the best compound because it passed all Lipinski parameters and had sufficient water solubility, high GI absorption, and high bioavailability. Beta-sitosterol is not good even though it has passed Lipinski parameters and has high bioavailability but has low water solubility and low GI absorption. However, gossypol has violated 2 out of 3 Lipinski parameters, low bioavailability, low GI absorption, and low water solubility, so gossypol can be said to be unsuitable as a drug.

Then in the final experiment, the toxicity test. In this test, linoleic acid has the highest LD50 value of 10,000 mg/kg body weight classified in class 6, which is the safest class, even exceeding the value of artemisinin which is only 4,228 mg/kg bodyweight included in class 5. At the same time, beta-sitosterol has a value of 890 mg/kg, which is included in class 4, and continued with gossypol with a value of 325 mg/kg, which is included in class 4.

From all tests that have been done, all compounds can be used as a drug, but depending on the processing of extracts up to the way of administration of compounds that will be used as alternative drugs. As in vitro research by the Neeraj Sethiya group, it can be proven that gossypol has high inhibitory power in *PfLDH*. It can be said that gossypol can also be used as a drug even though it has a deficiency in inhibiting *PfENR* (Sethiya et al., 2014). Whereas beta-sitosterol has also been proven to affect *Plasmodium* as an antimalarial drug by Anna Caroline C Aguiar, although the target drug mechanism described is not specific (Aguiar et al., 2012). Furthermore, the linoleic-linoleic acid proven by Damtew Bekele that linoleic acid can be used as an antimalarial drug and even has an insecticidal effect, especially to kill mosquitoes which are vectors of the cause of malaria (Bekele et al., 2018). *Baru laut* plants correlate with antimalarial effects

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against anti-inflammatory because if there is an antimalarial effect, the inflammatory process will be inhibited by inhibiting erythrocyte damage. Inflammation in malaria is caused by high levels of parasitemia which can cause cytokine storms. By suppressing parasites, it is hoped that the reduction of cytokines and inflammation will be suppressed (Ilavarasan et al., 2012).

CONCLUSION

The prediction of the potential of *Baru plant* compounds (*Thespesia populnea (L.) Soland ex. Correa*) proves that it has an antimalarial drug potential. The two active compounds that have antimalarials potential are beta-sitosterol and linoleic-acid. However, their potential is lower than the artemisinin derivate. The prediction of the mechanism of action of active compounds of *Baru laut* plants, namely beta-sitosterol and linoleic-acid, showed an indirect barrier to *PfENR/ Plasmodium falciparum enoyl acyl carrier protein* through diphosphopyridine nucleotide. Beta-sitosterol compounds have a higher binding affinity than other compounds, and the size of the binding affinity resembles that of artemisinin derivatives. The ADME prediction proves that linoleic acid has the best ADME ability to nearly matching artemisinin derivates because it has sufficient water solubility, high GI absorption, and high bioavailability.

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Research Article

Prevalence and risk factors of *Ascaris lumbricoides* infection in children of Manusak Village, Kupang District, East Nusa Tenggara Province, Indonesia

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ABSTRACT

Worm infection is one of the health problems in all tropical countries, including Indonesia. The most frequent helminthiasis is the infection caused by the Soil-Transmitted Helminth. Primary school-age children are an age group that is susceptible to helminthiasis. Worm infections can cause a serious impact if left untreated with no clean and healthy lifestyle. This study was conducted to determine the prevalence and risk factors of STH in children of Manusak Village, East Kupang Subdistrict, Kupang District, East Nusa Tenggara Province, followed by the characterization of subjects. The analytic observational design with the cross-sectional study was applied to this research. Research subjects were 130 children aged 6-12 years old. The infection was diagnosed microscopically by the Katokatz method. *Ascaris lumbricoides* were the only species found infecting a total of 50 children (38.4%.). The distribution of ascariasis was higher in girls (30 or 23.08%) than in boys (20 or 15.38%), in children whose parents have no formal education (41 or 31.54%), and who their professions are a farmer. Poor hygiene and sanitation such as no washing hands with soap (27 or 20.77%) as well as the habit of not wearing footwear (47 or 36.2%) and bowel habit on the open areas (35 or 26.92%) are the risks factors causing the high incidence of *A. lumbricoides* in the studied area. Enlightenment to the parents regarding good personal and environmental hygiene and sanitation along with chemotherapy from the government and related agencies is needed to achieve a durable reduction of the burden of ascariasis and other STH infection.

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INTRODUCTION

Ascaris lumbricoides is one of the soil-transmitted helminths (STH). STH are intestinal nematode worms that infect humans who ingest their eggs via the oral-fecal route. This worm consists of *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale* and *Strongyloides stercoralis*. The STH infections are widely distributed in tropical and subtropical areas, with the most incredible numbers occurring in Sub-sahara Africa, America, China, and East Asia. More than 1.5 billion people, or 24% of the world's population, are infected with STH. The high-risk group includes preschool children, school-age children, women of childbearing age (including pregnant women), and adults in certain high-risk occupations such as tea pickers or miners (Sastry & Bhat, 2019) or farmers (Ensink, Hoek, Mukhtar, Tahir, & Amerasinghe, 2005). The current comprehensive prevalence rate of STH in Indonesia is difficult to be ascertained. The prevalence rate in children is higher than in adults due to poor personal hygiene (Lee & Ryu, 2019). No report of a certain number of cases has been published.

Ascaris lumbricoides is the largest nematode of the gastrointestinal tract of humans. This nematode is cosmopolitan in distribution, where the typical habitat of the adult worm is the jejunum. The infection is acquired by the ingestion of the embryonated eggs, and the larvae pass through a pulmonary migration phase for maturation (Khuroo, Zargar, & Mahajan, 1990). The infection is transmitted through the fecal-oral route, from soiled hands and food contaminated with *A .lumbricoides*-infected human feces or unprocessed sludge or biosolids taken from sewage treatment systems where the ova accumulate (Asaolu & Ofoezie, 2018). Intestinal nematode infection is most prevalent among rural communities in warm and humid equatorial regions and where sanitation facilities are inadequate. Infection also occurs in urban areas. Even within areas of low prevalence, small localized regions of high prevalence can exist. Only cold or sweltering, arid climates are free of infection (Brooker, 2010). The number of infections is estimated that in 2010 about 818 million (771.7-891.6 million) people were infected with *A. lumbricoides* (Pullan *et al*, 2014).

Hygiene and sanitation are the factors are closely related to STH infection. The habit of washing hands with soap, wearing footwear, the cutting nails are the best way to prevent the transmission of helminthiasis. Sanitation is one of the risk factors for the disease, such as the use of improper latrines, which will cause contamination of the soil with feces around the yard and clean water availability (Kartini, Kurniati, Jayati, & Sumitra, 2017). The infection of STH is one of the neglected tropical diseases—lack of maximum effort and monitoring by health workers to prevent the disease. The STH-infected persons usually do not realize that they have been infected. The infection can be diagnosed by finding eggs and adult worms in the feces (Juhairiyah, Annida, & Indriyati, 2015). The incidence of helminthiasis in the Province of East Nusa Tenggara (NTT) is at the third position in Indonesia with a percentage of 28% (2018 NTT Health Service) after Banten Province, Which was 60.7%, and Nanggroe Aceh Darussalam Province (NAD) which was 59.2% (Zulhifah, 2016).

This study was conducted in Manusak Village, where poor sanitation and hygiene in this village may develop STH infection. Most of the population of Manusak Village works as farmers. The majority of the population were refugees from Timor Leste during the referendum of free Timor Leste from Indonesia in 2009 who did not return to the country of Timor Leste. The people in this area have a low economic condition, low environmental sanitation, not using footwear during play in the yard, some

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people do not use toilets for defecation and free pets outside the cage. This study aims to find out the prevalence risk factors of STH infection in primary school-age children in the refugee area of Manusak Village, East Kupang Subdistrict, Kupang District, East Nusa Tenggara Province, Indonesia.

METHODS

Ethical clearance

Ethical clearance was obtained from the Health Research Ethical Clearance Commission (HRECC) Faculty of Dental Medicine, Universitas Airlangga, Surabaya as described on the certificate number 053/HRECC.FODM/ II/2020.

Location

The research was conducted in the Manusak Village, East Kupang Subdistrict, Kupang District, East Nusa Tenggara (NTT) Province. Kupang District is situated in Timor island of Indonesia (Figure 1).

Geographically, Kupang District has a land area of 7,178.26 Km^2 and is the largest area in East Nusa Tenggara (ENT) Province. Kupang District covers 15.16 % of the total land area of ENT Province. Geographically, Kupang District is located at 123º16'10.66"-124º13'42.15" east longitude and 9º15'11.78"-10º.22 '14.25"south latitude.The territory is bordered by the Savu Sea and Ombai Strait to the north, the Indian Ocean and the Timor Sea to the south, District of South Central Timor and the District Oecusi of the country of Timor Leste to the south, and Kupang City, Rote Ndao District, Sabu Raijua District and Sawu Sea to the west (Pemerintah Daerah Kabupaten Kupang, 2013). Manusak Village is one of 8 villages in East Kupang Subdistrict, which consists of 3,800 population and contains 520 families. This village is a rural and slum area with low social and economic level, limited education level, limited hygienic criteria in the availability of latrines, that resulting in the disposal of sewage in any place such as in the bushes around the place of residence (BPK RI Perwakilan Prop NTT, 2019).

Figure 1. Location of Kupang District and Manusak Village. Kupang District, East Nusa Tenggara Province is located in Timor Island as same as the country of Timor Leste, and Manusak Village is a part of Kupang District.

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Research design

The analytic observational design with the cross-sectional study was applied to this research. Samples collections were done during January-February 2020. Stool samples were collected using stool pots which were distributed on a day before sample collection, followed by an explanation on how to collect stool samples, and the subjects who agree to give the sample were asked to sign the informed concern. The parents of the children are ethically represented to sign the informed concerns. The sampling must meet inclusion criteria that the subjects who had signed the inform concern and gave their stool samples, the children who did not take the anthelminthic medication within the last 6 months when the sampling was ongoing, and the samples which contained STH on microscopy examination. The exclusion criteria were the children who did not give the samples during the data collection and who had taken anthelminthic medication within the last six months when the sampling was ongoing. Stool pots contained stool samples were then labeled with the identity of the subjects. The collected samples were then transported to the Laboratory of Parasitology, Study Program on Medical Technology, Institute of Polytechnic of Ministry of Health, Kupang District prior to microscopy examination.

Kato Katz Method for stool sample examination

Kato Katz's method was done based on the technique explained by WHO in (WHO, 2019) modified based on the materials available in the Laboratory of Parasitology in the Study Program on Medical Technology in the institute of Polytechnic of Ministry of Health, Kupang District. A gram of fecal sample was placed on filter paper, and then a wire mesh was put on the feces. A piece of cardboard was prepared, a hole was made on it then the cardboard was placed on sliding glass. The wire mesh was placed on fecal sample examination top of the feces; then, the cardboard holes were filled with feces, and cardboard was removed. Feces on object glass was then covered with cellophane that has been soaked in the Kato solution. Cellophane tape was pressed with other glass objects to flatten the stool, and it was left for 20-30 minutes at room temperature. Objects glass was then examined under a light microscope using a 10x objective lens to identify the species of STH. The eggs per gram of feces were counted and calculated to determine the intensity of infection based on WHO (WHO, 1994).

RESULTS

Characteristics of subjects

Research subjects were 130 children aged 6-12 years old, consisted of 76 females (58.5%) and 54 males (41.5%). Primary data on the characteristic of subjects were obtained by direct interviews using a questionnaire. The results were presented in Table 1.

Kato Katz stool sample examination

The results of microscopy examination of stool samples showed that *Ascaris lumbricoides* was the only species found in 50 (38.4%) samples out of total of 130 samples. Therefore 80

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Table 1. Characteristic of subjects and their parents

Variable	Number (%)
Age (years)	
6-12	130(100)
Gender	
Female	76(58.5)
Male	54(41.5)
Level of education of parents	
No School	41(31.54)
Primary school	30(23.08)
Junior high school	25(19.23)
Senior high school	20(15.38)
College	14(10.77)
Profession of parents	
Farmer	107(82.31)
State officer	18(13.84)
Entrepreneur	5(3.85)

(61.6%) were negative. Other species of STH were not found in the collected samples. The distribution of positive samples based on the characteristic of subjects and their parents is presented in Table 2.

Table 2 above shows that among 50 positive samples, the distribution of ascariasis was higher in girls than in boys, in children whose parents have no formal education and whose professions are a farmer. Farmer is the kind

Table 2. Distribution of *A. lumbricoides* infection based on the characteristic of subjects and their parents

Variable	Number of the sample (%)			p
	Positive	Negative	Total	
Age (years)				
6-12	50 (38.46)	80(61.54)	130(100)	
Gender				
Female	30(23.08)	46(35.38)	76(58.5)	
Male	20(15.38)	34(26.2)	54(41.5)	
Level of education of parents				0.001
No School	27(20.77)	14(10.77)	41(31.54)	
Primary school	10(7.69)	20(15.38)	30(23.08)	
Junior high school	7(5.38)	18(13.85)	25(19.23)	
Senior high school	5(3.85)	15(11.54)	25(19.23)	
College	1(0.77)	13(10)	14(10.77)	
Occupation of parents				0.021
Farmer	47(36.2)	60(46.2)	107(82.31)	
State Officer	2(1.4)	16(12.31)	18(13.84)	
Entrepreneur	1(0.77)	4(3.08)	5(3.85)	

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of profession which dominated among the parents, and their children have also dominated the positivity of ascariasis case in the studied village. Interestingly, the number of positive samples was decreased along with the increase in the level of education. Chi-square analysis showed a strong significant correlation between the level of education of the parents (p=0.001) and their occupation (p=0.021) with the positivity of ascariasis.

Intensity of infection

The intensity of ascariasis in children of Manusak Village based on the number of EPF of feces is presented in Table 3. The intensity of infection among the positive samples (50) was found to be mild and moderate (WHO, 2017).

The number of samples with a mild intensity of infection contained each male and female were 5 (10%) each of children, while moderate infection contained 15 (75%) male and 35 (83.33%) female of children.

Risk factors of ascariasis in Manusak Village

Based on interviews and direct observations on the behavior of clipping, the nails showed dirty and clean nails; however no correlation of this behavior to the positivity of ascariasis (p=0.868). Handwashing habits before eating and after defecating (p=0.000), the habit of wearing footwear when playing and accompanied their parents to the garden (p=0.019), as well as bowel habits (p=0.035) are the risk factors in children to have *A. lumbricoides* infection (Table 3).

Tabel 3. Intensity of infection based on the number of EPG of feces in children of Manusak Village, Kupang District

***A. Lumbricoides* infection**	**Intensity of infection**	
	Mild	**Moderate**
Number of sample (%)	10 (20)	40(80)
Number of EPG of feces	1,000-4,000	6,000-9,600
Mean of EPG of feces	2,420	7,390

DISCUSSION

The STH infection in children has received more attention than in farmers, as shown by the implementation of deworming and providing albendazole treatment to school children in Indonesia (Sungkar, Ridwan, & Kusumowidagdo, 2017).

Children are more susceptible to parasitic infections than adults because of a lower immune response, poor hygiene and sanitation, and favorable environmental conditions for the development of parasites that eventually infect the host. The transmission of ascariasis in Manusak village was caused by poor sanitation and hygiene of the children, especially in defecating behavior. Although 100% of subjects own the family latrine, 26.92% out of them prefer defecating on the ground or garden or house yard (Table 3), and although defecating in the family toilet (11.54%), they are positively infected by *A. lumbricoides.*

Based on the results of microscopy examination of 130 samples, only species of *A. lumbricoides*

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Table 4. Risk factors of ascariasis and distribution of *A. lumbricoides* infection based on behavior of subjects of Manusak Village, Kupang District

Behavior	Number of the sample (%)			
	Positive	Negative	Total	p
Clipping fingernails behavior				0.868
Yes	23(17.7)	38(29.2)	61(46.92)	
No	27(20.77)	42(32.3)	69(53.08)	
Handwashing Habits				0.000
Washing	8(6.2)	39(30)	47(36.15)	
Not washing	42(32.3)	41(31.5)	83(63.85)	
Wearing footwear behavior				0.019
Wear	3(2.3)	17(13.1)	20(15.38)	
Do not wear	47(36.2)	63(48.5)	110(84.62)	
Bowel habits				0.035
Toilet	15(11.54)	39(30)	54(41.54)	
On the ground of garden and house yard	35(26.92)	41(31.54)	76(58.46)	

Table 5. Environmental sanitation and distribution of *A. lumbricoides* infection in children of Manusak Village

Variable	Number of the sample (%)			
	Positive	Negative	Total	p
Latrine Ownership				*
Yes	50(38.46)	80(61.54)	130(00)	
No	0	0	0	
Clean Water Source				0.148
River	47(36.2)	60(46.2)	107(82.31)	
Well	2(1.4)	16(12.31)	18(13.84)	
Tank	1(0.77)	4(3.08)	5(3.85)	

*Statistical analysis cannot be performed because latrine ownership is constant, all subjects have a family latrine.

(100%) with a positive number of 50 children (38.4%) were found. The species of *A. lumbricoides* is the most prevalent STH in the region of South Asia and South East Asia, but there was considerable geographic variation (Silver *et al*., 2018).

The focal nature of *A. lumbricoides* was associated with pH and the soil texture, those are factors that influence STH infection distribution. Furthermore, *A. lumbricoides* were stated to prefer acidic soil. Clay and loam soil are more favorable for eggs of *A. lumbricoides* development than sandy loam soil, which favorable for hookworm (Wardell *et al*., 2017). Those types of soil were found in Kupang District (Pemerintah Daerah Kabupaten Kupang, 2013).

The species of *A. lumbricoides* was the only species found by the Kato Katz method in this study. Other species might present in the samples but could not be detected by this method. The direct method has been applied to diagnose the samples. However, the same results were obtained. Kato Katz is a method

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which has great epidemiological relevance because its simplicity and low cost (by using this method not only detecting the parasite but also the parasite load quantification of the infected patients by calculating the number of egg per gram (EPG) of feces (Speich, *et al*, 2015).

However, the Kato-Katz technique has limitations in terms of sensitivity, especially when the small amount of stool was analyzed (usually 41.7 mg) and whenever the parasites present at low frequency (Taye, 2014).

The sensitivity of the Kato-Katz technique is increased by analyzing multiple thick smears from a single or, ideally, from multiple stool samples (Speich *et al*., 2015).

Hookworm might be present in the community but not detected by the Kato Katz method. A sufficient distance from the sampling area to the laboratory to transport the samples for processing showed that time delay between excretion and laboratory processing of stool samples significantly decreases the fecal egg count, especially hookworm eggs (Krauth *et al*, 2012).

When the sample was too little, and the intensity was too low, the existing hookworm egg could not be detected by Kato Katz method. A more sensitive method should be applied to solve this problem.

Alternatively, a molecular detection technique can be applied to detect and identify the parasite's species of the low frequency of STH (Lamberton and Jourdan, 2015).

Molecular diagnostic tools are highly sensitive and specific, such as multiplex PCR and real-time PCR (qPCR). Multiplex PCR enables the detection of multiple parasite species in a single reaction and can simplify diagnostics by replacing several individual tests with one molecular test. Multiplex PCR showed promising results for *A. lumbricoides*, *T. trichiura* and *N. americanus* (Phuphisut *et al*, 2014)

The qPCR, unlike conventional PCR, which can only indicate the presence of infection, qPCR enables quantification of parasites and associated infection intensity. The qPCR is more sensitive than Kato-Katz and the floatation technique (FS7) for detection of *A. lumbricoides* infections and co-infections. Multiplex qPCR assays have successfully detected *A. lumbricoides* infection alongside multiple intestinal parasites (Basumi *et al*, 2012; Mejia *et al*, 2013).

High incidence of ascariasis in Manusak Village compared with other districts in Indonesia was higher than that of ascariasis in 2-9 years old children in Batakte Village of West Kupang Subdistrict, Kupang District, where 12% out of 59 children was positive (Susilawati & Smaut, 2017), in Northwest Sumba District, where only 31% children infected with *A. lumbricoides* (Olin, Paun, & Rindu, 2019), while in Sorong District, Papua Province was only 3.4% (Yuwono, Husada, & Basuki, 2019), in Karang Asem District, Bali Province was only 0.8% (Bayu, Pradinata, Sudarmaja, & Ariwati, 2019), however in Banjarmasin City, South Kalimantan Province no ascariasis was found (Juhairiyah *et al.*, 2015).

Ascariasis in Manusak village was lower compared with that in Raja Basa District of Lampung Province, where ascariasis cases in children were 88.2% (Wintoko, 2014).

The high incidence of ascariasis might relate to the anthelminthic medication program from the local health center, which was not implemented properly by the children in Manusak village. In Indonesia, according to Decree Minister of Health, No. 424 / Menkes / SK / VI / 2006 regarding Guidelines for Worms Control mass treatment of intestinal worms, is if the prevalence of an area above 30% is carried out mass treatment two times a

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year. For a prevalence below 30%, treatment is carried out selectively for subjects who are positively found worm's eggs in their stools and carried out at the current health facility come for treatment. However, according to WHO 2006, for areas with high infection rates, the medication can be implemented every three times a year (Kementerian Kesehatan Republik Indonesia, 2006).

The direct information regarding the anthelmintic medication obtained from the subjects was that they received albendazole in August, but none of them took medicine because it was too big to swallow. A recommendation given to a community to crush the anthelminthic drug to be easy to swallow might overcome this problem (Vitamine angels, 2020).

However, no published report on the information on the distribution of anthelmintic as well as the use of albendazole and its resistance in Kupang District. Likewise, in the Health Profile of Kupang District 2018, there was no description of albendazole distribution. Only the distribution of vitamin A and iron-containing tablets were explained clearly (Dinas Kesehatan Kupang, 2018).

The intensity of infection was found to be mild and moderate. This finding was different from the study among elementary school children of Suka Village, North Sumatra, where the severe intensity was found in addition to mild and moderate intensities. Mild ascariasis is often asymptomatic. However, individuals with mild and moderate infection intensity are the source of transmission in the community (Bethony *et al*, 2006). Malabsorption of vitamin A and reduction of lactose digestion often occur in *A. lumbricoides*-infected children due to the obstruction of the small intestine by the worm, which leads to growth retardation, undernutrition, impaired cognitive function, and low educational achievements in children (Galgamuwa and Dharmaratne, 2018).

The *A. lumbricoides* infections and undernutrition have a negative impact on the growth and development of the infected person (Quihui-Cota *et al*, 2004).

Characteristics of parents of subjects included education and occupation, have been analyzed. The level of education and knowledge of parents is very influential on the growth, development, and formation of children's behavior (Nokali, Bachman, & Votruba-Drzal, 2010).

The level of education correlated significantly with *A. lumbricoides* infection with p=0.001. Interestingly, the number of positive cases increased oppositely with the level of education (Table 2). This is a fact that the low education of parents risky to cause ascariasis in their children. The low education may have the low knowledge on hygiene and sanitation as well as on worm infection, including preventive care and transmission. This low level of knowledge

of being infected. Therefore there is a need for proportion education on STH transmission (Oyebamiji, Ebisike, Egede, & Hassan, 2018).

Farmer is the occupation of parents with the highest number of ascariasis cases (36.2%) of their children. Occupation of parents correlated significantly with the infection with p=0.021 (Table 2). Farmer is one type of occupation that is in direct contact with the soil, which is possible for them to be infected with STH if the soil is contaminated with eggs of STH (Munawaroh, Arwati, & Wardhani, 2020). Risk factors associated with farmers are the use of wastewater for land irrigation, manure fertilizers as plant fertilizers, and the use of personal protective equipment during work, and handwashing behavior after work (Ensink *et al*., 2005).

oStatistically, there was no correlation between the habit of clipping fingernails with infection (p=0.868). The same result was shown by a report from Kulon Progro District in the province of Specific Region of Yogyakarta

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were no correlation of trimming fingernails and the STH infection with (p=0.085); however, fingernail biting increased the risk of STH infection (p=0.019) (Sofiana, Sumarni, & Ipa, 2011). A different result was reported that the habit of fingernails clipping of children in Raja Basa District of Lampung Province was 16,5% affected the contamination of nails with STH eggs (Wintoko, 2014).

Poor hygiene and sanitation in washing hands with soap before eating or after defecating (p=0.000), as well as the habit of wearing footwear (p=0.019) and bowel habit (p=0.035), are the risk factors causing the high *A. lumbricoides* incidence in the studied area. The number of children who did not wash hand with soap (32,4%) more than the number of children who did (6.2%) as well as the number of children who did not wear footwear (36.2%) than who did (2.3%) coupled with the habit of defecating on the open plantation (26.92%) more than on the toilet (11.54%). The association between handwashing and *A. lumbricoides* infection depended largely upon access to a water source (Garn *et al*., 2015).

Shoes are effective for blocking the penetration of STH to the skin. Unfortunately, shoe-wearing is uncommon in many areas where STHs are prevalent because the local populations are unaware of the health benefits of wearing shoes (Paige *et al*., 2017).

Although family toilets were available in all subject's houses, however, they prefer defecating in the open. The habit of defecation on the open plantation and bush was also found in Taabo, Co ˆte d'Ivoire, where 43.4% of participants were due to a deeply rooted tradition of open defecation (Schmidlin *et al*., 2013). The unavailability of clean water was thought to be a problem for the defecation in the toilet. In fact, clean water was available for their daily activities in all houses of the subjects. Apparently, the problem was the observance in implementing good personal hygiene and sanitation.

The interesting results of this study were that the strong correlation between the level of education of the parents play an important role in educating the children's behaviors of personal and environmental hygiene and sanitation as the number of positive cases increased oppositely with the level of education.

The limitation of this study was that other species of STH were not detected by the Kato Katz method. The finding of single species was an important thing to observe whether there was indeed only one species or some other species that were not detected by the Kato Katz method. Since the habit of not wearing footwear has a correlation with *A. lumbricoides* infection, the hookworm infection might exist in the community. The low sensitivity of the Kato Katz method for the detection of hookworm infection may be related to the rapid degeneration of delicate hookworm eggs with time. The PCR method might be used simultaneously with the microscopy examination so that the samples could be preserved in the field to maintain the parasite's DNA prior to further laboratory processing.

CONCLUSION

A high number of ascariasis cases in the studied area was due to the observance of the children in implementing good personal hygiene and sanitation. The level of education of their parents, which correlated with the infection, influenced the habit of their children. Therefore, the interference from the government and related agencies to provide enlightenment to the parents and children in different ways regarding good personal and environmental hygiene and sanitation along with chemotherapy is needed to achieve a durable reduction of the burden of ascariasis and other STH infection.

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Research Article

Development of augmented reality-assisted health education posters on Covid-19

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ABSTRACT

The changes in the social order of life in the new normal era due to the Covid-19 pandemic have caused various sectors of the work environment to create new habitual adaptation policies so that the service process continues to run well. One method used was to use poster media to be displayed in the office environment as a media for health protocol information. The purpose of this research was to create a poster based on *augmented reality videos* that were suitable for use as media for information on health protocols in public health centers in Kendari City. The research model for *augmented reality* media development uses a model developed by Lee & Owens that consists of four stages: assessment/analysis, design, development, implementation, and evaluation. Based on the findings in this study, obtaining the media expert's assessment results provided a feasibility level of 91.58%, categorized as very feasible. The tests conducted on material experts obtained a feasibility level of 89.09% that categorized as very feasible. Poster-based on *augmented reality videos* have been tested on Puskesmas health workers with a mean percentage of assessment of 80.42% that categorized as suitable for use. In comparison, the test results obtained from the public health services visitors obtained a percentage of 81.25% that have been categorized as suitable for use. The tests carried out on all test subjects showed that the poster-based on *augmented reality videos* was very suitable for use as a health promotion media at Puskesmas in Kendari City.

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INTRODUCTION

Indonesia continued to struggle against Covid-19 was a global pandemic since it first appeared in Wuhan at the end of 2019. Covid-19 was a dangerous and easily contagious disease. Covid-19 transmission between humans could occur in three ways, namely: (1) respiratory droplets and aerosols, (2) air transmission, and (3) surface transmission of objects. Covid-19 as a pandemic has disrupted the lives of three-quarters of the world's population who were in low and middle-income countries (Utama, Levani, Rumkhullah, & Paramita, 2020). Various handling and prevention efforts continuously have being made to deal with the development of Covid-19 that has changed the order of social life and threatens the stability of the Indonesian economy. Agung (2020) explained that the real impact of Covid-19 was death, economic recession, disruption of educational activities, and the most worrying were the psychological impact and behavior change on society. These impacts have massively changed the social and economic foundations of Indonesia. In order to reorganize the return passage of the Indonesian economy, the government has established many regulations in the life of the *"new normal"*.

The change order in social life in the new normal era has resulted in various sectors making and implementing new habit adaptation policies in the work environment so that the service process continues to run well. One of the methods used was to use poster media had to be displayed in an office environment as an information medium for new habits. Ulya, Iskandar, & Asih (2017) explained that poster was a medium that presents visual form information and stimulates the sense of sight. The poster was a visual communication tool in the form of images and writings had intended to attract people's attention so that the message to be conveyed can be accepted simply by others (Putri & Kurniawan, 2017). Based on this description, posters could say to be a means of presenting information in a form that was attractive, easy to understand, influences knowledge. They could motivate readers to follow the information presented.

Numerous studies had been conducted on the use of posters. Luthfia & Siswantara (2018) using posters and hand lettering as health promotion media regarding the dangers of smoking for adolescents. This study showed that hand lettering was more effective in increasing adolescent knowledge about the dangers of smoking than using posters. It showed that posters no longer became a major media in health promotion because other media could use the *hand lettering* forms that have proven to be more effective in increasing knowledge.

Utomo et al. (2018) tried to develop health promotion methods in several media, including visual media (posters and *leaflets*), audio-visual media (*slide* presentation using power points), and the game media called *Rabies Games for Kids*. The results showed that the posters and leaflets provided simultaneously gave higher knowledge and length memory than audio-visual media and game media. The research method used a pretest-posttest design was an experimental research method. Development research should use development models such as the Lee & Owens model, the ADDIE model, the ASSURE model, and so on depending on the needs and the research product had developed. The same problem also occurs in research by Hermina & Prihatini (2016) that used qualitative methods, while the research problem was the development of posters as a tool for nutritional education.

Based on the outline, poster media has provided benefits both as a health promotion medium and as a learning medium. It was because posters have the following advantages: (1) it could simplify and accelerate understanding

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of the messages presented; (2) could be complemented with colors so that it attracts students' attention; (3) simple in shape without the need for special equipment and easy to place, requiring little additional information; and (4) easy to manufacture and low price (Sumartono & Astuti, 2018). On the other hand, if an in-depth study had carried out, posters have several weaknesses, namely: (1) it required special skills in its manufacture; (2) reading skills had required to understand the contents of the poster; and (3) presenting messages only in the form of visual elements.

The description of the poster's weaknesses above can be accommodated by the development of posters based on *augmented reality videos*. Craig (2013) explained that *augmented reality* was a medium where digital information added to the physical world. *Augmented reality* also meant the actual objects in *real-time* that added with a virtual object that appeared when using tools or devices on the actual objects (Soepriyanto, Sulthoni., & Ulfa, 2017). *Augmented* reality used an interface in a figurative physical object that had manipulated virtual information imaginatively.

The description above showed several reasons for the importance of poster development based on augmented reality videos, as follows (1) posters that could only present visual information in the form of text and images were starting to get less response from readers because there are other media such as hand-lettering that made it easier to understand the information presented; (2) posters and audio-visual media as promotional media were often separated so that the recipient of the information still has to read and see two different media, even though the two media that had combined only in one media; (3) there was still no poster based on augmented reality videos that had developed as a health promotion media.

Primary healthcare facilities play essential roles in disease control and prevention. Changes in healthcare-seeking behavior during the Covid-19 pandemic, especially to primary care, might impact overall public health. Puskesmas is a first-level health service center in Indonesia that carries out its activities in a comprehensive, integrated, and sustainable manner in a community that lives in a particular area. In supporting the prevention of the spread of Covid-19, Puskesmas play an essential role as a first-rate facility for the public in disseminating information related to health education about Covid-19.

Starting from the description that has been presented, it could be said that posters have become a health promotion medium that has provided many benefits. On the other hand, posters still have weak points because they could only present visual information in the form of text and images, so they needed to be developed into a medium capable of presenting text, images, and videos. Media that could be meeting these criteria was only by using *augmented reality*, so it was necessary to develop posters based on *augmented reality videos*. The purpose of this research was to make posters based on *augmented reality videos* that were suitable for use as promotional media in the form of health protocols in the work environment of Puskesmas in Kendari City.

METHODS

The research model of media development *augmented reality* using a model developed by (Lee & Owens, 2004). Lee & Owens' model consists of four stages: assessment*/analysis, design, development, implementation, and evaluation*. The development models based on Lee & Owens, it could be seen in the figure below:

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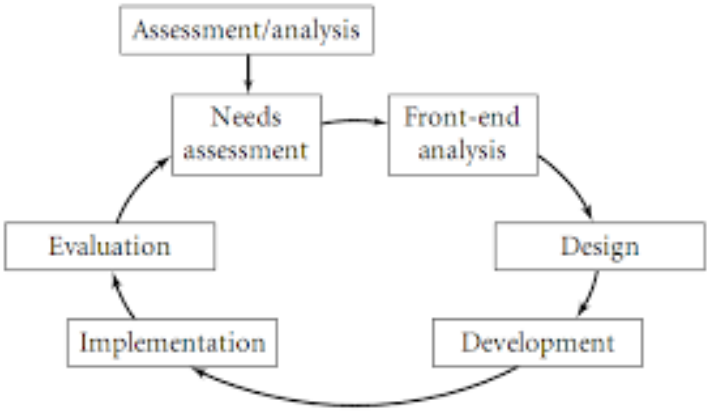

Figure 1. Lee & Owens Development Model Steps

The analysis stages aimed to determine the gap between the existing conditions and the expectations to be achieved. The population of this research was health workers at Puskesmas and visitors of Puskesmas in Kendari City. The samples in this study were 10 health care workers at Puskesmas and 20 visitors of Puskesmas in Kendari City which included Puskesmas Abeli, Puskesmas Nambo, Puskesmas Poasia, Puskesmas Jati Raya, and Puskesmas Lepo-Lepo. Samples were taken using a simple random sampling technique. At this stage, it was found that the respondents had different characteristics. The development also analyzed the available technology; developing augmented reality requires AR application developer software and 3D models. There was two software used to develop *augmented reality* media, namely *augmented reality* application developer *software* Vuforia and supporters Unity. Software developers *augmented reality* application had used to adjust the layout of a 3D image and enter the *script*. Supporting software had used to upload a *marker* that could be scanned. Both of the software were selected based on research Prasetiyo, Setyosari, & Sihkabuden (2017). Their research explained that the two applications could be used properly and cause the visualization to resemble the original object. In this study, the augmented reality media was developed by an expert who has a background as an alumnus of the State University of Malang Postgraduate Learning Technology Study Program. Meanwhile, researchers in development activities focus more on making videos and posters as media that must be provided before making augmented reality media. The technology available to implement *augmented reality* media was a *smartphone* device owned by health workers and visitors of the Puskesmas.

The design stage had carried out to determine the specifications of the poster that would be made, including a printed poster that contains a QR code as a marker for displaying 3D objects and videos that were added in the real environment, as well as an *augmented reality* videos application that could be installed on a smartphone. The poster content arrangement that included text and images was regulated by the developer with attention to attractiveness, typography, and layout. The development and implementation stages consist of developing markers, 3D products, videos, posters, and applications.

The last stage in the development of posters based on *augmented reality videos* was evaluation. This stage aimed to obtain responses from media experts, material experts, Puskesmas officers, and visitors to health centers in Kendari City. The

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instrument used to collect data using the Likert scale form. The research instrument developed generally focuses on (1) accuracy in selecting fonts and images, (2) accuracy in organizing posters, (3) ease of use of augmented reality media applications, (4) ease of understanding the information presented in posters and videos, and (5) the suitability between the poster and the video used. The eligibility criteria for the media in this development could be seen in Table 1.

RESULTS

This development research produces posters based on augmented reality videos that can be used as health promotion media in the Puskesmas environment. The development stages in this research include the development of markers, videos, posters, and applications. The marker design used was a QR Code with an image in the middle to make it easier for users to recognize 3D objects in the form of a video that would appear. Prasetiyo, Setyosari, & Sihkabuden (2017) described the selection of QR-Code as a marker because QR-Code has a contrasting color and a high level of augmentable. The marker design for the video poster at the health center could be seen in Figure 2 below.
and visitors to health centers in Kendari City. The instrument used to collect data using the Likert scale form. The research instrument developed generally focuses on (1) accuracy in selecting fonts and images, (2) accuracy in organizing posters, (3) ease of use of augmented reality media applications, (4) ease of understanding the information presented in posters and videos, and (5) the suitability between the poster and the video used. The eligibility criteria for the media in this development could be seen in Table 1.

Table 1. Eligibility Criteria Media

Percentage (%)	Validity Information	Conclusion
25,00-40,00	Invalid	Should not be used
41,00-55,00	Less valid	Should not be used
56,00-70,00	Quite valid	Can be used after major revisions
71,00-85,00	Valid	Can be used after minor revisions
86,00-100	Very valid	Very good to use

(Adopted from Akbar, 2016)

Figure 2. Video Poster Marker Design at Puskesmas

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Figure 3. Public Health Protocol Poster based on *Augmented Reality Videos*

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The final stage in this process is application development. This application's output is a file in the application package file (.apk) extension that can be installed on a smartphone. This application is named edukasicov19 and can be downloaded at the link http://bit.ly/aplikasi_edukasi_covid-19.

This study examined the importance of developing the posters based on *augmented reality videos* that had been implemented as a media for promoting health protocols in the new normal era in the work environment of Puskesmas. In getting a suitable poster for use, several tests must be carried out, including testing of media experts and material experts and field testing of health center officers and visitors to health centers in Kendari City.

The research begins with the testing in each of 1 person, media experts and material experts. The media expert aimed to see the media's feasibility level about the color suitability of visual and verbal elements, the layout of the poster content, the ease of understanding the information conveyed in posters, markers, application installation instructions, and the attractiveness of the entire poster content. The material expert aimed to see the media's feasibility concerning poster content, video content, completeness of health protocols, and suitability of posters and videos. The media expert assessed the media using a research instrument containing 19 statements with a maximum value is 5, so that the maximum value obtained was 95. Based on the data analysis results, the value given by media experts was 87, so the percentage of media expert scores was obtained from the media expert scores (87) divided by the maximum value (95) times 100%. Based on the results of tests conducted on media experts, it was found that the feasibility level was 91.58% which was categorized as very feasible for health protocol posters at the Puskesmas.

The material expert assessed the poster using a research instrument containing 11 statements with a maximum value is 5, so that the maximum value obtained was 55. Based on the data analysis results, the value given by material experts was 49, so the percentage of the material expert's score was obtained from the material expert's value (49) divided by the maximum value (55) times 100%. The tests conducted on material experts obtained a feasibility level of 89.09%, which is categorized as very feasible for health protocol posters at the Puskesmas. In detail, the test results of media experts and material experts on the developed posters can be seen in Figure 4.

The test results of media experts and material experts who have shown to be very feasible constitute a requirement that this research had continued with field testing. The field test had carried out on each of the ten health workers and 20 visitors to the Puskesmas in Kendari City. Health workers assess posters using a research instrument containing 19 statements with a maximum value is five so that the maximum value obtained is 95 multiplied by ten visitors to 950. Based on the results of data analysis, the score given by health workers is 764, so the percentage of the score for health workers is obtained from the score of the health worker (764) divided by the maximum score (950) times 100%. The test results obtained from health workers obtained an average percentage of 80.42% had categorized as suitable for use.

Puskesmas visitors assessed the posters using a research instrument containing 19 statements with a maximum value is 5, so that the maximum value obtained was 95 multiplied by 20 visitors to 1900. Based on the results of data analysis, the value given by the number of visitors to the puskesmas visitors was 1544. The percentage value of puskesmas visitors the number of visitors to the puskesmas (1544) was divided by the maximum value (1900) times 100%. The test results obtained from

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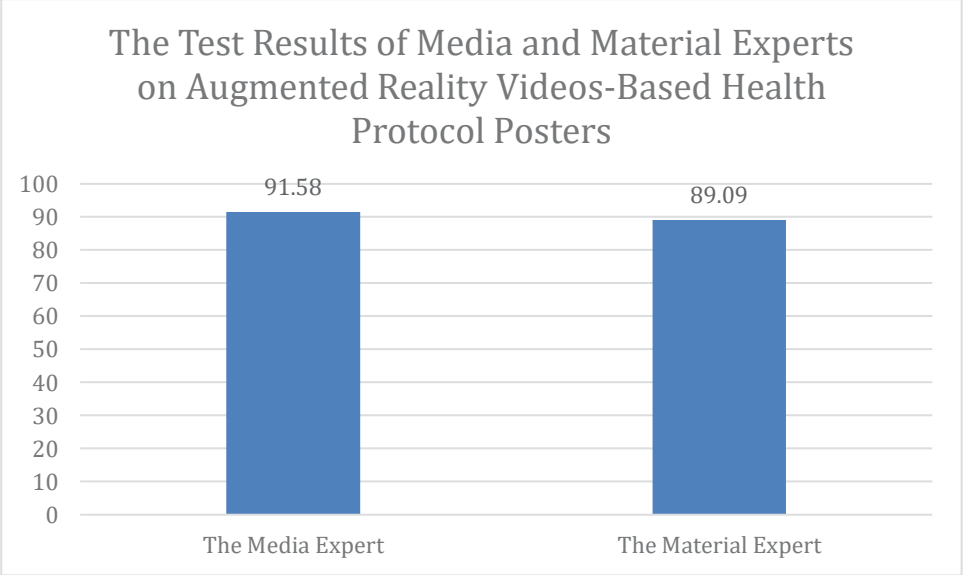

Figure 4. The Test Results of Media Experts and Material Experts on Posters of Health Center Health Protocols based on Augmented Reality Videos

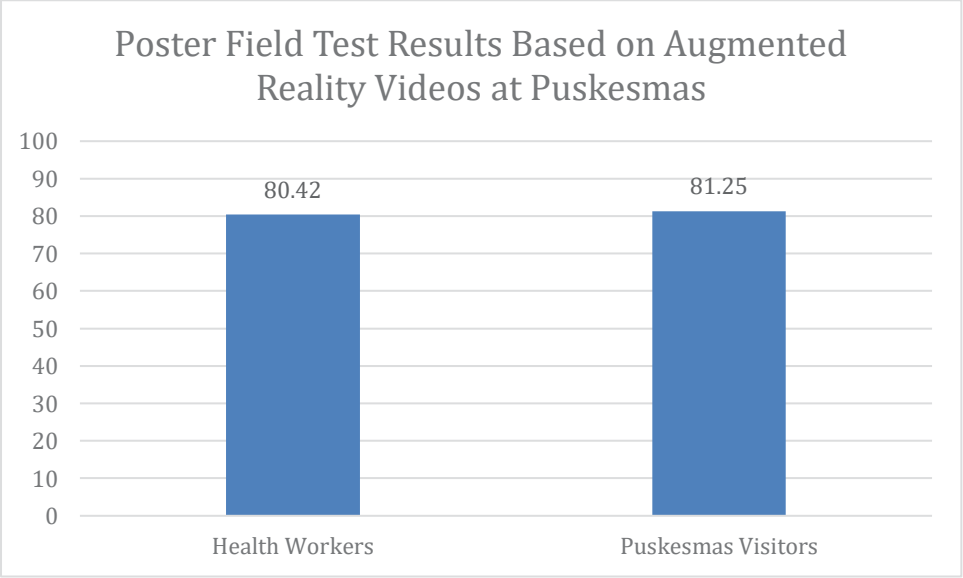

Figure 5. The Field Test Results against Posters Based on Augmented Reality Videos at Puskesmas

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DISCUSSION

The results of tests carried out on media experts, material experts, and field tests show that the poster based on augmented reality videos developed in this study was suitable for use as a health promotion media in the form of health protocols in the work environment of Puskesmas in Kendari City. Posters appealed if the verbal and visual elements have been organized appropriately. The addition of videos packaged using *augmented reality* on the posters further adds to the complexity of the media for delivering information and existing aesthetic values, thus attracting the attention of those who see them.

A media poster was a written message, both in the form of pictures and writing, that intended to attract many people's attention so that the message conveyed could be accepted by others easily (Sumartono & Astuti, 2018). Azis (2012) described in compiling a poster, the steps that should be considered were (a) determining the object to be posted, (b) formulating messages to be conveyed to the public, (c) formulating short, concise, and clear sentences so that the essence of the problem could be read casually, and (d) using suggestive words (cajoling).

The selection of posters that got the added real environment of augmented reality videos was not without reason. *Augmented reality* could combine virtual objects and the real world in one medium (Saputra, Salim, Idhayani, & Prasetiyo, 2020). Ilmawan & Kurniawan (2017) explained the advantages of augmented reality were: (1) more interactive; (2) effective in use; (3) could be widely implemented in various media; (4) simple object modeling, because it only displays a few objects; (5) manufacture that does not cost too much;and6) easy to operate. Similar statements were described by Adami & Budihartanti (2016) explained that *augmented reality*: (1) makes it easier and attracts interest in learning material, and (2) the excellent learning media because it can be accessed using Android so that it can be used by everyone as long as the *augmented reality* application has been installed on a *smartphone*.

The use of posters as a medium for health promotion had become the object of research that was often carried out in health. Wiji & Fitri (2020) using posters as a media strategy for nutrition education to increase knowledge of postpartum mothers, babies, and toddlers. Another research was conducted by Andriani, Suwarni, & Arfan (2020) by using posters as an alternative media to wash hands. Wiji & Fitri (2020) and Andriani et al. (2020) have something in common with this study, namely using poster media as a health promotion medium. The results also showed that posters were suitable for use as a health promotion medium. However, the difference was clear that the two studies above only focus on using posters as a promotional medium. In contrast, in this study, posters got an additional environment in augmented reality video, making it easier for readers to understand the information presented.

Yip, Wong, Yick, Chan, & Wong (2019) conducted research using augmented reality videos as a learning medium. The research concluded that student learning outcomes using *augmented reality videos* were higher than students who read papers. Ananda, Safriadi, & Sukamto (2015) examined the application of augmented reality as a learning medium to recognize planets in the solar system. Juannita & Adhi (2017) examined the developmentlearning media developmentdigestive system with android-based *augmented reality* features. Kamiana, Kesiman, & Pradnyana (2019) their research also concluded that based on the *augmented reality* book application testing process, the media was in an excellent category for use in the learning process. Significant differences between some of the above studies and this study included: (1) no *augmented reality* media

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had used as a health promotion media, and (2) *augmented reality* developed in this study was in the form of a marker that would be placed on the poster.

The results found that the poster based on *augmented reality videos* developed was very suitable for use as a health promotion media in the form of health protocols in the Puskesmas work environment. However, when viewed in more detail, several weaknesses need special attention, namely: (1) the reader needs direct guidance to install the developed application, (2) the video that appeared when the reader performs a marker scan cannot be enlarged to follow the smartphone screen size, and (3) the poster size should be larger than the A3 paper size.

The findings in this study were very important considering there were no posters developed with the addition of an *augmented reality video* environment that has been used as a health promotion media. The study results also contributed to the availability of posters that can be used in Public Health as a medium for preventing the transmission of the Covid-19 virus in the work environment. This study's findings could also become the inspiration for other institutes to make similar posters in their work environment. This finding further adds to the existence of Muhammadiyah in making a real contribution in helping the progress of the nation because this research is funded in the Program Research Grant Batch 4 Assembly Diktilitbang PP Muhammadiyah.

CONCLUSION

Based on the findings in this study, the information had obtained that the results of the media expert's assessment provided an eligibility level of 91.58% that categorized as very feasible for health protocol posters at Puskesmas. The tests conducted on material experts obtained feasibility was 89.09%, that categorized as very feasible for health protocol posters at the Puskesmas. Posters based on *augmented reality videos* were also tested on Puskesmas health workers with a mean percentage of assessment of 80.42% that categorized as suitable for use. In comparison, the test results obtained from visitors of the puskesmas gained a percentage of 81.25% that categorized as suitable for use. The tests carried out on all test subjects showed that the poster based on *augmented reality videos* developed in this study was very suitable for use as a health promotion media at Puskesmas in Kendari City.

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Research Article

Relationship between modified Nutrition Risk in the Critically Ill (mNUTRIC) Score and nutrition intake with quadriceps femoris muscle thickness in critically ill patients

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ABSTRACT

Muscle wasting in critical illness is seen from inadequate nutrition intake and stress catabolism. Modified Nutrition Risk in the Critically Ill (NUTRIC) Score is a screening tool that measures starvation, inflammation, disease severity, and organ dysfunction. The relationship between muscle strength and muscle thickness causes the evaluation of muscle thickness is quite relevant. This study aimed to analyze the relationship between modified NUTRIC score and nutrition with muscle wasting in critically ill patients. The study was conducted on 30 patients in the ICU Dr Soetomo Hospital Surabaya. Nutritional intake and thickness of the quadriceps femoris muscle were monitored for one week. There was a relationship between mNUTRIC score with quadriceps femoris muscle thickness on days 3rd, 5th, and 7th. In the comparison between the low-risk group and the high-risk group, it was found that there was a significant difference in the change in the percentage of muscle thickness difference on the 3rd, 5th and 7th-day observation. There is a relationship between protein debt with quadriceps femoris muscle thickness ($p = 0.008$) with a positive correlation with moderate correlation strength ($r = 0.477$) on day 7. In conclusion, the modified NUTRIC Score had a moderate relationship with quadriceps femoris muscle thickness in critical patients from day 3rd until day 7th. The calorie intake has not had a relationship with quadriceps femoris muscle thickness. Protein intake had a moderate relationship with quadriceps femoris muscle thickness only on day 7th measurement in critical patients.

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INTRODUCTION

The mortality rate in critically ill patients is slowly falling compared to the last few decades. Improving the functional outcome of patients with critical illness is the focus of clinicians at this time. Muscle wasting is a common problem that occurs in patients in the Intensive Care Unit (ICU). Weakness and loss of muscle mass often contribute to physical and functional limitations (Casaer & Ziegler, 2015).

Muscle wasting occurs early and quickly during ICU treatment and contributes significantly to ICU acquired weakness (ICUAW) in 50-100% of ICU survivors. Decreased skeletal muscle mass is associated with increased mortality, prolonged treatment time with mechanical ventilation, and length of stay (LOS) in the ICU and hospital (Pardo et al., 2018; Z. Puthucheary, 2019). ICUAW is currently recognized as an important factor in patients with "difficult-to-wean" in the ICU, which is associated with prolonged ICU and hospital stay (Formenti, Umbrello, Coppola, Froio, & Chiumello, 2019). Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients (Weijs et al., 2014).

In healthy conditions, muscle mass is maintained through a balance between protein breakdown and synthesis. Muscle wasting is a consequence of catabolic conditions that lead to depression of muscle protein synthesis and an increase in muscle protein breakdown (Gao, Arfat, Wang, & Goswami, 2018). Protein is continuously degraded and replaced (turn over) by a process that is balanced over time. There is a loss of 20-30 g of protein in healthy people without protein intake or a loss of 1% of total body protein per day. During stressful (hypermetabolic) conditions, there is an increase in protein degradation that exceeds the rate of protein synthesis (Preiser, Ichai, Orban, & Groeneveld, 2014).

Skeletal muscle atrophy occurs in response to various stressors, including decreases in external loading and neural activation, increases in inflammatory cytokines and glucocorticoids, and malnutrition. Immobilization is a catabolic condition for muscle that causes significant loss of muscle mass (Bodine, 2013). A study with 24 healthy patients who performed one-legged knee immobilization using full leg cast showed a reduction in the cross-sectional area of 3.5 ± 0.5 and 8.4 ± 2.8% following 5 days and 14 days of immobilization. This suggests that even short periods of muscle disuse can cause substantial loss of skeletal muscle mass and strength (Wall et al., 2014).

The causes of muscle wasting during critical illness can be seen from two main perspectives, namely inadequate nutritional intake and catabolism due to stress. Striated muscles are the body's largest protein and amino acids reserves that can be mobilized to maintain and overcome critical illness conditions. It is hoped that the intake of nutrients and protein can reduce the risk of muscle wasting due to the use of the body's protein and amino acid reserves (Pardo et al., 2018; Z. A. Puthucheary et al., 2013). Stress-induced catabolism is a process related to the degree of inflammation (which is closely related to disease severity) that requires nutritional screening that takes into account the severity of the disease and the metabolic conditions. The Nutrition Risk in the Critically Ill (NUTRIC) Score is a screening tool that considers this aspect and has been validated in critical patients (Lee & Heyland, 2019; Rahman et al., 2015). This scoring system represents a model that measures starvation, inflammation, disease severity, and organ dysfunction factors that can affect nutritional status at ICU admission and have implications for patient outcomes (Heyland, Dhaliwal, Jiang, & Day, 2011).

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Table 1. Modified NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50-<75	1
	≥75	2
APACHE II	<15	0
	15-<20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6-<10	1
	≥10	2
Number of Comorbidities	0-1	0
	≥2	1
Days from hospital to ICU *admission*	0-<1	0
	≥1	1

Source: Rahman et al, 2015

Patients with high scores (5–9) are associated with worse clinical outcomes (mortality, ventilation). These patients are most likely to benefit from aggressive nutritional therapy. Patients with low scores (0-4) have a low risk of malnutrition. The Modified NUTRIC Score has been validated in predicting 28th-day mortality. Patients with a maximum score of 9 have a mortality of up to 53%. There was no mortality in patients with a NUTRIC score of 0 or 1. The odds of mortality at 28 days were multiplied by 1.4 (95% CI, 1.3e1.5) for every point increase on the NUTRIC score. Higher NUTRIC scores are also significantly associated with higher 6-month mortality (p <0.0001) (Rahman et al., 2015).

Manual muscle strength measurement in a standardized manner has been shown to be beneficial in patients, but it requires a conscious and cooperative patient condition which is not usually possible in the ICU. The relationship between muscle strength and muscle thickness leads muscle thickness evaluation relevant enough as it reflects muscle the strengthness (Formenti et al., 2019; Pardo et al., 2018). Monitoring muscle mass in critical patients is expected to detect patients at risk and predict the outcome that occurs due to decreased skeletal muscle mass in critically ill patients. In addition, monitoring muscle mass during treatment in the ICU can help doctors to evaluate the success of nutritional interventions during treatment (Pardo et al., 2018; Parry et al., 2015) It was reported that there was a loss of 12.5% cross-sectional area (CSA) or cross-sectional area of the rectus femoris after 7 days of ICU treatment. This illustrates that muscle wasting occurs early and quickly in critical patients (Pardo et al., 2018; Z. A. Puthucheary et al., 2013).

Accurate assessment of body composition and lean mass is a challenge. Anthropometric measurements such as tricipital skin-fold thickness and upper arm circumference cannot accurately measure sarcopenia in critically ill patients because of subcutaneous edema in critical patients (Martín, Monares Zepeda, & Lescas Méndez, 2017; Pardo et al., 2018).

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The quadriceps femoris muscle can document muscle wasting because it's easiest to describe and evaluate even in conditions of massive muscle loss. The quadriceps femoris muscle is important in the remobilization process because it functions for simultaneous hip flexion and knee extension (Formenti et al., 2019; Pardo et al., 2018).

To evaluate the anatomy of the thigh and leg muscles, several examination techniques can be used, such as computerized tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (USG). CT and magnetic resonance imaging (MRI) can accurately estimate muscle mass. However, these methods cannot be performed quickly, require high costs, provide unnecessary radiation exposure, and risky transportation makes these techniques inapplicable in ICU patients (Martín et al., 2017; Pardo et al., 2018). Ultrasound can be used as a valid and practical measurement tool for documenting muscle mass (Pardo et al., 2018). Ultrasound can measure and estimate muscle thickness and volume with good accuracy. In addition, ultrasound measurements can be performed non-invasively, instantaneously, and can be repeated. Ultrasonography measurement of quadricep muscle thickness shows good intra and inter-observer reliability (Pardo et al., 2018). Parameters obtained from ultrasound examination can help doctors monitor lean mass changes dynamically and guide doctors in evaluating nutritional intake in intervening in muscle wasting in critical patients in the ICU.

Therefore, clinicians need to prevent muscle wasting, know the factors that influence it, and quantify patients who are at high risk for muscle wasting. Modified NUTRIC score as a scoring system which is expected to represent patients at high risk of complications and mortality. This study aimed to investigate whether there was a relationship between nutritional intake and modified NUTRIC score with quadriceps femoral muscle thickness in critically ill patients.

METHODS

The research was conducted in the Intensive Care Unit (ICU) of Dr. Soetomo hospital Surabaya during January-April 2020 that sampled patients aged between 18 to 65 years old. The research protocol was approved under the number 1683/KEPK/XI/2019 by the Committee on Institutional Ethics and Research Development (RSUD Dr. Soetomo, Surabaya, Indonesia). The sampling technique was consecutive sampling; patients who met the inclusion and exclusion criteria will be collected until the required sample size was fulfilled.

We selected the patients aged between 18 and 65 years old, and the patient's family stated readiness to include the patient in the research. This research sample was taken consecutively from the population that met the inclusion criteria. We excluded patients with deformities, lesions, fractures, and amputations of the lower extremities that were impossible to measure, patients with neuromuscular disease or critical illness neuropathy, patients with a history of chronic kidney disease, patients with a history of previous liver disease (cirrhosis of the liver, acute liver failure, or hepatoma) and palliative patients. After the subject meets the inclusion and exclusion criteria, the subject will be grouped into high-risk (5-9) and low-risk (0-4) patients based on the modified NUTRIC Score during ICU admission.

Measurement started with collecting the general characteristics data of the subjects who met the inclusion and exclusion criteria who had agreed and signed the informed consent. General characteristics data include patient identity, clinical data, and supporting data. General patient characteristics were collected: gender, weight, height, body mass index, diagnosis, and

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comorbidities were recorded. Bodyweight was measured by weighing the patient. The patient's height was measured with a measuring tape.

Then we obtained the clinical data from recording vital signs (blood pressure, MAP, pulse, rectal temperature, respiratory rate, and GCS). The Modified NUTRIC Score was calculated when the patient entered the intensive observation room. APACHE II Score and SOFA Score were also be measured.

Nutritional data was recorded daily, total daily calorie intake (kcal / day), and daily protein intake (g / day). Provision of calories and protein is given based on the ideal body weight obtained from measuring height using a measuring tape. Calorie debt is calculated based on the difference in calorie needs based on the predictive formula of ideal 25 kcal / kg / day and the amount of calorie intake given. Protein debt was calculated based on the difference in protein needs based on the predictive formula of 1.2 grams / kg of ideal body weight / day with the amount of calorie intake given.

The quadriceps femoris muscle thickness was measured by ultrasonography on the 1st, 3rd, 5th, and 7th day of ICU treatment. The examination was carried out with an ultrasound machine using a 12 Mhz linear transducer. Each examination was carried out on both feet at the midpoint of the upper part of the patella and the superior anterior iliac spine. Measurements were taken of the rectus femoris and vastus intermedius muscle for 3 times and the measurement results are the average of the examination. The difference in thickness of the quadriceps femoris muscle during the first week was obtained from the difference in measurement at the time of examination with the first-day examination.

This research data was presented in the form of tables, graphs or diagrams and text or writing that clarifies the graph diagram. The research data were tabulated and analyzed by computer software with the Kolmogorov Smirnov normality test and Pearson or Spearman Correlation test with SPSS. Data of patients who dropped out of the study due to death on day 3 and 7 were also analyzed.

RESULTS

There were 30 patients undergoing treatment in the Intensive Care Unit (ROI) Dr. Soetomo Hospital Surabaya. The basal characteristics of the subjects (table 1) showed that the male subjects were more than female subjects (63.3% vs 37.7%). The age group with the most patients is the 31-45-year-old group at 50%. Most of the patients (16 subjects) have normal body mass index (53.3%). There were 5 patients (16.7%) with undernutrition body mass index and 2 subjects (6.7%) with obese body mass index. The most common diagnosis was intraabdominal infection in 7 subjects (23.3%), pneumonia in 6 subjects (20%), multiple trauma in 5 subjects (16.7%), traumatic brain injury in 5 subjects (16.7%), subjects with other sepsis. 4 subjects (13.3%) and heart failure in 3 subjects (10%). Of the 30 subjects, 14 subjects (46.7%) had an APACHE II Score with a range of 11-20. Most of the subjects (76.7%) had SOFA scores ranging from 2-7, there were 2 subjects with SOFA scores >11. Furthermore, 22 of 30 subjects or 73.3% had an mNUTRIC Score in the range 0 to 4, and there were 8 subjects (26.7%) with an mNUTRIC Score ≥5.

The average change of the quadriceps femoris muscle thickness difference in the third day there was a change in the percentage difference of -2.751 ± 0.443% in the low-risk mNUTRIC group (0-4) and the highest increased on the seventh day of -3.867 ± 0.847cm. In the high-risk group (≥5) there was a change in the percentage difference in muscle thickness of -4.315 ± 0.661 cm on the third day of observation and to -7.103 ± 0.787 on the

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Table 2. Characteristics of research subject

Variables	Amount	Percent (%)
Sex		
1. Female	11	37.7%
2. Male	19	63.3%
Age group		
1. 17-30	4	13.3%
2. 31-45	15	50%
3. 46-60	7	23.3%
4. >60	4	13.3%
BMI		
1. <18,5	5	16.7%
2. 18.5-24.9	16	53.3%
3. 25.0-29.9	7	23.3%
4. >30	2	6.7%
Diagnosis		
1. Intraabdominal infection	7	23.3%
2. Pneumonia	6	20.0%
3. Multiple Trauma	5	16.7%
4. Brain Injury	5	16.7%
5. Sepsis	4	13.3%
6. Heart Failure	3	10.0%
APACHE II Score		
1. 1-10	5	16.7%
2. 11-20	14	46.7%
3. 21-30	9	30.0%
4. >30	2	6.7%
SOFA Score		
1. 2-7	23	76.7%
2. 8-11	5	16.7%
3. >11	2	6.7%
mNUTRIC Score		
1. 0-4	22	73.3%
2. ≥5	8	26.7%

day of observation. Based on the statistical test, it was found that the significance was p = 0.000 on the three observation days. From these results, it can be concluded that there is a significant difference in the quadriceps femoris muscle thickness between low-risk and high-risk groups.

There is a relationship between the mNUTRIC score and the quadriceps femoris muscle thickness percentage difference on day 3,5,7 with a significant value of p = 0.000. These results indicate that the correlation between the mNUTRIC score and the quadriceps femoris muscle thickness percentage difference on days 3,5,7 is significant. The Spearman correlation value of -0.637 on the 3rd day indicates a negative correlation with a strong correlation between the mNUTRIC score and the quadriceps femoris muscle thickness percentage difference.

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The spearman correlation value of -0.591 on the 5th day indicates a negative correlation with moderate correlation strength between the mNUTRIC score and the quadriceps femoris muscle thickness percentage difference on the 5th day. The spearman correlation value of -0.696 on the 7th day indicates that there is a negative correlation with a strong correlation between the mNUTRIC score and the quadriceps femoris muscle thickness percentage difference on the 7th day.

From the correlation analysis of the APACHE II Score and the quadriceps femoris muscle thickness percentage difference at day 3,5,7, it was found that a significant value was obtained with $p < 0.050$, which indicates that the relationship between the two variables is significant. From the correlation analysis between the SOFA Score and the percentage of thickness difference at day 3,5,7, a significant value was obtained with $p < 0.050$, which indicates that the relationship between the two variables is significant.

In this study, a significance value of $p > 0.05$ indicates that there is no significant relationship between calorie debt on day 3,5,7 and the percentage of muscle thickness difference on day 3,5,7. And $p = 0.96$ which indicates that the correlation between calorie debt and protein debt with the quadriceps femoris muscle thickness percentage difference on the 3rd and 5th day with the change in the quadriceps femoris muscle thickness percentage difference ($p > 0.050$). On the 7th day, there was a significant relationship between total calorie debt for 7 days with the quadriceps femoris muscle thickness percentage difference ($p = 0.008$).

Table 3. Characteristics of the quadriceps femoris muscle thickness difference.

	Low Risk	High Risk	P Value
Day 3	-2.751 ± 0.443	-4.315 ± 0.661	p = 0.000
Day 5	-3.485 ± 1.051	-5.315 ± 0.705	p = 0.000
Day 7	-3.867 ± 0.847	-7.103 ± 0.787	p = 0.000

Comparative analysis with paired T test for the difference of day 3rd, Mann-Whitney test for the difference of day 5th and 7th.

Table 4. The correlation test results of the mNUTRIC Score and quadriceps femoris muscle thickness percentage difference.

	Day 3	Day 5	Day 7
mNUTRIC *Score*	r: -0.637; p 0.000	r: -0.591; p 0.001	r: -0.696 ; p 0.000
APACHE II *Score*	r: -0.581; p 0.001	r: -0.479; p 0.007	r: -0.635 ; p 0.000
SOFA *Score*	r: -0.498; p 0.005	r: -0.413; p 0.023	r: -0.410; p 0.024

Spearman correlation test with p = 0.05 was significant

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Table 5. Results of the correlation test of total calorie debt with the quadriceps femoris muscle thickness.

	Quadriceps femoris muscle thickness percentage difference		
	Day 3	**Day 5**	**Day 7**
Calorie debt	r: -0.079; p 0.676	r: -0.159; p 0.403	r: 0.322; p 0.83
Protein debt	r: 0.263; p 0.160	r: -0.039; p 0.840	r: 0.477; p 0.008

Spearman correlation test with p = 0.05 was significant

DISCUSSION

Ultrasonography (USG) muscle examination is a convenient non-invasive tool for evaluating muscle mass loss in critically ill conditions. A study by Pardo et al. Measuring the quadriceps femoris muscle thickness in 29 patients treated for more than 7 days in the ICU, showed that patients lost up to 16% of muscle at the first week of ICU and 24% at the 21st day of treatment (Pardo et al., 2018). In this study, the average loss of quadriceps femoris muscle was -3.168% on day 3, -3.973% on day 5, and -4.730% on day 7. The results of this study differed from previous studies due to several aspects. In this study, patients had a better severity rate than in previous studies. The average APACHE II score was 18, which was estimated to have average intra-hospital mortality of 25% for non-operative patients and 12% for postoperative patients. This is different from the study of Pardo et al., where the patient is in a more severe condition (an estimated 44% mortality) so that he receives aggressive therapy such as muscle relaxants, which makes the patient prone to muscle wasting.

There is a significant correlation between the high-risk mNUTRIC group (≥5), compared with low risk group (0-4) with the difference in muscle thickness on days 3rd, 5th, and 7th. Overall the correlation of these factors has a strong correlation strength. This is consistent with Puthucheary, et al. The study showed a greater reduction in the cross-sectional area of the rectus femoris in patients with multi-organ failure on day 7 than patients with single organ failure. On the third day of examination, there was also a significant difference between the two groups of patients with multiorgan failure with one organ failure, where muscle mass loss occurred prematurely in critical patients (Z. A. Puthucheary et al., 2013).

The severity of muscle wasting is directly related to the severity of the disease, where more organ failure (SOFA> 2) is associated with increased muscle loss (Z. A. Puthucheary et al., 2013). This is consistent with the results of this study where there was a significant correlation between the APACHE II Score and the SOFA Score with the percentage of muscle loss on days 3rd, 5th, and 7th. From the analysis, it was found that there was a correlation with moderate and strong correlation strength between APACHE II Score and SOFA Score with percentage difference in muscle thickness. The increase in disease severity was indicated by an increase in the APACHE II Score and SOFA Score and was correlated with changes in the quadriceps femoris muscle thickness.

In this study, it was found that calorie intake was given slowly and increased gradually. Overall, the nutrition given was 39% (9.91 ± 5.14 cal/kg body weight/day) on the second day of treatment. On day 3 the mean calorie intake

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was increased gradually to 62.4% (15.61 ± 5.18 cal / kkBBI / day). On the next day of treatment, calorie intake was increased gradually until it reached 87.6% of the daily requirement and reached 100% of the requirement within five days of treatment.

The appropriate calorie intake is a key factor in critically ill patients. Nutrition starts with a small amount and is gradually increased until it reaches the recommended target calorie needs. In this study, the calorie intake was given slowly and gradually increased. From this study, there was no relationship between calorie debt and muscle changes during the first week. This is in accordance with the research of Pardo et al., which showed no correlation between calorie or protein definitions and muscle mass in the first week of treatment (Pardo et al., 2018). In this study, a consensus formula was used to determine daily calorie and protein needs which could cause differences in calorie needs between actual patient needs and the intake given.

It is recommended to provide a daily protein intake of 1.2 to 2.0 grams/kg/day in critically ill conditions. (McClave et al., 2016; Singer et al., 2019). However, this target is difficult to achieve in clinical practice. From this study, an average protein intake of 1.12 g/kg/day was reached by 43.4% of patients on the 7th day of care. In this study, the results show that there is a relationship between protein intake and the quadriceps femoris muscle thickness. This is consistent with the results of a study in 119 critically ill patients who compared the amino acid intake of 0.8 g/kg/day with 1.2 g/kg/day with parenteral nutrition. Higher amino acid administration was significantly associated with antebrachial muscle thickness by ultrasound evaluation (Ferrie, Allman-Farinelli, Daley, & Smith, 2016). Another study on 60 critical patients who received protein intake intervention (average 0.75 g/kg/day) found that there was less loss of quadriceps muscle thickness on discharge than the standard group in the intervention group (Fetterplace et al., 2018). The two studies are in accordance with the results of this study where on the 7th day, there was a significant and positive correlation with moderate strength correlation between total calorie debt for seven days with the percentage difference from the change in the thickness of the femoral quadriceps muscle ($p = 0.008$). The similarity of the results of this study compared to previous studies is because the average amount of protein intake given is relatively the same. This suggests that protein supplementation is associated with muscle mass loss in critically ill patients, according to clinical guidelines.

The weakness in this study is that measurement of the quadriceps femoris muscle thickness was only performed in the first seven days of treatment. Long-term measurements of the quadriceps femoris muscle thickness are expected to describe better changes in the metabolic conditions of critical patients. Long-term monitoring is expected to observe improvement or to worsen metabolic conditions. Changes in metabolic conditions lead to changes in muscle measurement parameters that can be used to predict prognosis in critically ill patients.

A study of 280 ultrasound examinations of quadriceps thickness performed on 29 critically ill patients showed that examination of quadriceps muscle thickness revealed good intra-and inter-observer reliability. It was found that Intra-observer reliability's ICC was 0.74 [95% CI 0.63; 0.84] and Inter-observer reliability's ICC was 0.76 [95% CI, 0.66; 0.86] at the "midpoint" site. (Pardo et al., 2018). In this study, only one researcher performed an ultrasound examination. This is intended to avoid inter-observer subjectivity.

The use of an indirect calorimeter is expected to be able to determine caloric requirements more precisely. Calorie requirements changes

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can provide a rough idea of the metabolic state of the patient. An indirect calorimeter is expected to reduce the energy deficit and observe the relationship of better caloric and protein intake with loss of muscle mass in critical patients.

Another weakness of this study only measures the quadriceps femoris muscle thickness and not measuring the cross-sectional area of the muscles. One study showed the measuring of the cross-sectional regions as a replacement parameter of muscle strength versus muscle thickness. The difficulty of obtaining a complete picture of the rectus femoris muscle is a major concern in cross-sectional areas using a conventional high-frequency linear probe (Z. A. Puthucheary et al., 2017).

This study is expected to increase clinician's attention to muscle mass loss in the ICU, monitor nutritional protocols and exercise interventions to maintain muscle mass. Nutrition monitoring in the ICU with clinical, biological, and technical examinations is expected to prevent and detect nutrition-related early complications. The Modified NUTRIC Score can be used to predict the risk of complications due to critical illness, including loss of muscle wasting. Functional recovery in critically ill patients is one of the focuses in future studies

CONCLUSION

Modified NUTRIC score has a moderate relationship with the quadriceps femoris muscle thickness in critically ill patients. There was no relationship between nutritional intake and the quadriceps femoris muscle thickness in critically ill patients. Protein intake has a moderate relationship with the quadriceps femoris muscle thickness in critically ill patients**.**

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Research Article

Effect of positive end-expiratory pressure value on change in end-tidal carbon dioxide as a predictor of fluid responsiveness in Patients Undergoing Passive Leg Raising Maneuver

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ABSTRACT

Identification of patients' fluid status in the emergency room should be made before giving fluid therapy. This study aimed to determine the effect of positive end-expiratory pressure on change in end-tidal carbon dioxide during passive leg raising maneuver to predict fluid responsiveness. Thirty subjects aged 18-65 years in the resuscitation room, all on the ventilator, were divided into three groups according to their positive end-expiratory pressure value: low (0-5 cmH2O), moderate (6-10 cmH2O), and high (>10 cmH2O). Every subject underwent passive leg raising to simulate fluid administration. Values of blood pressure, heart rate, cardiac output, and end-tidal carbon dioxide were recorded before and after the maneuver. Analysis of the three groups found a significant correlation between change in end-tidal carbon dioxide with a cut-off value of 5% and 1 mmHg with fluid responsiveness of subjects in the low (p = 0.028) and moderate (p = 0.013) but not in the high positive end-expiratory pressure group (p = 0.333). In conclusion, change in end-tidal carbon dioxide in mechanically ventilated patients undergoing passive leg raising maneuvers can be used as a predictor of fluid responsiveness, but this method cannot be used on patients with high positive end-expiratory pressure (> 10 cmH2O).

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INTRODUCTION

Almost half of the critically ill patients with unstable hemodynamic is not fluid responsive; for those patients, resuscitation with fluid bolus is dangerous. It can cause complications like iatrogenic saltwater drowning, Severe Acute Respiratory Distress Syndrome, Acute Kidney Injury, and death (Marik, Cavallazzi, Vasu, & Hirani, 2009; Schuller & Schuster, 2006). Researches to find a parameter to predict patients' fluid responsiveness has been done, classically with static parameters such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), left ventricular end-diastolic area (LVEDA), inferior vena cava (IVC) diameter, and intrathoracic blood volume index (ITBVI). That static parameter has its limit that they only predict preload value. Nonetheless, every heart works in the different part of Frank-Starling curve, so does every preload value. We can't directly predict the effect of preload increase on stroke volume or cardiac output (Zochios & Wilkinson, 2011).

Most dynamic parameters to predict fluid responsiveness are based on heart-lung interaction. The physiologic basis is the cyclic change of right and left ventricle preload caused by positive pressure ventilation. The bigger the change, the bigger the chance that the patient is fluid responsive. Pulse pressure variation, stroke volume variation, IVC distensibility index, and more recently, internal jugular vein variability have been studied, satisfying sensitivity and specificity, but they still share the same weakness. Arrhythmia, spontaneous respiration, low tidal volume or high-frequency ventilation, and low lung compliance have been found to decrease their accuracy (Michard, Chemla, & Teboul, 2015; Monnet et al., 2012).

A recent study in fluid responsiveness shows good performance of old but new methods known as passive leg raising. The principle of this maneuver is moving vein blood from the lower extremity to systemic circulation by raising patients' legs by 45 degrees. During the maneuver, change in cardiac output is monitored with echocardiography, esophageal Doppler, or arterial pulse contour analysis. An increase of more than 10% in cardiac output or stroke volume is considered as a positive result for fluid responsiveness. Its physiological basis is like a fluid challenge, but in PLR, the increase in intravascular volume is caused by auto-transfusion that is reversible. Those maneuvers differ from fluid bolus in the fluid challenge that uses external fluid administration and increases total intravascular volume permanently (Monnet et al., 2012; Monnet & Teboul, 2015). One study found from echocardiography and radial artery pulse pressure that the hemodynamic effect of PLR is equal to 300 mL fluid administration in 20 minutes (Boulain et al., 2002). The increase in venous return will increase right ventricle preload, right ventricle cardiac output, followed by an increase in left ventricle cardiac output. The effect of passive leg raising to heart preload will diminish when the legs are back in horizontal position, so PLR can be considered a short, safe, and reversible volume challenge (Monnet et al., 2012).

Continuous cardiac output monitoring during PLR needs relatively expensive and sophisticated devices and operators' expertise. There is a need to find simple bedside cardiac output surrogate. Carbon dioxide is produced in the body due to aerobic metabolism, diffused to blood and brought to the lung, then diffused back to alveoli. Carbon dioxide in gas form then goes through the bronchus and upper airway and can be detected in exhaled breath as end-tidal carbon dioxide with capnography (Ortega, Connor, Kim, Djang, & Patel, 2012). Studies found that end-tidal carbon dioxide can be used to measure cardiac output change in situations like low cardiac output or massive

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bleeding (Jin et al., 2000; Weil, Bisera, Trevino, & Rackow, 1985). The underlying mechanism is that EtCO2 is determined by three factors: carbon dioxide produced by aerobic metabolism in cell, pulmonary blood flow (in no shunt condition equal to cardiac output) that bring carbon dioxide from peripheral tissue to lung, and lung ability to diffuse CO2 out to alveoli as minute ventilation. If two of three factors don't change in a short time, then a change in EtCO2 will represent the change in the third factor (Basappanavar et al., 2018; Pantazopoulos et al., 2015).

Some studies have evaluated the ability of the change in EtCO2 as cardiac output surrogate during the fluid challenge or PLR maneuver. Monnet et al. found that change in EtCO2 during PLR with a cut-off value of 5% can predict fluid responsiveness with a sensitivity of 71% and specificity of 100%, better than pulse pressure variation (Monnet et al., 2013). Another study in France that compares several predictor for fluid responsiveness such as change in heart rate, pulse pressure, systolic blood pressure, femoral blood flow, and pulse pressure variation, and EtCO2 in ICU patients with mechanical ventilation and clinical signs of shock found that change in EtCO2 more than 1 mmHg during volume expansion with 500 mL crystalloid is the strongest predictor of fluid responsiveness (Lakhal et al., 2017). A study in China in patients with septic shock found that change in EtCO2 greater than or equal to 5% during PLR may predict fluid responsiveness with 75.8% sensitivity and 93.4% specificity (Xiao-Ting et al., 2015). These studies gave hope, but as its finding is still relatively new, no study has been made specifically to find its limitation yet.

Positive end-expiratory pressure (PEEP) is part of positive pressure ventilation that improves recruitment and oxygenation. It has a positive effect on respiration but has a resultant negative effect on the circulation system. Heart-lung interaction happened because of their anatomic location, encased within the same rigid chest wall, and the lungs encompass the heart in the cardiac notch. The heart acts, therefore, as a pressure chamber within another pressure chamber. The surrounding pressure is not atmospheric in the thoracic cavity but the pleural pressure (PPL). Changes in PPL relative to atmospheric pressure over the respiratory cycle cyclically affect the gradient for venous return and preload and afterload. With mechanical ventilation, the application of PEEP, and the absence of spontaneous breathing efforts, PPL is positive throughout the respiratory cycle, with several physiological consequences: (i) elevated alveolar pressure (PAL) combined with the recumbent position alters pulmonary blood flow by creating lung areas with zone 1 conditions (compression of alveolar vessels) and increasing the proportion of areas with zone 2 conditions, causing increased pulmonary vascular resistance (PVR) and dead space ventilation with loss of functional residual capacity (FRC); (ii) increased intrathoracic pressure (ITP) reduced transmural pressure (PTM) of large intrathoracic blood vessels as venae cavae and thoracic aorta, thereby diminishing intrathoracic blood volume; (iii) ITP is transmitted to the pericardium in the cardiac fossa where the heart is trapped and exposed to pressure elevation. As right atrial pressure (RAP) is elevated with positive ITP, venous return goes down, thus cardiac output also goes down (Grübler Martin, Olivier, David, & Stefan, 2017). Since higher PEEP equals higher ITP, it will also raise RAP. According to Frank-Starling curve, there will be a different increase in CO or SV for the same volume administration for different RAP baseline. We suspect PEEP can confound EtCO2 (ΔEtCO2) change to predict fluid change responsiveness in mechanically ventilated patients who underwent PLR maneuver to simulate fluid administration.

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METHODS

This study design is observational analytic with prospective cohort study, with sampling method of consecutive sampling. This study has been ethically approved by *Komite Etik Penelitian Kesehatan* RSUD Dr. Soetomo Surabaya with ethical clearance certificate number 1799/KEPK/1/2020. The population of this study was critically ill patients with mechanical ventilation. The sample for this study was 30 adult patients with mechanical ventilation who were admitted to the resuscitation room of the Emergency Room of RSUD Dr. Soetomo Surabaya between January-February 2020 and met inclusion and exclusion criteria. The inclusion criteria of this study were: (i) Adult patients (18-65 years old) with mechanical ventilation; (ii) Not more than one hour since intubation performed; (iii) Not breathing spontaneously/still under relaxant, and (iv) With ventilator setting of tidal volume 6-8 mL/kg predicted body weight (PBW). The exclusion criteria of this study were: (i) Patient had a contraindication for passive leg raising (wound, trauma in lower extremity or abdomen); (ii) Patient with suspected intraabdominal hypertension; (iii) Patient has a contraindication for echocardiography (wound, trauma); (iv) Patient with lung edema, traumatic brain injury, or suspected of increased intracranial pressure; (v) Patient wear compression stocking; and (vi) Patient whose family refused to be included in this study.

After the information to consent was explained and the family agreed to sign the informed consent, the patient was positioned at 45 degrees in a semi-recumbent position for five minutes before the PLR maneuver. Vital signs would be measured twice, before and during the PLR maneuver. Subjects were grouped according to their positive end-expiratory pressure ventilator parameter values into three groups: low (0-5 cmH2O), moderate (6-10 cmH2O), and high (> 10 cmH2O). Heart rate (HR0), mean arterial pressure (MAP0), and ETCO2 (ET0) of the subject were recorded from the monitor, and echocardiography to obtain cardiac output (CO0) was performed. The patient's upper body was then lowered to horizontal, and his legs were raised at 45 degrees up, and cardiac output was then remeasured before 90 seconds. Heart rate (HR1), mean arterial pressure (MAP1), and ETCO2 during PLR (ET1) were then recorded from the monitor. The patient then reverted to the original position and monitored for possible side effects. If during PLR patients suffering from hemodynamic instability, desaturation, agitation, or sign of lung oedema, the maneuver stopped, subject reverted to original position and given treatment.

The collected data analyzed with SPSS 17.0 software. Fluid responsiveness was defined by increased of cardiac output by 10% or more during PLR. Statistical tests were performed to compare parameter values before and after passive leg raising, correlation of change in parameter value to change in cardiac output, and correlation of change in end-tidal carbon dioxide to fluid responsiveness in three groups of subjects. The significance level is 0.05, and the confidence interval is 95%.

RESULTS

Thirty patients who became the subject of this study consisted of 18 males (60%) and 12 females (40%). The mean age is 47.33 ± 11.28 years, with a median of 51.5 years old. The characteristic of the subjects was described in Table 1. The most frequent diagnosis is pneumonia, followed by septic shock, tuberculosis, alcohol intoxication, and others (lung carcinoma, lung contusion, Guillain barre syndrome, asthma, and ketoacidosis diabetes). Nine subjects (30%) used low PEEP (0-5 cmH2O), eighteen subjects (60%) used moderate PEEP (6-10 cmH2O), and three From

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subjects (10%) used high PEEP (>10 cmH2O). No adverse event that prompted the PLR maneuver to stop happened.

Table 1. Characteristic of the subject

Parameter	Variable	n (%)
Sex	Male	18 (60)
	Female	12 (40)
Age	18 – 21 y.o.	1 (3.3)
	22 – 31 y.o.	3 (10)
	32 – 41 y.o.	5 (16.7)
	42 – 51 y.o.	6 (20)
	52 – 61 y.o.	13 (43.3)
	62 – 65 y.o.	2 (6.7)
Height	< 140 cm	-
	141-150 cm	4 (13.3)
	151-160 cm	16 (53.3)
	161-170	10 (30)
	>170 cm	1 (3.3)
Diagnosis	Pneumonia	11 (33.3)
	Septic shock	5 (16.7)
	Tuberculosis	5 (16.7)
	Alcohol intoxication	3 (10)
	Others	6 (20)

Table 2. Comparison between parameters before and after PLR in fluid responder group and non fluid responder group.

Parameter	Fluid responder			Non fluid responder		
	Before PLR	During PLR	p	Before PLR	During PLR	p
MAP (mmHg)	87 ± 7.2	88.4 ± 6.5	0.242	90.1 ± 11.8	91 ± 9.7	0.251
HR (bpm)	89.4 ± 10.2	90.4 ± 9.9	0.416	94.7 ± 12.2	96 ± 10.6	0.115
$EtCO_2$ (mmHg)	32.9 ± 2.1	35.4 ± 2.1[#]	<.001	32.2 ± 1.8	33.3 ± 1.8[#]	<.001
CO (L/minute)	4.1 ± 0.3	4.7 ± 0.2[#]	<.001	4.7 ± 0.5	4.9 ± 0.5[#]	<.001

[#] Paired sample t-test compared to parameter before PLR with significant p value < 0.05

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Table 3. Chi-square test between two $\Delta EtCO_2$ cut off value ability to predict fluid responsiveness of the subject.

$\Delta EtCO_2$ cut off value	$\Delta EtCO_2$ value	Fluid Responsive?		p
		Yes (n, %)	No (n, %)	
5%	≤ 5%	0 (0%)	17 (100%)	< .001#
	>5%	9 (69.2%)	4 (30.8%)	
1 mmHg	≤ 1 mmHg	0 (0%)	17 (100%)	< .001#
	>1 mmHg	9 (69.2%)	4 (30.8%)	

Chi-square test with significant p value < 0.05

Table 4. Chi square test between two $\Delta EtCO_2$ cut off value ability to predict fluid responsiveness of the subject, grouped according to their PEEP level.

$\Delta EtCO_2$ cut off value	PEEP group	$\Delta EtCO_2$ value	Fluid responsive?		p
			Yes (n, %)	No (n, %)	
5%	Low	≤ 5%	0 (0%)	7 (100%)	0.028#
		>5%	2 (100%)	0 (0%)	
	Moderate	≤ 5%	0 (0%)	8 (100%)	0.013#
		>5%	6 (60%)	4 (40%)	
	High	≤ 5%	0 (0%)	2 (100%)	0.333
		>5%	1 (100%)	0 (0%)	
1 mmHg	Low	≤ 1 mmHg	0 (0%)	7 (100%)	0.028#
		>1 mmHg	2 (100%)	0 (0%)	
	Moderate	≤ 1 mmHg	0 (0%)	8 (100%)	0.013#
		>1 mmHg	6 (60%)	4 (40%)	
	High	≤ 1 mmHg	0 (0%)	2 (100%)	0.333
		>1 mmHg	1 (100%)	0 (0%)	

Chi-square test with significant p value < 0.05

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examination before PLR maneuver, mean CO (CO0) is 4.52 ± 0.497 L/min, mean ETCO2 (ET0) is 32.4 ± 1.9 mmHg, mean MAP (MAP0) is 89.71 ± 10.606 mmHg, and mean HR is 93.13 ± 11.708 bpm. From examination during PLR, mean CO (CO1) is 4.83 ± 0.417 L/min, mean ETCO2 (ET1) is 33.87 ± 2.097 mmHg, mean MAP (MAP1) is 90.27 ± 8.859 mmHg, and mean HR (HR1) is 94.33 ± 10.512 bpm. Nine (30%) of the subjects are fluid responder, fulfilled the definition of fluid responsive (increase in CO during PLR more than or equal to 10%). Paired sample t-test to compare parameter value before and during PLR maneuver shows significant difference only for ETCO2 (p = <.001) and CO (p = <.001) pairs in all subjects, fluid responder group, and non-fluid responder group (Table 2).

Subject then analyzed according to their PEEP group, low (0-5 cmH_2O), moderate (6-10 cmH_2O), and high (>10 cmH_2O) with the same two $\Delta EtCO_2$ cut off value by chi-square test (Table 4). The result is in subject group of low and moderate PEEP, $\Delta EtCO_2$ value with cut off of 5% and 1 mmHg were associated with fluid responsiveness, with p value of 0.028 and 0.013, consecutively. In high PEEP group, $\Delta EtCO_2$ value with cut off of 5% and 1 mmHg was not associated with fluid responsiveness (p = 0.333).

In the high PEEP group, we performed paired sample t-test to know why $\Delta EtCO_2$ value is not associated with fluid responsiveness (Table 5). From the analysis of $EtCO_2$ parameter before PLR (ET0) to $EtCO_2$ during PLR (ET1) and CO before PLR (CO0) to CO during PLR (CO1), we found there is no significant change in end-tidal carbon dioxide and cardiac output before to during PLR.

DISCUSSION

This study aims to represent the population of critically ill patients in the emergency room. Most of the subjects in this study are male, like two other studies about intubation in emergency rooms in Hongkong and Singapore (Tam & Lau, 2001; Wong, Fong, & Ho, 2004). The median age of subjects in this study is 51.5 years. Three other studies about intubation in the emergency room in Asian hospitals get lower median age (Fathil et al., 2010; Tam & Lau, 2001; Wong et al., 2004).

We found no difference between static parameters (HR and MAP) before and during PLR for fluid responders and non-fluid responders. We also found no difference between static parameters between both groups. Several studies have found that static parameters couldn't be used to predict fluid responsiveness (Boulain et al., 2002; Caille et al., 2008; Marik & Cavallazzi, 2013). Both $EtCO_2$ and CO shows a significant increase before and during PLR for fluid responder and non-fluid responder. There is a difference though that the increase is more substantial in

Table 5. Paired sample t-test in high PEEP group to compare EtCO2 and Cardiac output before to during PLR.

Parameter	Timing	Mean ± SD	p
CO (L/menit)	Before PLR	4.19 ± 0.208	0.161
	During PLR	4.42 ± 0.180	
$EtCO_2$ (mmHg)	Before PLR	31.67 ± 3.055	0.057
	During PLR	33.0 ± 3.606	

[#] Paired sample t-test with significant p value < 0.05

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the fluid responder group. Previous studies showed that $\Delta EtCO_2$ strongly correlated with change in CO (Basappanavar et al., 2018; Nassar & Schmidt, 2016).

Several previous studies used two different $\Delta EtCO_2$ cut off value to identify fluid responder with PLR maneuver: >5% (Monnet et al., 2013; Xiao-Ting et al., 2015) and >1 mmHg (Lakhal et al., 2017) with different sensitivity and specificity. Our study compared both cut-off values and found no difference with a sensitivity of 100% and specificity of 81%.

Our study found that $\Delta EtCO_2$ is only associated with fluid responsiveness status in low and moderate PEEP groups. In the high PEEP group (>10 cmH2O), there is no association between $\Delta EtCO_2$ value and fluid responsiveness status, both with cut-off values of 5% and 1 mmHg. Other research has studied the effect of high PEEP on other predictors of fluid responsiveness. A study that compared several predictors of fluid responsiveness in shock patient with ARDS (high PEEP and PIP) and non-ARDS, found that the accuracy of PPV to predict fluid responsiveness in ARDS patient decreased, but both PLR and end-expiratory occlusion test with pulse contour cardiac index as monitor still has good performance (Monnet et al., 2012). Another study in postoperative ICU patients found that SVV threshold value to identify fluid responsiveness increased if PEEP value increased to 10 cmH2O (Kang et al., 2014).

The effect of high PEEP level in disassociation of $\Delta EtCO_2$ with fluid responsiveness that uses PLR can be explained according to PEEP relationship with intrathoracic pressure. PEEP in mechanically ventilated patients increased intrathoracic pressure, followed by an increase in RAP that can be seen from an increase in CVP (Luecke & Pelosi, 2005). Another study in Iran found that CVP increased for every increase in PEEP, with higher CVP increase happen in lower PEEP baseline (Shojaee et al., 2017).

Guyton predicted that an increase in intrathoracic pressure results in the shifting of the heart function curve to the right along the RAP axis, which was later proved, and this effect was found to be more significant on high PEEP (Bressack & Raffin, 1987; Marini, Culver, & Butler, 1981). Researches on pig hearts found that the same bolus volume has less effect in increasing CVP, RAP, and CO on the pig with higher PEEP (Berglund, Haldén, & Jakobson, 1994; Renner et al., 2008). We hypothesize that the heart function curve shifting then changes heart response to fluid administration, so fluid bolus with the same volume result in lower RAP and CO increase. This results in high PEEP that actually in lower PEEP would be a fluid responder. The PLR maneuver didn't result in an increase in CO that is significant enough to fulfill the fluid responsive definition. This is proved in Table 5, where both the value of EtCO2 and CO during PLR doesn't increase significantly. This study has a limitation that we could not exclude the possibility that high PEEP also affects the blood volume from the inferior extremity that comes back to systemic circulation during PLR maneuver through PEEP effect on intraabdominal pressure.

CONCLUSION

$\Delta EtCO_2$ as cardiac output surrogate can be used to identify fluid responsiveness in mechanically ventilated with low and moderate PEEP level who were undergoing PLR maneuver, with cut-off value of 5% or 1 mmHg, but it lost its ability in a patient with high PEEP (> 10 cmH2O). We suggest that future studies should compare with other cardiac output monitoring, such as arterial pulse contour analysis, and do the diagnostic testing to rate the sensitivity and specificity of these tests before its gold standard.

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Research Article

Effectiveness factors analysis of near-miss incidence referral in obstetric complications at Waras Wiris Andong General Hospital on Boyolali District

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ABSTRACT

Maternal mortality in Indonesia is still very high, and the biggest problem is obstetric complications. It is possible that the mother who has obstetric complications is safe and recovered (near miss) or died. This research was an observational analytic epidemiological study conducted to determine the effectiveness of near-miss incidence referral in obstetric complications using a cross-sectional approach. The sampling technique used was a random sampling system with 85 respondents. The effectiveness of referral affects near-miss incidence, meaning that mothers who get referral according to procedure only have a 0.107 times greater chance of not occurring near miss. Pregnant women who had a history of the disease had a risk of 0.157 times greater for the absence of near-miss than mothers who did not have a history. Pregnant women with high risk have 0.157 times no near-miss than those with low risk. Maternal antenatal examination affects the incidence of a near miss. It was found that the mother's history of illness, the risk of pregnancy owned by the mother and the effectiveness of referrals could affect the incidence of near miss in obstetric complications. In conclusion, there is an influence between the effectiveness of the referral and the near-miss incident at the Waras Wiris Andong Regional Hospital, Boyolali Regency

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INTRODUCTION

In its life cycle, women experience several important life stages and need special attention, as in pregnant women. Every year around 160 million women around the world experience pregnancy. However, around 15% suffer severe complications, and a third are life-threatening complications (Adisasmita, 2007).

Reducing maternal mortality is one of the fifth MDGs (Millennium Development Goals) programs that has not yet been achieved. Based on World Health Organization (WHO) data in 2015 an estimated 830 pregnant women die every day, and 99% of cases occur in developing countries. Maternal Mortality Rate (MMR) is one of the main indicators used to measure the success of the *safe motherhood* program. In some areas in Indonesia, such as in Boyolali, MMR tend to increase. Based on Boyolali health service reports, the maternal mortality rate in Boyolali in 2011 (116 / 100,000) with 18 cases, 2012 (97.97 / 100,000) with 15 cases (Biro Pusat Statistik, 2015).

Mothers who experience life-threatening complications have the possibility of surviving and recovering (*near miss*) or not being saved and experiencing maternal death (Souza, 2007). One of the events closest to maternal mortality is *near*-miss (Mantel, 1998). A Maternal *near miss* is a woman who almost died, but survived complications during pregnancy, during delivery, or within 42 days after the termination of pregnancy (WHO, 2005; 2011). The incidence of *a near-miss* in Indonesia varies from 0.7 per 1000 births to 12 per 1000 births, depending on the criteria used, with the main causes of *near misses* being bleeding and hypertension. *Near miss* due to abortion is also quite commonly found in the amount of 13.0% (Adisasmita 2008).

Based on data obtained from the Waras Wiris Andong Regional Hospital in Boyolali District, the incidence of *a near-miss* in obstetric complications in 2017 was 100 cases. As for the maternal mortality rate in Boyolali Regency during 2017, there were 12 maternal deaths due to obstetric complications.

Care services for pregnant women or commonly called *Antenatal Care* (ANC) are fundamental things that pregnant women must obtain to prepare for the pregnancy to run well (Colti et al, 2014). The leading causes of death in pregnant women can be classified into direct and indirect causes. Overall, 80% of deaths among pregnant women are caused directly, and 20% are not directly. The direct cause of death can be caused by obstetric complications such as bleeding (25%), infection (15%), eclampsia (12%), unsafe abortion (12%), prolonged labor or without a tear of the birth canal (8%), and other direct causes (Brinkmann, S. and Kvale 2005; Nurdianto et al, 2019a, 2019b, Nurdianto et al., 2020a;2020b).

The cause of the delay in obtaining services at health facilities is inseparable from the current referral system in Indonesia (Rochyati, 2005; Anggondowati, 2018) In the era of the National Health Insurance (JKN), the government is expected to reduce the MMR. The method is when there is an ANC, the village midwife must always screen pregnant women. Is the pregnant woman included in high risk or not. If pregnant women are included in the high-risk criteria, it is recommended to be referred to a higher health facility for further examination or treatment. But in the field of implementation, many JKN participants who come to check themselves only bring a referral letter from the midwife or village midwife, with their status as public patients.

According to these patients, they cannot get a referral from the Public Health Service (Puskesmas) to go to the hospital, arguing that

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it can still be handled at the puskesmas level. Finally, patients cannot use their facilities as JKN participants. When in the hospital if the pregnant woman still receives polyclinic services and is done outpatient, it may not be too burdensome for the patient. However, if the visit had to be taken at the time of the visit, most of the patients refused and went home because of the cost.

Most near miss and maternal deaths can be prevented if they receive adequate treatment in a health facility (Akbarani, 2013). Many influential factors such as time actors, transportation, costs, the responsiveness of health workers, and referral flow are crucial in referring cases of obstetric complications to get the right help (Anggondowati, 2008; Khosla et al., 2000). Therefore, on this occasion, the author aimed to analyze the factors that affect the effectiveness of near-miss referral in obstetric complications in the Waras Wiris Andong Regional Hospital Boyolali Regency.

METHODS

This research was an observational analytic epidemiological study that was conducted to determine the extent to which the effectiveness of referral events *near-miss* in the case of obstetric complications. The design in this study uses a *cross-sectional* approach in which the researcher collects data at one time simultaneously by making observations based on a questionnaire that describes the situation for a moment through primary data analysis at the time of the research. This design was chosen with the consideration that it can be used to look at the effectiveness of near-miss incidence referral in obstetric complications in the Waras Wiris Andong Regional Hospital Boyolali. (Lemeshow et al., 1990; Notoatmojo, 2010)

The sample in this study were all women who had obstetric complications at the Waras Wiris Andong Regional Hospital in Boyolali Regency from January 2018 to February 2018 period. Determination of the sample size of an unpaired categorical analytic study in a population determined using a formula and the results obtained were 85 respondents (Murti, 2010). The result of the study will be carried out with statistical analysis with the Chi-square test and multivariat analysis using SPSS 21 application. This study has obtained ethical clearance from the Health Research Ethics Moment of Rumah Sakit Umum Daerah (RSUD) Saiful Anwar Malang with number 305/209/K.1/289/2017.

RESULTS

The results of this study show the cross-tabulation between the characteristics of women who experience complications, including age, parity, a distance of pregnancy, education, and examination of the pregnancy carried out by the mother during pregnancy with a near-miss at the time of delivery.

Based on the age of mothers <20 years or> 35 years who experienced near-miss as many as 1 mother (5.3%) and in the age category 20-35 years most did not experience near miss as many as 53 mothers (82.8%). Based on the analysis of the Chi-square test, the *p*-value was 0.756> α (0.05), which means that there was no relationship between maternal age and near-miss.

In parity, mothers with children ≤ 4 experienced near-miss as many as 13 mothers (16.7%) and in parity > 4 mothers who experienced near-miss, namely as many as 1 (14.3%). Based on the results of the Chi-square test analysis, the *p*-value was 0.871 > α (0.05) which means that parity has no relationship with near-miss events.

Based on the distance of pregnancy, it can be seen that the majority of mothers who have a pregnancy distance of 0 years or 2 - 9 years experience near miss as many as 13 mothers

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(16.5%) and mothers who have a distance of <2 years or> 9 years who experience near miss 1 events mothers (16.7%). Based on the analysis of Chi-square test results, obtained *p*-value of 0.989> α (0.05), which means there is no relationship between the distance of pregnancy with near-miss events.

Based on maternal education, most of those who experienced near-miss was educated > junior high school (SMP) by 13 mothers (16.1%), and maternity education in the category of ≤ SMP mostly experienced near-miss by 4 mothers (57.2%). The analysis results obtained *p*-value = 0.641 > α (0.05) which means that a mother's education is not related to near-miss events.

Pregnancy checks can be known that most of the mothers with a good pregnancy examination did not experience near miss as many as 62 mothers (87.3%) and mothers who did fewer pregnancy checks mostly experienced near-miss as many as 5 mothers (35.8%). Chi-square test analysis results obtained a p-value of 0.043 <α (0.05), which means that antenatal care has a relationship with near-miss events.

Based on a height that was cross-tabulated with near-miss events, mothers who had a height of ≤ 145 cm and experienced near-miss events of 1 mother (100%) and mothers who had height> 145 cm mostly did not experience near miss 71 mothers (84.5%). The results of the analysis with Chi-square obtained *a* p-value of 1,000> α (0.05) which means it can be concluded that there is no relationship between height and near-miss events.

Based on the nutritional status by a cross-tabulation with near-miss events, 69 mothers (88.4%) did not experience near-miss events, and 88 mothers with 88 nutritional status did not experience near-miss events (100%). The results of the analysis with Chi-square obtained *a* p-value of 0.999 > α (0.05) which means it can be concluded that there is no relationship between nutritional status and near-miss events.

Based on the Hb level cross-tabulated with near-miss events in women with obstetric complications, it can be seen that most of the mothers with Hb levels> 11 g% or no anemia did not experience near-miss events of 36 mothers (83.7%) and in mothers with Hb levels <11 g%, 7 mothers (16.7%) experienced near-miss events. The results of the analysis with Chi-square obtained *a* p-value of 0.962 > α (0.05), which means that it can be concluded that there is no relationship between Hb levels with near-miss events.

Based on the history of maternal diseases that were cross-tabulated with near-miss events in women with obstetric complications, it can be seen that most mothers who did not have a history of illness did not experience near miss as many as 60 mothers (92.3%), and those who had a history of the disease the majority also did not experience near miss as many as 11 mothers (55%). The results of the analysis with Chi-square obtained *a* p-value of 0.000 < α (0.05), which means that it can be concluded that there is a relationship between the history of the illness suffered by the mother with the near-miss.

10 mothers had a high risk of experiencing near miss (30.4%). Whereas most mothers who had low-risk did not experience near miss as many as 43 mothers (92.3%). The results of the analysis using Chi-square obtained *a* p-value of 0.010 <α (0.05), which means that the risk during pregnancy has a relationship with the incidence of near-miss.

Based on the results of the cross-tabulation between the use of KIA Handbooks with near-miss events it is known that most respondents whose KIA Handbooks were filled incorrectly did not experience near-miss events as many as 61 mothers (87.1%), while mothers whose KIA Handbooks were not properly filled

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inexperienced near-miss events as many as 5 mothers (33.3%). Based on the analysis of Chi-square test results obtained *p*-value of 0.062> α (0.05), which means there is no relationship between the use of the KIA Handbook and the near-miss event.

The results of multivariate analysis to examine the effect of maternal characteristics, maternal health status, the effectiveness of referrals to near-miss events are shown in table below. The results of the analysis show the significant value in the last step of the logistic regression using the *Backward Wald* method which is seen as a whole; three categories have a significant value smaller than the confidence level of 0.05 (5%), ie for the history of the disease suffered by the mother has a valuable significance of 0.012 ($p = 0.012 < \alpha = 0.05$), the risk of pregnancy has a significance value of 0.043 ($p = 0.043 < \alpha = 0.05$), and the effectiveness of referral has a significance value of 0.005 ($p = 0.005 < \alpha = 0.05$).

The variable history of the illness suffered by the mother has a significance value of $0.012 < \alpha = 0.05$, which means that there is an influence of the history of the disease suffered by the mother with near-miss events. Mothers who have a history of the disease are 0.157 times more likely to develop near-miss compared to women who have no history of illness.

The pregnancy risk variable has a significance value of $0.043 < \alpha = 0.05$, which means that there is an influence on the risk of pregnancy with near-miss events. Mothers who have a high risk are likely 0.213 times more likely to have a near-miss than a mother who has a low risk.

The referral effectiveness variable has a significance value of $0.005 < \alpha = 0.05$, which means that there is an influence of the effectiveness of the referral with near-miss events. Mothers who are referred incorrectly or not according to procedures have a 0.107 times greater chance of developing near misses when compared to mothers who are referred correctly.

Table 1. Logistic Regression Test Results for Mother Characteristics, Maternal Health Status, Utilization of KIA Handbook, Effectiveness of References to Near Miss Events

Variable	P-value	*Exp (B)*
Disease History	0.012	.157
Risk of Pregnancy	0.043	0.213
Effectiveness of Referrals	0.005	.107

DISCUSSION

Maternal characteristics by level of education mostly have more than junior high school level of education (SMP). The level of education is not directly related to the near-miss incident because the level of education of the mother only affects the access and utilization of health services. mothers who have high levels of education will tend to pay more attention to self and family health and seek antenatal care (Adisasmita, 2017). If you are pregnant, you will choose childbirth help with a professional health worker. They are easier to get and receive information given related to their health and pregnancy.

Characteristics of maternity mothers based on parity in this study most mothers gave birth ≤ 4. The second to fourth births are the safest deliveries. The risk will increase in subsequent pregnancies. A risky first delivery can only be managed with better antenatal care. Mothers with high parity will be at greater risk of complications during labor that can cause near-miss. In women who often give birth, the uterine muscle is often stretched, resulting in thinning of the uterine wall, which eventually causes contraction of the uterus to be weak. Rupture of the uterus is a labor complication that often occurs in mothers who have previously given birth to several children (Waterstone, 2001; Manuaba, 2007; Prawiroharjo, 2014).

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The results of both bivariate and multivariate analysis showed no influence or relationship between the distance of pregnancy with near-miss events. The results of this study are consistent with the results of Arulita's research (2009), which states that pregnancy spacing is not a factor influencing obstetric complications that can cause maternal deaths. With a value of p = 0.222. The recommended pregnancy interval for a safe pregnancy to last for at least 2 years allows the mother's body to recover from the extra needs of pregnancy and lactation. The distance of pregnancy too close, causing mothers to have a higher risk for uterine bleeding early postpartum and maternal mortality (Manuaba, 2007; Prawiroharjo, 2014; Astari, 2014).

According to research conducted by Agudelo AC and Belizan JM and supported by previous studies, a pregnancy distance that is too long ≥ 10 years will increase the risk for preeclampsia/eclampsia, gestational diabetes, bleeding in the third trimester and also shows an increased risk for the occurrence maternal death, therefore, this woman with a gestational distance ≥ 10 years requires special attention during the antenatal examination (Agudelo and Belizan, 2020).

The bivariate analysis results showed that the antenatal examination affected the near-miss incidence with a value of p = 0.043. However, the results of multivariate analysis showed that antenatal examination is not a variable that affects the incidence of near-miss. The results of this study are consistent with WHO study which states that poor antenatal care is not a risk factor that influences the incidence of complications that cause maternal death (WHO, 2011).

The antenatal examination standards that have been set are regular at least 4 times during pregnancy to health workers with intervals of 1 time in the first trimester, 1 time in the second trimester, and 2 times in the third trimester with a minimum examination standard of 10 T, namely: weight measurement and measure height, measure blood pressure, measure nutritional status by measuring upper arm circumference, measure uterine fundal height, determine the fetal presentation and fetal heart rate (DJJ), screen for tetanus immunization status and provide tetanus toxoid immunization (TT) when needed, minimal iron tablets 90 tablets during pregnancy, laboratory tests (special and routine), case management, consultation (counseling) including planning for the prevention of complications (P4K) and postpartum birth control (Depkes, 2008; Nurdianto, 2020c).

Maternal health status with near-miss events indicates that height is not related to near-miss events. Height is an indicator used to determine the health status of a mother, especially at the time of delivery. There are three restrictions on mothers with a height of less than 145cm. This is the first pregnant woman who needs special attention. The area of the mother's pelvis and fetal head size may be disproportionate, in this case, two possibilities occur, the mother's pelvis as a birth canal is narrow with the fetus/head not large, normal size pelvis but the large child / large head, second pregnant women, with a pregnancy then the baby is born just months but dies in time (baby age) 7 days or less, Pregnant women before pregnancy had never delivered enough months, and low birth weight <2500 grams. The danger that can occur is that labor is not going well, the baby is difficult to be born, in danger. Medical assistance needs cesarean delivery (Rochyati 2011).

Another maternal health status is nutritional status by measuring the Upper Arm Circumference (Lingkar Lengan Atas / LILA) (Manuaba, 2007; Prawiroharjo, 2014). The results showed no relationship between the nutritional status of respondents to the

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incidence of a near miss. The results showed that most respondents had good nutritional status, meaning that good nutritional status was that respondents had upper arm circumference or Lila more than 23.5 cm. The study results are consistent with the research from the 2001 SKRT analysis which showed no significant relationship between nutritional status as measured by LILA with the incidence of labor complications (Manuaba, 2007; Prawiroharjo, 2014).

Mothers with poor nutritional status are at risk for bleeding and infection during the puerperium. Malnutrition before and during pregnancy, especially the condition of mothers with *stunting* in childhood that reflects severe malnutrition, will provide a risk of parturition due to cephalopelvic disproportion, which will increase the risk of malnutrition maternal death during labor (Say et al., 2014).

The study results for hemoglobin levels showed no relationship between the respondents' hemoglobin levels to the near-miss event. This is not following Arulita's research (2009) which concluded that mothers who suffer from anemia during pregnancy have a 4 times greater risk for labor complications than mothers who do not suffer from anemia (OR = 4.0; 95% CI: 1.7 - 9.6; p = 0.001).

According to WHO, maternal deaths in developing countries are related to anemia during pregnancy. Pregnant women with severe anemia will be more vulnerable to infections during pregnancy and labor, increasing the risk of bleeding that will continue with death. Several studies have shown that the risk of maternal death increases in mothers who suffer from anemia during pregnancy (WHO, 2016).

The results of both bivariate and multivariate analysis showed that the study showed that there was an influence on the history of the disease suffered by the mother with near-miss events. Mothers who have a history of the disease are 0.157 times more likely to develop near misses compared to women who have no history of the disease. History of diseases that can aggravate pregnancy and childbirth include hypertension, heart disease, asthma, diabetes mellitus, infectious diseases such as Toxoplasmosis, Tuberculosis, Malaria (Nurdianto 2020a; 2020b; WHO, 2007).

This is by Arulita's research (2009) which shows that the risk for maternal death in mothers who have the disease is 210.2 times greater than mothers without a history of the disease with a value of p = 0.002 (OR adjusted = 210.2; 95% CI: 13.4 - 5590.4).

A history of maternal illness is defined as a disease that the mother suffered before pregnancy or childbirth or disease that arises during pregnancy that is not related to the direct obstetric cause but is exacerbated by the physiological effects of pregnancy so that the mother's condition becomes worse. Maternal deaths due to illnesses suffered by the mother is a cause of indirect maternal death (*indirect obstetric death*).

The results of both bivariate and multivariate analysis showed that the study showed that there was an influence of maternal pregnancy risk factors with near-miss events. Pregnancy risk variables had a significance value of 0.043 <α = 0.05, which means there was an influence of pregnancy risk with near-miss events. Mothers who have high risk are 0.213 times more likely to develop near-miss than women with low risk. This is related with Akbarani (2013) states that mothers with high-risk categories will experience obstetric complications when labor is 19.14 times higher than mothers with low-risk categories (Akbarani, 2013).

The results showed there was no relationship between the use of KIA Handbooks with near-miss events. This is consistent with research

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by Colti, et al (2014) which states there is no relationship between the role of health workers in the use of the KIA Handbook to the incidence of childbirth complications (Colti, 2014).

Utilization of the KIA Handbook through complete recording of the health of pregnant women by midwives is expected to have a contribution in reducing maternal and infant mortality rates, namely by detecting early risks of pregnancy that can threaten the lives of mothers and babies (Nurdianto, 2020c; Nurdianto et al., 2021).

Obstetric complications can be detected if the pregnant woman performs an Ante Natal Care (ANC) checkup routinely or at least four times during pregnancy. Recording the results of examinations is a midwife's competency standard and part of a quality *Antenatal* service standard. Each time the examination, the midwife must record the results on the medical record, Mother's Card, and KIA Handbook. At present, the recording of the results of antenatal examinations is still very weak, so the data cannot be analyzed to improve the quality of *antenatal care*. The function of the KIA Handbook is as information and recording tools for analyzing the health condition of pregnant women. With the complete and accurate recording of the health of pregnant women in the KIA Handbook, if analyzed the data can be an early warning against high-risk threats of pregnant women, thus they will avoid 3 L (late detection, late referral, late handling). Midwives must recognize high-risk pregnancies/abnormalities, if found midwife abnormalities can take the necessary actions and refer to the next cell action (Mangun, 2008).

The results of both bivariate and multivariate analyses indicate that research shows an effect of maternal referral effectiveness with near-miss events. The referral effectiveness variable has a significance value of 0.005 $<\alpha = 0.05$, which means that there is an influence on the referral's effectiveness with near-miss events. According to the procedure, mothers who were referred incorrectly or not were 0.107 times more likely to have a near-miss than those who were referred correctly.

This is following Arulita's research (2009) which shows that ineffective referrals or late referrals during obstetric complications will cause mothers to have a risk of 50.8 times more likely to experience maternal death (near-miss) when compared to mothers who are referred by effective.

The results of this analysis indicate that late referrals or ineffective referrals to mothers who experience complications during pregnancy, childbirth, and the puerperium present a greater risk for near-miss. 3 delays influence this ineffective reference. The first delay is the delay in decision-making. The second is the delay in reaching the referral place and the third is the delay in handling the case at the referral place. The ineffectiveness of this referral will worsen the mother's condition due to the mother not getting adequate treatment following the existing complications. Thus, death can be life-threatening to the mother.

CONCLUSION

There is an influence of the history of the disease suffered by the mother, the risk of pregnancy, and the effectiveness of the referral with near-miss events in obstetric complications in the Waras Wiris Andong Regional Hospital Boyolali Regency.

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Research Article

Nephroprotective effect of virgin coconut oil in *Plasmodium berghei* ANKA infected Balb/c mice

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ABSTRACT

Malaria is a parasitic infectious disease caused by *Plasmodium*, which remains a world health problem with an estimated 219 million cases worldwide. In severe malaria infection, several organs of the body can be affected, including the kidneys. One of the pathophysiology associated with the worsening of this disease is oxidative stress. The use of antioxidants is expected to prevent this, and one product that has a high antioxidant content is virgin coconut oil (VCO). This study aimed to analyze the effect of VCO on the kidney in *Plasmodium berghei* ANKA-infected mice. This study was an *in vivo* laboratory experimental study with a randomized post-test only control group design using 35 BALB/c mice infected with *P. berghei* ANKA, weighing 20-30 grams. VCO with the Javara® brand is used with doses of 1, 5, and 10 ml/kg body weight (kgBW)/ day. The parameter assessed were levels of BUN, creatinine, and renal histopathological changes. The administration of VCO on the treated group shows minimal tubular necrosis and glomerulonephritis compared to the negative control group. The BUN and creatinine levels in the treated group were also lower than the negative control group. The results showed that VCO has a nephroprotective effect against *P. berghei* ANKA infection in mice.

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INTRODUCTION

Malaria remains one of the essential protozoan diseases in the world (WHO, 2018). This tropical disease still remains a public health problem in several countries, including Indonesia (Kemenkes RI, 2016; WHO, 2015). The annual death rate because of this disease is still over a million, especially affecting children below five years old and pregnant women.

The primary pathogenesis mechanism in this infection is the hemolysis of erythrocytes infected with *Plasmodium*, which releases malaria merozoites and endotoxins (consisting of hemozoin complexes and parasitic DNA), thereby stimulating the host immune response (Phillips et al., 2017). Another pathogenesis of severe malaria is sequestration (cytoadherence and rosetting) which causes microvascular obstruction in vital organs (such as liver, kidney, and brain) and rosetting. This phenomenon results in disruption of cytokine and nitric oxide regulation, which can cause or aggravate local and systemic inflammation (Harijanto et al., 2016). The kidney is one of the organs that can experience severe malaria (WHO, 2015). As many as 40% of patients infected with *P. falciparum* can experience kidney complications in the form of acute kidney injury (AKI) (Plewes et al., 2014). Several factors that contribute to AKI are hypovolemia, vasoconstriction, hemolysis, parasitemia, and microcirculation dysfunction (Silva Junior et al., 2017). Impaired kidney function is characterized by increased levels of blood urea nitrogen (BUN) and creatinine ((Isa et al., 2013; Kalia et al., 2015). Kidney histology research in malaria shows acute tubular necrosis, glomerulonephritis, and interstitial nephritis (Akil, 2019; Koopmans et al., 2015).

The artemisinin combination therapies are the first-line treatment for malaria in endemic countries; however, resistance is reported (Menard & Dondorp, 2017). Many studies on the development of herbal medicines for malaria therapy include pathophysiological modifications of oxidative stress by using antioxidants. One product that contains many antioxidants is virgin coconut oil (VCO) which is derived from fresh coconut or *Cocos nucifera* produced without heating or adding chemicals (Durasevic et al., 2019). High antioxidant content can reduce fat peroxidation and reduce oxidative stress by increasing catalase enzyme activity in the kidneys and increasing glutathione in the liver and kidneys (Arunima & Rajamohan, 2013; Zakaria et al., 2011). VCO could also protect the kidney from nephrotoxicity by blocking oxidative stress, inflammation, and apoptosis and by downregulating the signaling pathway of NF-κB/iNOS/caspase (Famurewa et al., 2020). There is no previous study yet showing the effect of the oil on malaria infection. Thus, this study aimed to explore the possible nephroprotective effect of VCO supplementation against *Plasmodium berghei* ANKA infection in mice.

MATERIAL AND METHODS

Experimental animal and parasite strain

Thirty-five male Balb/c mice (25-35 g) were obtained from and maintained at the Animal House, Department of Biochemistry, Universitas Airlangga, Surabaya, Indonesia. These animals were acclimatized for two weeks in a group of seven in cages with wooden shaves for bedding material. They were fed with a standard pellet diet and drinking water *ad libitum*. They were also maintained under standard laboratory conditions and subjected to a natural photoperiod of 12 hours light/ 12 hours dark cycle. This study meets the ethics requirements for research in experimental animals and is approved by the ethical committee clearance for preclinical research Universitas Airlangga with registration number 745/HRECC.FODM/XI/2019.

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The asexual blood-stage *Plasmodium berghei* ANKA strain parasites were maintained *in vivo* in mice. The parasite were obtained from the Department of Parasitology, Universitas Airlangga, Surabaya, Indonesia. Each mouse was inoculated intraperitoneally with 0.2 ml of infected blood containing $1x10^7$ infected erythrocyte/IE from donor mice with rising parasitemia of 30-45%.

Virgin coconut oil

The VCO used was by trade name Javara®, obtained from the supermarket in Surabaya City, East Java, Indonesia with BPOM RI MD no. 207928001388. According to the producer, Javara® is made from a fresh coconut through the cold press without additives.

Experimental design and treatment of mice

Thirty-five *P. berghei* infected mice were randomly divided into five groups (two control and three experimental groups), each having seven mice (Table 1). The animals in G1 were designated as negative control and received distilled water; G2 as a positive control (received DHP at the dose of 187,2 mg/kg body weight); G3-G5 as experimental groups with VCO treatment at the dose of 1, 5, and 10 ml/kg body weight/day, respectively. The VCO dose used in this research was based on the previously conducted study (Zakaria et al., 2011). The administrations of different treatments were given orally by using a standard intragastric tube once daily for four consecutive days (D0-D3). All animals were sacrificed 24 hours after the last treatment.

Serum biochemical Analysis

Twenty-four hours after the last dose of treatment or at D4, the mice were sacrificed, and the blood samples were collected by heart puncture. The blood sample for serum biochemical analysis of kidney function consisting of BUN and creatinine (Table 2) were collected in a vacutainer and analyzed using an automated machine (Dimension EXL-Siemens).

Histopathological study

The kidney was obtained from each mouse after twenty-four hours of the last dose of treatment or at D4. The kidney was washed and then fixed in 10% formal saline. The fixed tissues were then embedded in paraffin, sectioned (5μm) with a rotary microtome, and stained with hematoxylin and eosin (H&E). The kidney sections were evaluated histologically with a camera attached to a light microscope (Nikon Eclipse) and NIS Element F 4.60.00 64bit software. The extent of *P. berghei*-induced kidney damage was evaluated based on pathologic lesions in kidney sections stained with the H&E method.

Statistical Analysis

The data were expressed in median (minimum-maximum). The value of the treated and control groups was compared using Kruskal Wallis parametric test with $p < 0.05$ being considered significant, using the IBM SPSS Statistic 23 for Mac.

Table 1. Grouping of animals and treatment

Groups	Treatment
G1	Untreated infected control (negative control). They were fed with distilled water
G2	Infected with *P. berghei* and treated with DHP (positive control)
G3	Infected with *P. berghei* and treated with VCO 1 ml/kg BW/day
G4	Infected with *P. berghei* and treated with VCO 5 ml/kg BW/day
G5	Infected with *P. berghei* and treated with VCO 10 ml/kg BW/day

VCO: virgin coconut oil, DHP: dihydroartemisinin + piperaquine; kg BW = kilogram body weight

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RESULT

1. The Effect of VCO on Serum Biochemical Parameter

Table 2 presents the effect of a VCO supplemented diet on the kidney function of *P. berghei* ANKA infected mice. The BUN and creatinine serum are the markers of renal function. The BUN levels in all treatment groups are still within the normal reference value range (Charles River, 2012). The BUN levels in the G3 and G5 groups were lower than those in the group that was not given VCO (G1) or in the group given DHP (G2). This shows that VCO administration causes lower BUN levels. The analysis of differences in BUN levels was performed using the non-parametric Kruskal-Wallis test (p = 0.018), followed by the Mann-Whitney post hoc test. The results of the Mann-Whitney test for BUN levels showed that there was a significant difference between the G3 group compared to the other groups.

The creatinine levels in all treatment groups are still within the normal reference value range (Charles River, 2012). This shows that in *P. berghei* ANKA infection, creatinine levels do not rise above normal values. The creatinine levels in the G4 and G5 groups were lower than those in the G1 and G2 control groups (Figure 2). The analysis of differences in creatinine levels was performed using the non-parametric Kruskal-Wallis test. The Kruskal-Wallis test results showed p = 0.388, which means that there was no significant difference between treatment groups so that further tests were not carried out.

Table 2. Evaluation of kidney function test in various experimental group on day 4

Group	BUN	Creatinin
G1 (untreated, distilled water)	16 (14 – 28)	0,32 (0,16 – 0,66)
G2 (DHP)	16 (13 – 20)	0,36 (0,18 – 0,38)
G3 VCO 1 ml/kgBW/day	14 (9 – 15)*,a,b,c,d	0,46 (0,18 – 0,72)
G4 VCO 5 ml/kgBW/day	16 (14 – 24)	0,27 (0,11 – 0,60)
G5 VCO 10 ml/kgBW/day	15 (14 – 20)	0,26 (0,19 – 0,42)

Values are median (minimum – maximum).
The normal value of BUN = 18 mg/dl and creatinine = 0,4 mg/dL (Charles River, 2012).
The * sign shows significant differents with p<0,05, a compared to G, b compared to G2, c compared to G3, d compared to G4, and e compared to G5.

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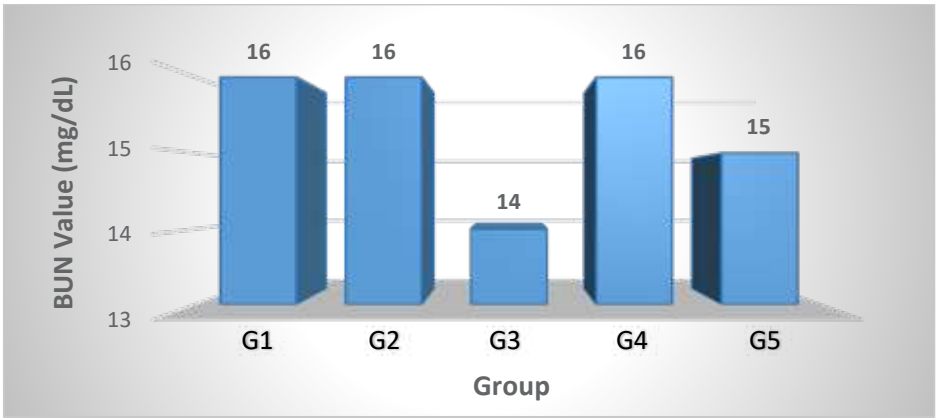

Figure 1. Comparison of BUN in *P. berghei* ANKA infected mice

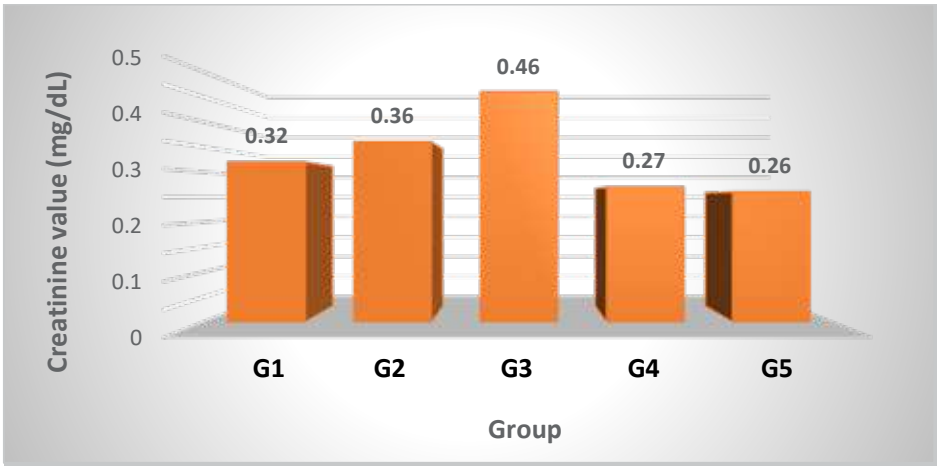

Figure 2. Comparison of creatinine in *P. berghe*i ANKA infected mice

2. Histopathological Study of the Kidney of P. berghei infected mice Treated with VCO

The effect of VCO supplementation on renal histology is presented in Table 3. The histopathological alteration in the kidney was tubular necrosis (yellow arrow) that can be observed in the medulla and cortex, glomerulonephritis (yellow triangle), and interstitial nephritis (yellow rectangle). The treatment with VCO shows mild changes compared to the control groups.

Table 3 shows that acute tubular necrosis in the kidneys of mice between treatment groups is significantly different (p = 0.007). The Mann-Whitney post hoc test results showed significant differences between all VCO treatment groups (G3, G4, and G5) compared to the G1 group. All mice kidneys in the VCO treatment group only showed mild acute tubular necrosis (100%); that is, there was only a change of less than 10%. This is different from the G1 group, which showed mild necrosis with changes of 10-25% (42.9%) and moderate necrosis with changes of 26% -75% (57.1%), while the necrosis that occurred in the G2 group mainly was mild (85.7%) and only 14.3% were moderate.

The glomerulonephritis in the kidneys of mice between treatment groups is significantly different (p = 0.015). The Mann-Whitney post

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hoc test results showed that all VCO treatment groups (G3, G4, and G5) were significantly different compared to the G1 group. Glomerulonephritis in the VCO group mostly showed mild changes in contrast to changes in the G1 group, where most of them experienced moderate changes. The group showing mild glomerulonephritis, an alteration of less than 30%, was 71.4%, while the group that showed moderate alteration was 22.9%. The kidneys of mice that presented no glomerulonephritis were 5.7%.

The interstitial nephritis that occurred between the treatment groups was not significantly different ($p = 0.131$). The kidneys of mice that showed mild interstitial nephritis were 54.3% less than 30%, moderate changes were 30-50% at 31.4%, and severe changes were 2.9%. There were 11.4% of mice that did not experience changes in interstitial nephritis in the G2, G3, and G5 groups.

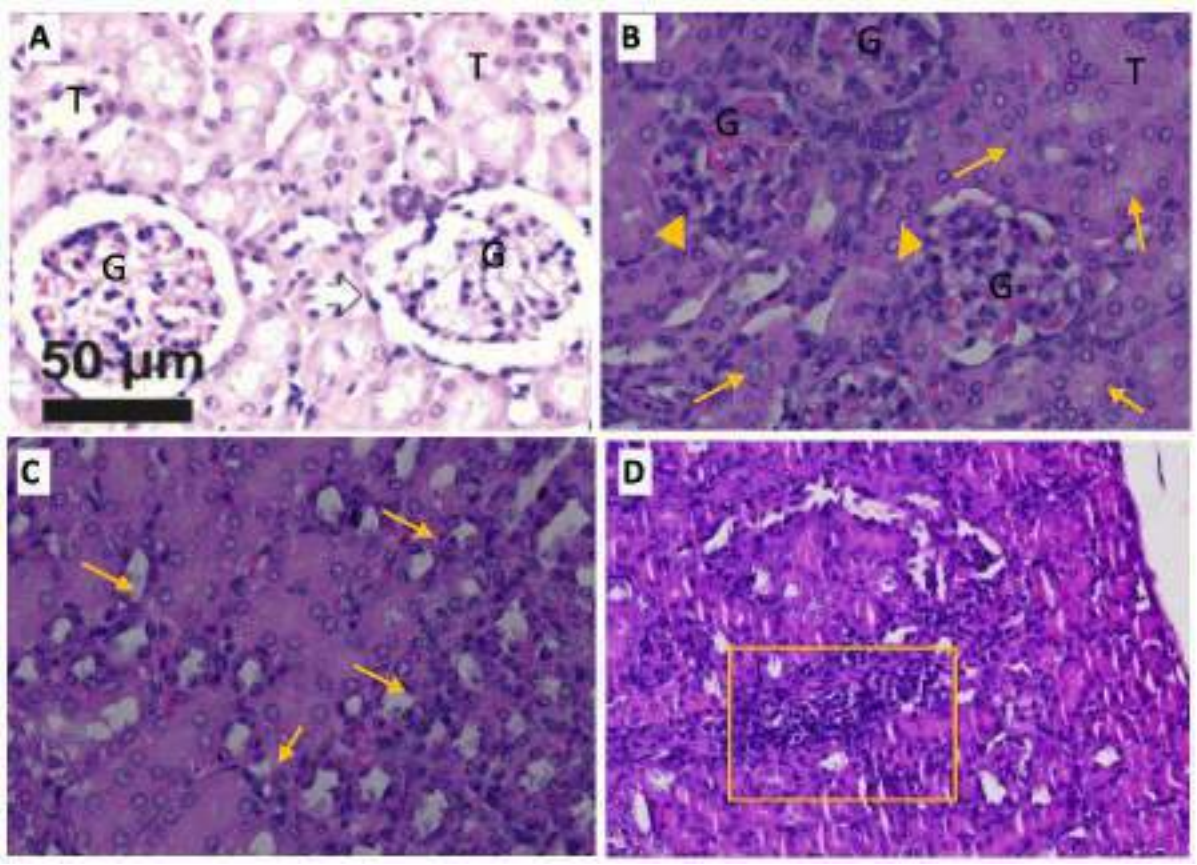

Figure 3. The histologic photomicrograph was observed in *P. berghei* ANKA infected mice with HE stain. Figure A shows a normal kidney with 400x magnification (Source: Lopes et al., 2018); B and C shows 400x magnification and D with 100x magnification. Figure B shows acute tubular necrosis (yellow arrow) and glomerulonephritis (yellow triangle) located in the cortex, Figure C shows tubular necrosis in the medulla; and Figure D shows interstitial nephritis (rectangle).

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DISCUSSION

Kidney dysfunction could be assessed by looking at the alteration in kidney biochemical parameters, namely BUN and creatinine. Particular diseases or medications could cause those alterations. However, several studies showed that VCO could protect the kidney from such alteration (Akinnuga et al., 2014; Famurewa et al., 2020; Nwafor et al., 2020; Sinaga et al., 2019). Daily administration of the oil can significantly reverse the degenerating and destructive effects of diabetes in Wistar rats' kidneys through antioxidant and anti-inflammatory mechanisms (Akinnuga et al., 2014). The phyto-oxidants in VCO could also protect the Wistar rats' kidneys against the paraquat nephrotoxicity in a dose-dependent manner (Nwafor et al., 2020). Administration of VCO can also reduce levels of urea and creatine when rats perform maximum physical activity (Sinaga et al., 2019). The VCO diet also inhibited the renal damage caused by gentamicin with a significant decrease in kidney serum markers (Famurewa et al., 2020).

The effect of VCO on the kidneys in this study was assessed by assessing the alteration in renal histopathology, BUN, and creatinine. The group that was given VCO showed better results than without VCO in the kidneys of mice infected with *P. berghei* ANKA. This result was due to the nephroprotective effect of VCO, as shown in research with methotrexate or gentamycin induction (Famurewa et al., 2017, 2020).

Impaired renal function is characterized by levels of BUN and creatinine exceeding the normal reference limit. This study showed that *P. berghei* ANKA's acute infection did not cause high BUN and creatinine levels in all treatment groups. The two renal biochemical parameters in all treatment groups were still within the normal reference limit. Different results were found in several other studies (Adetutu et al., 2016; Elias et al., 2012). The results of BUN and creatinine in this study indicate that there has been no impairment of renal function as indicated by the value of these two parameters is still below the normal reference or only slightly increases (Charles River, 2012). The effect of VCO administration resulted in lower BUN in the G3 and G5 groups than in the group not given VCO (G1), so it can be concluded that VCO has nephroprotective potential.

Two things mainly cause the alteration that occurs in the kidneys. First, the attachment of *Plasmodium*-infected erythrocytes to the endothelium, and the second one is the rosette phenomenon, which is an infected erythrocyte clotted with normal erythrocytes (Barsoum, 2000; Rowe et al., 2009). Both of these can interfere with microcirculation (Sriboonvorakul et al., 2018). This condition is associated with hemodynamic abnormalities such as hypovolemia and shock (Silva Junior et al., 2017), followed by endothelial activation, accompanied by the release of cytokines and several other inflammatory mediators that play a role in the mechanism of renal impairment in malaria. In addition to cytoadherence, there is also activation of the host's immune response to oxidative stress products during infection (Adetutu et al., 2016). Therefore, giving VCO containing antioxidants can reduce further oxidative damage due to reactive oxygen species.

The histopathological examination of the kidneys observed in this study was acute tubular necrosis, interstitial nephritis, and glomerulonephritis. In this study, there were mild to moderate glomerular and tubular abnormalities (Table 3). Tubular necrosis and glomerulonephritis in the three VCO groups were milder than those in the G1 group, which did not receive VCO. The BUN and creatinine parameters are still within normal limits even though there have been histopathological changes in the kidneys. This shows that the clinical biochemical renal function is still

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good (Table 2). The changes in kidney histopathology in the form of acute tubular necrosis in the VCO treatment group are milder than the G1 control group, so it can be concluded that the severity of tubular necrosis that occurs in *P.* berghei ANKA infection can be reduced by giving VCO or VCO has nephroprotective potential.

There are some of the limitations of this study. There is no analysis of the VCO content fraction/ isolate and no analysis of oxidative stress markers (such as malondialdehyde and catalase). Both analyses should be performed in the future to better understand the effect of VCO antioxidants in malaria infection.

CONCLUSION

The VCO has a nephroprotective potential in *P. berghei* ANKA infection. Acute tubular necrosis and glomerulonephritis in the three VCO groups were milder than those in the G1 group. The BUN levels in the G3 group (treated with VCO at a dose of 1 ml/kgBW/ day) were significantly different from other groups.

Based on the research process that researchers in this study have undertaken, what needs to be done is to analyze the fraction/isolate of VCO content and analysis of oxidative stress markers so that the effect of antioxidants on kidney function can be better understood.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Research Article

Parental first concern according to age and type in children with Autism Spectrum Disorder

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ABSTRACT

Parents' developmental problems are a further diagnostic step for children with Autism Spectrum Disorder (ASD). Research is needed to find a picture of the child's behavior complained of by parents. Investigations about parents' first concerns with ASD and comparisons of the same with children diagnosed with other developmental disorders are rare.We want to examine the type and age of parents' concerns in children with ASD and other developmental disorders. A cross-sectional study was conducted in Child Developmental Centre in Surabaya, Indonesia, from August 1 to December 30, 2019. T-test and chi-square tests were used to analyze differences in subject variables and types of concern. Most parents of both children diagnosed with ASD and non-ASD indicated first concern were in communication, social skill, and behavior problem. The average age of ASD children (54,77 months) is older than non-ASD children (51,44 months), but the average age of parents' first concern was younger for children with an ASD diagnosis (30,14 months) compare with non-ASD children (31,39 months). There is no specific difference type between parental concerns of children with ASD and non-ASD. The average age of first concern was significantly younger for children with an ASD diagnosis than other developmental disorders.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopment disorder characterized by deficits in social communication and social interaction and limited or repetitive behaviors or interests (American Psychiatric Association, 2013). Globally, the number of autistic patients is expected to increase. The Center for Disease Control and Prevention (CDC) in 2014 said the prevalence rate had increased to 1 per 59 children (CDC,2018). One reason is the increase in public awareness and knowledge of parents about the symptoms of autism (Boyd *et al*., 2010).

The high number of children with ASD calls for a proper early diagnosis for early intervention to be done immediately, producing optimal outcomes in children with ASD (Kelley, Naigles, and Fein, 2010). A study by Barbaro and Dissanayake stated that clinicians were expected to be able to diagnose children with autism at an early age, even at the age of 2 years (Barbaro and Dissanayake, 2012) but several studies have shown that patients with ASD were diagnosed in the later age. Research in the United States reports the average age of diagnosed ASD children around four years (Zwaigenbaum *et al*., 2009). Another study in Lebanon says the average age to diagnose ASD is four years and seven months (Akoury-Dirani, Alameddin, and Salamun, 2013).

In contrast to the late diagnosis of ASD in children, parents' concerns about the possibility of developmental delays often appear earlier. Parents can recognize the disorder in children. This can be useful for the early identification of ASD, as mentioned in a study by Becerra-Culqui. The study by Becerra-Culqui claims that the average age of children with ASD when parents first complained about the disorder was 31.5 months (Beccerra-Culqui *et al*., 2018). Another study by Richard said that the average age for complaints from parents to ASD children was 14 months. The study also stated that it is crucial for clinicians to pay attention to parental complaints as part of the diagnostic process (Richards, Mossey, and Robins, 2016).

In addition to the age when parents first raise their concern, studies on the types of concern itself also need to be conducted. Communication disorders become the most common initial complaint reported among parents of children with ASD (Beccerra-Culqui *et al*., 2018; Kozslowki *et al*., 2011; Zablotsky *et al*., 2017). Researchers also report other behaviors that also raised parents' concerns, such as limited/ recurring behavior disorder and socialization disorder (Richards, Mossey, and Robins, 2016; Kozslowki *et al*., 2011).

Parents' concern is the first indicator that a child has a developmental problem. It can be the first step in identifying children who need further screening or assessment. Research conducted to assess the first complaint in parents of children with ASD and compared with other developmental disorders has not been done much. Therefore, this study aims to evaluate and compare the initial complaints reported by parents of children with ASD and not ASD. The study also assessed whether there was an age difference between the onset of the first complaint between ASD and non-ASD children.

METHOD

Study design

A cross-sectional study was conducted in Child Developmental Centre in Surabaya, Indonesia, from August 1 to December 30, 2019.

Participants

One hundred and nineteen children who visited the Child Growth and Development Center in Surabaya from August 1 to December 31, 2019, were screened to participate in this study. Two

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hundred and one children were included, and they fulfill the following criteria: aged between 2 and 6 years with complaints of developmental disorders, parents or guardians agreed to participate in the study and sign informed consent. Children with blindness, deafness, Down syndrome, intellectual disabilities, and cerebral palsy were excluded from the study.

Data collection

The study sample was divided into two groups: The first group was for children who met the diagnostic criteria for ASD, and the second group was for children who have atypical development but did not meet the diagnostic criteria for ASD. The diagnosis of ASD was made by a Growth and Development pediatrician based on the criteria from the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) (American Psychiatric Association,2013). Parents of these children would then fill a socio-demographic data and a questionnaire on the age at which the complaints first appear and the types of complaints.

Ethics

This research was approved by Ethics Committee Universitas Airlangga Institutional Review Board (170/EC/KEPK/FKUS/2019).

Material

Parents' responses on concern were categorized into five items, as adapted from research by Hess (Hess and Landa, 2011). Responses are categorized into the following items: Communication (including speech, verbal communication, and non-verbal communication), motor (including fine motor and gross motor), socialization, behavior/ temperament (including stereotyped/repetitive behaviors, and interests; challenging behavior, for example, aggression; temperamental characteristics such as stubbornness), and sensory (including sensory defensiveness or sensory seeking). All respondents' answers were recorded. If parents complain about more than one problem, every complaint would be recorded according to these categories. The percentage of complaints is calculated both for ASD and non-ASD.

American Academy of Pediatrics (AAP) (2020) stated that the diagnosis of ASD must be established according to DSM-5 criteria (Hyman *et al*., 2020). In the DSM-5, core symptoms were divided into two domains social communication and social interaction and restrictive, repetitive patterns of behaviors). To meet diagnostic criteria for ASD by using the DSM-5, all 3 symptoms of social, affective difference need to be present in addition to 2 of 4 symptoms related to restrictive and repetitive behaviors. The DSM-5 notes that a diagnosis may be made at older ages, when the social or school environment demands may result in functional impairment (American Psychiatric Association, 2013).

Data analysis

T-test and chi-square test were used to analyses differences in subject variable characteristics and types of complaints of research subjects using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA

RESULT

The demographic data for the two groups are present in Table 1. There were no significant differences between the ASD and non-ASD groups in age, sex, order of children and number of siblings, and age and education level of parents.

There were no significant differences between the ASD and non-ASD groups for the parents' first concern about their child's development. The average age when parents first raise their concern was 30.14 months (range = 12-60 months) for children with ASD. This is earlier compared to the non-ASD group, which has an average of 31.39 months (range 10-72 months).

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Table 1. Demographic for subjects and each diagnostic group

Variable	ASD n = 66	Not ASD n = 135	
Child			
Gender, n (%)			
- Male	51 (77,27)	100 (74,07)	0,75
- Female	15 (22,73)	35 (25,93)	
[a]Age (month)			
mean (sb)	54,77 (14,16)	51,41 (14,18)	0,13
median (min-max)	57 (25-72)	52 (24-72)	
[a]Age of concern (month)			
mean (sb)	30,14 (12,34)	31,39 (13,25)	0,49
median (min-max)	24 (12-60)	27 (10-72)	
Birth order, n (%)			
- First	32 (48,48)	66 (48,88)	0,65
- Second	19 (28,79)	45 (33,33)	
- Third or more	15 (22,73)	24 (17,79)	
Number of siblings, n (%)			
- None	27 (40,91)	56 (41,48)	0,57
- One	22 (33,33)	53 (39,26)	
- Two	14 (21,21)	20 (14,81)	
- Three or more	3 (4,55)	6 (4,45)	
Mother			
Age (year)			
Mean (sb)	35,02 (5,17)	33,54 (5,80)	0,81
Median (min-max)	35 (24-47)	33 (20-48)	
Education, n (%)			
- Low	34 (51,51)	84 (62,22)	0,19
- High	32 (48,49)	52 (37,38)	
Father			
[a]Age (year)			
mean (sb)	37,91 (5,22)	36,04 (6,41)	0,02
Median (min-max)	38 (26-48)	35)22-52)	
Education			
- Low	33 (50)	69 (51,11)	1,00
- High	33 (50)	66 (48,89)	

Chi-square test, [a]*Mann-Whitney* test (data distribution is not normal)

Table 2. Percentage of concern by ASD and non-ASD parent groups.

Category	ASD n (%)	Non-ASD n (%)	X^2
Communication	65 (98,40%)	102 (75,55%)	0,00
Social skill	45 (68,18%)	89 (65,92)	0,87
Behavior/temperament	29 (43,93%)	15 (11,11%)	0,00
Sensory	10 (15,15%)	3 (2,22)	0,00
Motoric skill	6 (9,09%)	7 (5,18%)	0,45

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Among the parents of children diagnosed with ASD, the first concerns reported were communication (98.40%), social skills (68.18%), and behavior/temperament disorders (43.93%). Concerns reported by parents of non-ASD children for the first time were communication (75.55%), social skills (65.92%), and behavior/temperament disorders (11.11%) (Table. 2). Parents of children with ASD were significantly more likely to report communication problems ($p < 0.001$), behavior or temperament disorder ($p = 0.001$), and sensory problems ($p = 0.001$) compared to parents of non-ASD children.

DISCUSSION

The expression of parental concerns may be a clinician's first indicator that a child is experiencing developmental difficulties. Therefore, parental input can be essential in identifying children who need further screening or assessment for early diagnosis and intervention, as mentioned in a study by Richard (2016) (Richards, Mossey, and Robins, 2016). AAP also says parental concerns as an essential component of ASD screening (Hyman *et al*., 2020). However, despite the importance of parental concerns in early diagnosis and intervention of ASD, studies that compare parents' first concern between non-ASD children and ASD children are still limited.

The average age of concern for parents of ASD children found in this study is 30.14 months, which is relatively older than the findings in other studies done by Kozlowski (12.94 months), Richard (13.77 months), Becerra-Culqui (32 months), and Zuckerman (30 months) (Kozslowki *et al*., 2011; Richards, Mossey, and Robins, 2016; Beccerra-Culqui *et al*., 2018; Zuckerman, Lindly, and Sinche, 2015). This difference occurs because previous studies use at-risk populations and are conducted on tertiary referral sites. This caused symptoms to be more prominent, thus more recognizable for parents (Beccerra-Culqui *et al*., 2018; Kozslowki *et al*., 2011). A study in China shows a similar average age, which is 3.1 years. This study also stated that the presence of negative stigma and lack of knowledge about ASD also caused parents to raise their concerns at a later age (Qian, Reichle, and Bogenschutz, 2012). The same condition is also present in this study, where parents have low awareness of ASD symptoms and assume that the symptoms will decrease and disappear as the child develop. This caused parents to report concerns about their children's behavior around the age of 3 years old.

This study also reports that parents of non-ASD children first reported their concern at an average age of 31.39 months, longer than parents of children with ASD. This aligns with the results of studies conducted by Zuckerman and Kozloswki which also found that parents of non-ASD children reported concerns about their child's development several months later than parents of ASD children (Zuckerman, Lindly, and Sinche, 2015; Kozslowki *et al*., 2011). However, this finding contradicts the AAP statement that early signs are difficult for parents to detect if ASD symptoms are mild and the child's cognitive abilities are average or above average (Hyman *et al*., 2020).

It has been suggested that mothers with old age and a history of infertility tend to dismiss their children's late developmental signs, resulting in an older age of concern (Chawarska *et al*., 2007). This does not appear to be the case. Results of this study showed that age, mother's education, number of siblings, and birth order were not contributing factors in the age of concern in children with ASD. Studies by Chawarska (2007) and Herlihy (2015) further suggested that birth order and the number of siblings can be significant if the previous children have ASD (Chawarska *et al*., 2007; Herlily *et al*., 2015). However, this study cannot come to a similar conclusion because these supporting data were not collected.

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The results of this study showed that the first concern for most parents in both groups is communication problems, followed by social skills, behavior/temperament problems, sensory and motor skills. These results indicate that the initial complaints reported by parents of children with ASD care not necessarily relate to symptoms of autism. This finding consists of the results of previous studies on similar subjects (Richards, Mossey, and Robins, 2016; Kozslowki *et al*., 2011; Hess and Landa, 2011; Coonrod and Stone, 2004).

In this study, we found that communication problems are the most common complaint seen in both groups. Although communication problem is one of the core aspects of the DSM-5 criteria to diagnose autism, it is not exclusive to autism disorder only and can indicate other global development delays (Richards, Mossey, and Robins, 2016; Kozslowki *et al*., 2011). Parents in the children with ASD group almost all complained about communication problems, compared to 75.5% of parents of non-ASD children. This result shows that communication problems often occur in children who receive various diagnoses of developmental disorders.

Another most common parental concern we found in this study concerns the ability to make social interactions. There is no significant difference in complaints of social interaction between parents of children with ASD and parents of non-ASD children. This study also finds that parental concern about socialization skills arises when the child is around three years of age. A possible explanation for the lack of significant difference between these groups is that these symptoms are not always realized by parents, especially those who have no experience of caring for older siblings or have compensatory mechanisms for children (Coonrod and Stone, 2004; Twymana *et al*., 2009; Karp *et al*., 2017). Socialization skills are also usually acquired in older children when they start to interact with their peers, which might explain why the parental concern of socialization skill might arise later, despite findings by Twyman in 2009 about how socialization impairment can be detected in children as young as 18 months old (Beccerra-Culqui *et al*., 2018; Hess and Landa, 2011; Twymana *et al*., 2009).

The next parental concern that arises in this study is behavior/temperament issues reported by parents when the child is around 3 years old or as the problems arise. Parents tend to dismiss the behavioral problems to realize the concern when the normal developmental phase has passed. It is very hard for parents to recognize ASD-specific behavior in the early years since it usually appears when they are around 2 years old. A study by Sacrey in 2015 found that behavioral issues tend to arise when the child is around 2-3 years old (Herlily *et al*., 2015; Canu *et al*., 2020; Sacrey *et al*., 2015). This condition can be exacerbated by issues caused by other behavioral disorders like ADHD (Zablotsky, Bramlett, and Blumberg, 2017).

One of the least-reported parental concerns in this study is only focusing on certain objects or unusual responses to touch, taste, smell, and/or sound, which is a new criterion to diagnose ASD based on DSM-5 (American Psychiatric Association, 2013). This symptom will often appear in children with ASD, which is following with the result of this study that finding this symptom can differentiate between children with ASD and non-ASD children.

There has been no correlation between parental concern on motor function and ASD. Previous studies have stated that motor disturbance in children with ASD may happen early, even as early as 18 months (Sacrey *et al*., 2015; Lee and Bo, 2015). There is a possibility that in this study, parents did not raise a concern about the motor function of their children until these children have passed the normal developmental phase.

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CONCLUSION

This study found no specific difference type between parental concerns of children with ASD and non-ASD. The main concern of parents of both groups is communication problems, socialization skills, and behavioral issues. Parents of children with ASD would first report concerns at an early age compared to parents of children with no ASD diagnosis.

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Case Report

Successful triple valve surgery in a malnourished patient: what to prepare?

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ABSTRACT

Valvular heart disease accounts for 10% to 20% of all cardiac surgical procedures in the United States. The decision to intervene, as well as the type of intervention for a patient with severe valvular heart disease, should be based on an individual risk-benefit analysis. Once a patient is considered a candidate for cardiac surgery, a comprehensive patient evaluation of medical conditions and comorbidities helps improve operative outcomes and minimize the mortality rate. Patients with severe valvular heart disease with chronic heart failure at times, progressing to malnutrition. Patients undergoing cardiac surgery experience a systemic inflammatory response, which contributes to acute organ injury leading to a higher incidence of comorbidities and worse malnutrition. Therefore, preoperative risk assessment and nutritional assessment are critical to performing safe cardiac surgical procedures. We report a case of a malnourished 17-year-old man with multiple valvular heart disease with optimum preoperative preparation, including nutritional status leading to the good outcome of complex cardiac surgery even in high-risk patients.

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INTRODUCTION

Valvular heart disease has a high prevalence, especially in developing countries, although Indonesia's data is very limited. In recent decades, the epidemiology of valvular heart disease has changed dramatically as socio-economic development and population composition change with older mean ages. However, rheumatic heart disease is still the main etiology of valvular heart disease in the developing country (Soesanto, 2012). The definitive management of valvular heart disease (VHD) includes percutaneous intervention and surgery. In Indonesia, surgery remains the main option for VHD due to valve abnormalities; for example, valve morphology due to rheumatic heart disease. When surgery is decided, a thorough assessment of the patient's condition and comorbid factors is mandatory, including nutritional status (Brinkley & Gelfand, 2013; Moore, Chen, Mallow, & Rizzo, 2016).

Malnutrition and heart disease have been shown to have a strong association, and malnutrition is a predictor of surgery outcome, morbidity, mortality, length of patient care, and cost of hospitalization. Unfortunately, nutritional status is still a factor that is often neglected in the perioperative phase of patients undergoing heart valve surgery (Chermesh et al., 2014; Okoshi, Capalbo, Romeiro, & Okoshi, 2016).

In this case, we present how optimal preoperative preparation involving good nutritional preparation can provide good operative outcomes even with complex surgical procedures in high-risk patients.

CASE REPORT

Male, 17 years old, came to the hospital with shortness of breath for a month, and the symptom was getting worse a week before admission. Dyspnea is felt continuously even at rest, and the stomach is enlarged in the last one month with swelling in both legs. The patient slept in a sitting position. There was no cough or fever. The patient had known he had heart disease for ten years and is often hospitalized for acute heart failure. The patient was last hospitalized six months ago, and after that, the patient was lost to follow up because of his financial problem.

Physical examination showed acute heart failure signs with a general condition of weakness with hypotension (blood pressure 70/50 mmHg) and respiratory rate 28x/minute. On examination of the head and neck, there was icterus, dyspnea, and increased jugular venous pressure (JVP). Chest examination revealed retraction, a diastolic murmur at the apex grade III/IV, and a diastolic murmur of the ICS II right parasternal line. On pulmonary examination, there were bilateral rales. The abdomen showed ascites and hepatomegaly with the liver palpable up to 12 cm below the arcus ribs. There was edema in both legs with cold roots.

The echocardiography examination showed valves with severe MS (planimetric MVA 0.8 cm^2, MVA by mean PHT 0.7 cm^2, MVA by VTI 0.9 cm^2; MV by mean PG 29.35 mmHg, MV by mean PHT 278ms with Wilkins score (2-3-2-2), mitral annular dilatation (4.1 cm) with moderate MR (MR ERO A 0.4 cm^2), MR reg vol 36 ml, Carpentier type I, valve metoaptation RCC and NCC with moderate AR (AR Sdec 3,3 m/s2, AR PHT 387 ms), severe TR (TR ROA/RAA 35%; hepatic reverse flow (+), moderate PR (PR Sdec 2,7 m/s2). Dilated LA (LA major 7.1 cm, LA minor 5.8vm), normal LV (LVIDd 5.0 cm), dilated RA (RA major 6.5 cm, RA minor 5.0 cm) with estimated RAP 15 mmHg, dilated RV (RVDB 3.6 cm) with severe pulmonary hypertension (est. PASP 116.10 mmHg). There was no thrombus/ intracardiac vegetation, and spontaneous echo contrast was obtained in the left atrium. Normal LV systolic function (EF by Teich 71%, by biplane 72%, decreased RV systolic function (TAPSE 1.5 cm0, segmental

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analysis), normokinetic LV there is LVH (LVMI 77.14 g / m2, RWT 0.411).

The ECG examination showed that sinus rhythm tachycardia was 120 bpm with the right frontal axis deviation, normal horizontal axis. The laboratory examination showed anemia (Hb 10.8 gr/dL), hypoalbuminemia (2.63 g/dL), increased direct bilirubin (3.01 mg/dL), and total bilirubin (4.59 mg/dL). Cardiomegaly, with a cardiothoracic ratio of 65%, was obtained from the chest radiograph. From catheterization of the right heart, the pressure in the pulmonary artery was 82/35, RV gradient 15.01, RVA 0.73cm. From LVED pre 16 mmHg left heart catheterization. Ventriculography: Post LVED 19 mmHg, MR grade III CO 3.56 CI 3.14, Aortography: AR grade II, Stroke Volume 37.06, SVI 32.72.

Patients with severe malnutrition, body weight 20 kg, height 140 cm, BMI 10.2 kg/m^2 (underweight). Subjective Global Assessment (SGA) score in this patient was 29 and classified into severely malnourished, and from MUST scoring patient was included a high-risk category. The preoperative risk was also assessed using EuroSCORE I and EuroSCORE II, which included this patient as a high-risk category (7.53% and 33.12%, respectively).

A multidiscipline discussion was held and decided that the operation would be carried out after the patient was relieved from acute heart failure and if the nutritional condition was good because the patient was in severe malnutrition. During hospitalization, because the patient was malnourished and hypo albumin, the patient was also consulted to the Nutrition Team, and it was planned to provide an appropriate high calorie and high protein diet and supplementation with albumin so that the patient's weight could increase and the condition during surgery was more optimal. During hospitalization, the patient developed cardiogenic shock and episodes of atrial fibrillation with sinus recurrence with digoxin. After treatment for approximately one month in the hospital, acute heart failure has been resolved, and the patient's weight has gained 8 kilograms. BMI has gained from 10 kg/m^2 to 14,29 kg/m^2, so the team decided to undergo Double Valve Replacement (DVR) and Tricuspid Valve Repair surgery.

The patient was admitted to the ICU for seven days with a stable condition then continued with the regular treatment room with the results of an echocardiographic evaluation, namely:

Postoperative Trans Thoracal Echocardiography

Valves:

1. Prosthetic mitral valve, good location, and function (peak velocity 1.9 m/s, mean gradient 3.03 MR-PR MV / VTI-LVOT 0.82)

   Effective Orificium Area 2, cm^2
   Pressure Half Time 98 ms

2. Prosthetic aortic valve is well located and functioned (peak velocity 2.51 m/s. Mean gradient 18.46 mmHg, doppler velocity index 0.64, AVA VTI 1.3cm^2

3. TR light (TR max PG 49.42 mmHg)

4. Medium PR (PR Sdec 4.3 m / s2) Cardiac Chamber Dimensions: LA / LV / RA / RV dilated. No thrombus or vegetation was found.

Normal LV systolic function (EF by Teich 62%)

LV E / A fusion diastolic function

RV systolic function decreased (TAPSE 1.0 cm)

Normokinetic LV segmental analysis,

LVH concentric remodeling

After surgery, the patient was discharged with the anticoagulant warfarin and had a significant weight gain.

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DISCUSSION

Significant stenosis or regurgitation can be found in one or multiple valve diseases, especially in rheumatic and degenerative heart disease etiologies. Until now, there is still very limited data regarding valvular heart disease affecting more than one valve (Falk et al., 2017). The prevalence of valvular heart disease in the United States is 2.5% with an increased prevalence proportional to age, 2% in the age group before 65 years, to 8.5% in the age group between 65-75 years and 13.2% above 75 years with the most affected valves are mitral and aortic valves (Brinkley & Gelfand, 2013; Maganti, Rigolin, Sarano, & Bonow, 2010; Manjunath, Srinivas, Ravindranath, & Dhanalakshmi, 2014; Moore et al., 2016). A study in China recruited 3948 adult subjects with valvular heart disease; it is mentioned that 1.04% had multiple valve heart disease (Shu et al., 2016). In line with these data, a study in India with 13,289 subjects having valvular heart disease had a prevalence of 21.4% of subjects had a combination of mitral stenosis and aortic regurgitation (Manjunath et al., 2014).

There are several basic principles for the management of patients with multiple valve heart disease (Falk et al., 2017):

1. If there are stenosis and regurgitation in one valve, treatment or correction is prioritized for the dominant abnormality or valve with a more severe degree, but if stenosis and regurgitation are found in the same degree, the management and intervention are according to the severity index of stenosis and regurgitation.
2. If more than one valve is affected, the management follows the algorithm for each valve lesion.
3. The decision to perform surgery must consider additional risks because the procedure is more complex.

In this patient, the echocardiography examination showed severe MS, severe MR, and moderate AR were accompanied by severe secondary TR due to severe MS. According to the 2017 ESC Guidelines regarding Valvular Heart Disease, Mitral Valve Replacement (MVR), Aortic Valve Replacement (AVR), and Tricuspid Valve repair (TVr) with LA reduction will be carried out.

Preoperative Assessment of Valvular Heart Disease

The principle of VHD surgery preparation is almost the same as preoperative heart disease. Complete medical history and physical examination of the patient along with complete cardiac and extracardiac supporting examinations are mandatory to achieve a standardized surgery preparation so the surgical outcome can be optimized with minimal complication (Bojar, 2011).

Several scoring systems have been developed to help to determine the perioperative risk stratification of cardiac surgery, including the EuroSCORE and Society of Thoracic Surgery Risk score (STS score). The evaluation of each patient's demographic factors, heart disease, and noncardiac comorbidities is needed to assess postoperative morbidity and mortality. Cardiac surgeons are using EuroSCORE I, which is now being deprecated, and started using EuroSCORE II, which is more accurate in distinguishing between low and high risk in patients with valvular heart disease and can better assess postoperative outcome. Classification of risk groups according to the EuroSCORE II scoring system is divided into three risk groups, namely low risk (0-2%), medium risk (3-5%), high risk (>6%)(Bojar, 2011).

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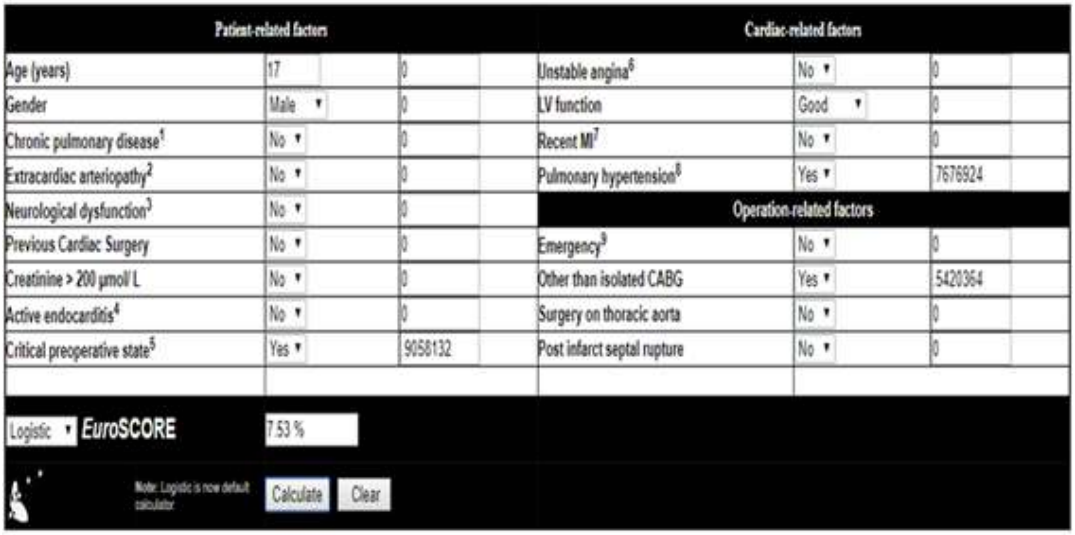
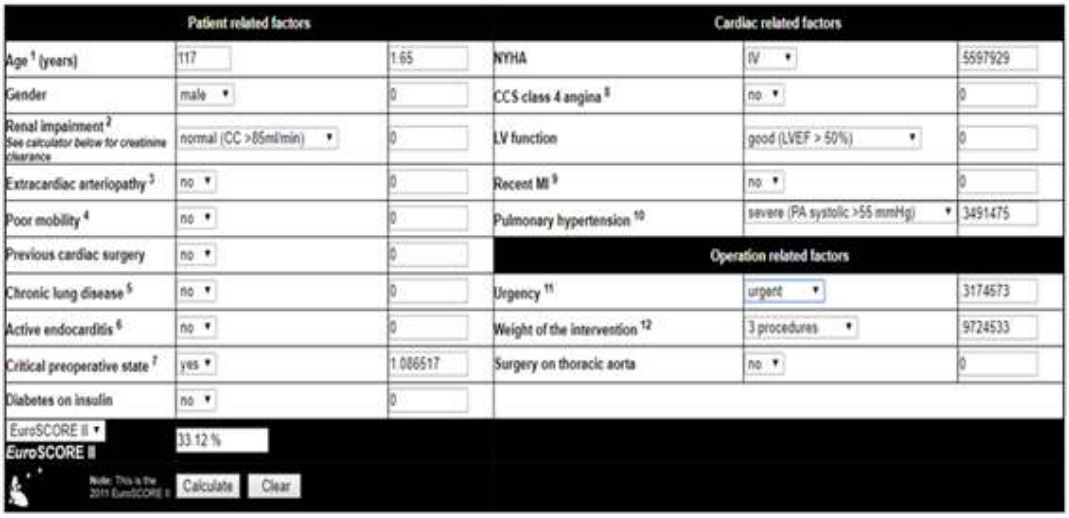


Patient-related factors			Cardiac-related factors		
Age (years)	17	0	Unstable angina[6]	No	0
Gender	Male	0	LV function	Good	0
Chronic pulmonary disease[1]	No	0	Recent MI[7]	No	0
Extracardiac arteriopathy[2]	No	0	Pulmonary hypertension[8]	Yes	7676924
Neurological dysfunction[3]	No	0	Operation-related factors		
Previous Cardiac Surgery	No	0	Emergency[9]	No	0
Creatinine > 200 µmol/ L	No	0	Other than isolated CABG	Yes	5420364
Active endocarditis[4]	No	0	Surgery on thoracic aorta	No	0
Critical preoperative state[5]	Yes	9058132	Post infarct septal rupture	No	0
Logistic EuroSCORE	7.53 %				
Note: Logistic is now default calculator	Calculate	Clear			

Figure 1. Preoperative Risk assessment using the European System for Cardiac Operative Risk Evaluation I (EuroSCORE I) (Source: Bojar, 2011)



Patient related factors			Cardiac related factors		
Age [1] (years)	117	1.65	NYHA	IV	5597929
Gender	male	0	CCS class 4 angina [8]	no	0
Renal impairment [2] See calculator below for creatinine clearance	normal (CC >85ml/min)	0	LV function	good (LVEF > 50%)	0
Extracardiac arteriopathy [3]	no	0	Recent MI [9]	no	0
Poor mobility [4]	no	0	Pulmonary hypertension [10]	severe (PA systolic >55 mmHg)	3491475
Previous cardiac surgery	no	0	Operation related factors		
Chronic lung disease [5]	no	0	Urgency [11]	urgent	3174573
Active endocarditis [6]	no	0	Weight of the intervention [12]	3 procedures	9724533
Critical preoperative state [7]	yes	1.086517	Surgery on thoracic aorta	no	0
Diabetes on insulin	no	0			
EuroSCORE II	33.12 %				
EuroSCORE II	Calculate	Clear			

Figure 2. Preoperative Risk assessment using the European System for Cardiac Operative Risk Evaluation I (EuroSCORE II) (Source: Bojar, 2011)

The patient, in this case, was included high-risk patients on both EuroSCORE I and EuroSCORE II with significantly different risk percentages (7.53% vs. 33.12%), while the STS score could not be taken into account because the patient underwent three valve corrections whereas the STS score only listed one valve with or without CABG.

Malnutrition in Valvular Heart Disease

Malnutrition is common in patients with both structural and congenital heart disease. Structural abnormalities result in insufficient nutrients to meet the needs of biological metabolism; reduced body mass also reduces myocardial function and ventilation, prolongs the healing period, and decreases the immune system with an increased risk of infection.

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Therefore, patients with structural and congenital heart disease are classified as a high-risk group for malnutrition (Monteiro et al., 2012). Malnutrition is an independent prognostic factor for mortality in patients who have fallen into heart failure, which is then termed "cachexia cardiac". The impaired heart will induce a systemic response characterized by neurohormonal and inflammatory activation. Initially, both processes have cytoprotective benefits, but over time they will maladapt. The cytokines that play a role mainly TNF-α, originally called cachexia, regulate more than 150 genes (Rahman et al., 2014).

Heart failure is believed to be a multi-systemic disease on the basis of chronic inflammatory pathophysiology. TNF-α can interfere with the gastrointestinal system causing changes in the intestinal barrier and transport protein dysfunction along with the increasing gastrointestinal permeability and then causing bacterial translocation. This process plays a role in reducing nutrient absorption in patients, which then leads to malnutrition. TNF - α will directly cause a direct depressive effect on the myocardium; besides that, it will also activate various cellular effects through the nuclear factor-κB (NF-κB) pathway, which causes ischemia, increased insulin resistance, decreased exercise capacity, and decreased appetite so that it will worsen cachexia (Pompéia et al., 2012; Rahman et al., 2014).

Inflammation on Cardiac Surgery

Patients undergoing cardiac surgery will suffer from a complex systemic inflammatory syndrome, which manifests as pyrexia, tachycardia, leucocytosis, hypotension, edema, and organ failure. Some stimuli will cause an inflammatory reaction during and after surgery. Trauma due to surgery will activate neutrophils, endothelial cells, platelets, and trigger the release of pro-inflammatory mediators such as TNF-α and various kinds of interleukins (IL). Contact between foreign surfaces during activation of the Cardiopulmonary Bypass (CPB) machine will activate leukocytes, platelets, and several cellular components such as the complement system as well as the calicrein cascade, which induces inflammatory mediators such as TNFα, IL-1, IL-6, and IL-8. After a period of ischemia during aortic cross-clamping, the tissue reoxygenation process will also trigger an ischemic response, namely ischemia and reperfusion injury (I / R injury). Enteral hypoperfusion at the time of surgery also increases mucosal permeabilities of the gastrointestinal tract, thereby facilitating bacterial translocation. This inflammatory process also underlies the complications of various organs' dysfunction after cardiac surgery (Hill et al., 2018; Rahman et al., 2014).

Role of Nutrition and Nutrition Status Scoring in Patient undergoing Cardiac Surgery

Malnutrition is a sub-acute or chronic nutritional disorder, either excessive or nutritional deficiency accompanied by inflammatory activity that causes changes in body composition and reduced body function. Cardiac surgery patients who are malnourished have been shown in various studies to experience worse surgical outcomes, including higher morbidity and mortality.

To minimize these problems, examining good nutritional status predictors will help the clinician determine further management and whether a surgical correction is needed. Detecting patients at a high risk of malnutrition is essential for adequate management. Nutritional assessment scores have recently been updated but have not been validated for the cardiac patient population and are rarely used in cardiac surgery. Currently, there are several scoring modalities that can be used to assess nutritional status, including the Short Nutritional Assessment Questionnaire

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(SNAQ), the Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), Nutrition Risk Screening 2002 (NRS-2002), Mini Nutritional Assessment. Short-Form (MNA-SF) and Subjective Global Assessment (SGA). Lomivorotov et al. reported a reasonably high malnutrition rate in patients undergoing cardiac surgery, namely 4.6–19.1%. Investigators suggest that most of the screening tools available are insensitive to assess postoperative risk.

In clinical practice, malnutrition is usually diagnosed formally or informally through history taking and anthropometric measurements. Body Mass Index (BMI) links body weight and height. In the general population, BMI <20 kg / m2 may indicate severe malnutrition in the elderly or malignant population but not in the patient population with cardiovascular disease because of edema, which can be a confounding factor in calculating lean body mass. The acute and chronic disease usually affects lean body mass or lean mass more because the decrease in muscle mass may not be reflected by a decrease in BMI. However, BMI is still very popularly used to assess a patient's nutritional status quickly.

Subjective global assessment (SGA) combines elements of history and physical examination and has been validated as a tool for assessing malnutrition in a variety of conditions. When SGA is applied to cardiac patients, most of them will be assessed for malnutrition than the standard anthropometric measurement combined with albumin and leukocyte values (Gonçalves, Jesus, Gonçalves, Deiró, & Dias, 2016; Rahman et al., 2014; Stoppe et al., 2017).

The Malnutrition Universal Screening Tool (MUST) is a relatively new nutritional assessment score. This score combines BMI, unintentional weight loss, and acute illness to predict nutritional risk. This score is easy to apply because it is designed for a variety of populations without specific measurements. The MUST score aims to stratify patients into groups requiring only observation or intervention. The MUST score has been studied to predict mortality in cardiovascular patients, but no studies have used this score in a population that has already fallen into the cardiac cachexic phase (Gonçalves et al., 2016; Stoppe et al., 2017).

Malnutrition should be treated as a dynamic condition. It can be diagnosed early when abnormalities in laboratory tests are combined with a history of weight loss and a physical examination of decreased muscle mass. Laboratory tests that are usually associated with malnutrition are anemia, hypo albumin, and prealbumin, low total cholesterol, and lymphopenia. Malnutrition is often not diagnosed if we only use BMI because of the overload condition, which is a confounding factor for BMI. Drastic changes in body weight are usually caused by overload conditions and response to diuretic therapy, but slower changes in body weight usually indicate changes in nutritional status, especially when accompanied by a stable patient's condition and build-up of muscle mass (Lomivorotov et al., 2013; Ringaitienė et al., 2016; Stoppe et al., 2017).

In this case, we found a patient with chronic malnutrition that was quite severe supported by anamnesis, physical examination of muscle mass loss, and laboratory results that showed anemia, hypoalbumin, thus requiring the Nutrition team intervention to optimize preoperative conditions. And according to the available literature, with the intervention of The nutrition team and the interventions for heart failure therapy, the patient gained 5 kilograms in 1 month. The patient underwent surgery and got good results. Post-surgery with valve replacement correction and improved cardiac function, the patient experienced a significant improvement in nutritional status after surgery.

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CONCLUSION

Valvular heart disease has a fairly high prevalence, especially in developing countries, although there is no data yet for prevalence in Indonesia. Patients with an indication for surgery are expected to achieve an excellent postoperative outcome with a better quality of life. Therefore, preoperative evaluation is very important because it is related to the safety and success of cardiac surgery procedures, especially in valvular heart disease. Several data that need to be prepared before surgery are the patient's medical history, physical examination, both cardiac and extracardiac, stratification of the risk of surgery using the STS and EuroSCORE scoring system, and several supporting examinations in order to minimize postoperative morbidity and mortality. The supporting tests used to complement the preoperative process are laboratory tests, non-invasive examinations (echocardiography, exercise tests, MRI, and CT scan), to semi-invasive cardiac catheterization. Malnutrition and heart disease have also been shown to have a strong association, and malnutrition is a predictor of surgical outcome, morbidity, mortality, length of patient care, and hospitalization costs. Unfortunately, nutritional status is still a factor that is often neglected in the perioperative phase of patients undergoing heart valve surgery. Optimal preparation and complementary investigations can reduce the mortality and morbidity of postoperative patients with a higher survival rate.

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Case Report

Anosmia and Covid-19 in Yogyakarta, Indonesia: a case series

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ABSTRACT

Covid-19 (coronavirus disease 2019) had spread to the whole world. This kind of virus attacks the human respiratory system, and it caused death. In other words, there were many symptoms of Covid-19, which attacks the respiratory system. One of the symptoms was anosmia or smell disorder. This research might provide information about the anosmia in Covid-19 patients. This study aimed to investigate and present a series about anosmia and Covid-19 in Yogyakarta on June 2020. Three cases from three patients of RT-PCR-confirmed SARS-CoV-2-infected patients diagnosed with smell disorder were presented, starting from the symptom until the patients were getting treatments. This research also explained anosmia as one of the symptoms of Covid-19.Anosmia or losing olfactory function or smell disorder which could distract people's healthy. Then, in this situation, it could be one of the symptoms of Covid-19.

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INTRODUCTION

In the world of health this year, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or presently known as coronavirus disease 2019 (Covid-19) is a major issue. SARS-CoV-2 is included in the family of coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome (MERS) –CoV, (Lai, et. al,. 2020; Kang, et. al., 2020). In December 2019, Covid-19 was first reported in Wuhan, China, (Zhu, et. al,. 2020; Wu, et. al., 2020). Covid-19 then spread rapidly across the countries, including Indonesia, (Azwar, et. al., 2020). The World Health Organization (WHO) declared a pandemic for the first time on On 11 March 2020, (Cucinotta & Vanelli, 2020).

Covid-19 can be caused by symptoms of smell disorders or anosmia, based on previous research. According to Gane, et. al., (2020), there is an increased presentation of asymptomatic anosmia in the UK population during the early phases of the pandemic. In several other countries, the same is true. German virologist Hendrick Streeck reported a loss of sense of smell and taste in more than two-thirds of 100 people who have interviewed mild symptoms of Covid-19 (Brodwin, 2020). A bulletin detailing the vital link between Covid-19 and anosmia or hyposmia was published by the Ear, Nose, and Throat Society of the UK and the British Rhinological Society on 20 March 2020. The American Academy of Otolaryngology also states that the symptoms used for screening for Covid-19 are added to anosmia, hyposmia, and dysgeusia (in the absence of other respiratory diseases), (Brann, et. al., 2020). Although some of anosmia were one of symptom drom Covid-19, Indonesia's anosmia cases, especially in Yogyakarta, still have not yet reported as many as other countries.

Coronavirus-19-related anosmia and hyposmia is a newly emerging concept in the medical literature (Mubaraki, et. al., 2021 (p. 1). As anosmia could be the symptom of Covid-19, physicians should be more aware of handling the patients and their own healthy (Hariyanto, et. al., 2020). Mutiawati, et. al., (2021) supported that anosmia could be the earliest symptom of Covid-19. Therefore, people include physicians, should be more aware of this case.

This case series reported three patients who had been diagnosed with Covid-19 used RT-PCR test. Then, this research focused on anosmia as their symptom, and the patients' treatment was nasal irrigation. In this case series, the researchers aimed to identify anosmia's clinical presentation in Covid-19 patients in Yogyakarta, Indonesia.

CASE REPORT

The case series had been conducted with three anosmia patients during June 2020. The patients did history taking and physical examination and have been asked to fill the form for this research.

The first case came from a 33 years old female, a general practitioner, who presented with smells disorders. There was a history of flu-like symptoms in the last 1 week. The patient had a fever, myalgia, fatigue, and dry cough. The patient had no nasal obstruction symptoms, facial pain, and no history of respiratory system diseases such as rhinosinusitis, hypertrophy of chonca, or brain disease. The vital sign within normal limits. Anterior rhinoscope examination showed inferior and media chonca within normal limit, and there were no discharge, nasal septum within normal limit. The patient was diagnosed as Covid-19 based on positive result of real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasopharyngeal and oropharyngeal swab specimens five days after the symptoms. The patient was given the

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Covid-19 treatment and regular nasal irrigation with saline nasal irrigation. The smells disorder was getting better within 5 days.

The second case came from a male 20 years old, student, presented to ENT clinics with loss of his sense of smell for 3 days. The patient did not have other symptoms like fever, nasal blockage, facial pain, or runny nose. There was no history of respiratory system disease and brain disease before the test of Covid-19. The general vital sign and the nasal examination within normal limit, and there was no hypertrophy conchae and discharge on the nasal cavity. The patient was suggested to perform a real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for Covid-19 from nasopharyngeal and oropharyngeal swab, and the result was positive. The patient suggested performing nasal irrigation with saline nasal irrigation and intranasal steroid. Then, smell disorder was getting better within 1 week.

The third case came from a male 28 years old, a doctor, who presented with smell disorder. There was a history of flu-like symptoms in the last 3 days. The patient had a fever, myalgia, fatigue, dry cough, diarrhea, nausea, and vomitus. In this patient, there was no history of the nasal disease, sinus paranasal, and brain disease. The inferior and medial conchae were within normal limit, septum nasi within normal limit, and no discharge in anterior rhinoscopy examination. The patient was diagnosed as Covid-19 based on a real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasopharyngeal and oropharyngeal swab specimens 2 days after the symptoms. The patient had smell disorder 3 days after the positive result of the RT-PCR assay. Then, he was given the Covid-19 treatment and regular nasal saline spray. The smells disorder is getting better within 4 days.

DISCUSSION

Anosmia is one of the smell disorders that may attack human's immune and cause several impacts on the respiration organ (Carrillo-Larco & Altez-Fernandez, 2020). Gane, et. al., (2020) stated that its other name is olfactory dysfunction, making people have difficulties smelling. This problem is a serious problem for every human being. The upper respiration consists of nose, pharynx, and larynx. They have the essential roles in keeping human's healthy by did respiration well (Eliezer, at. al., 2020). If they cannot do it well, people can get sick such as smell and taste disorders.

According to Hopkins, et. al., (2020), anosmia can be defined as well-reported coronas virus symptoms. The study that has been conducted shows that otolaryngologists reported anosmia as one of the symptoms of Covid-19 and this is happen almost in all cases (Lechien, et. al., 2020). It has been supported with a statement that stated that anosmia and hyposmia often occur unnoticed in Covid-19 patients (Hornuss, et. al., 2020). The other founding showed that anosmia may be one of the diseases that occurred when a person got Covid-19. The previous study reported that the incidence is not known and the pathogenesis of the disease behind this manifestation is still not fully understood, (AlKetbi, et. al., 2020; Marinosci, et. al., 2020).

Meanwhile, the pathophysiology of those symptoms had not been accepted. Any kind of animals have proven the high levels of angiotensin-converting enzyme (ACE2) proteins expression by nasal and olfactory support cells, which the SARS-CoV-2 uses to infect the cells. Many people believe that the symptoms might be part of the neurological manifestations of Covid-19, with evidence suggesting propagation of the virus through the

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olfactory path (Dev, et. al, 2021). Therefore, without knowing the exact cause and effect of Covid-19, people should be aware of their health and check for their respiration healthy to measure that they do not lose their smell function.

The result showed that the first, second, and third patients had differences when they got into Covid-19. For the differences, the first patient had a fever, myalgia, fatigue, runny nose, and dry cough and smell disorder, while the second patient had smell disorder without other symptoms. Besides, the third patient had smell disorder, flu, fever, myalgia, fatigue, dry cough, diarrhea, nausea, and vomitus. Each patient has their symptom, but in general, they got smell disorder before they were diagnosed as a positive Covid-19. One way to detect a patient is with a sniffing test because it relates with the olfactory function, and by sniffing test, people will know either they were detectes of having anosmia. In the three cases, anosmia only has been counted subjectively based on the patients' symptom. That were caused by the unavailability of facilities to did smelling test such as sniffing test. In the other case that happened, anosmia usually occurred before the patient did test to detect Covid-19, the patient usually felt the anosmia with other diseases, such as fever, asthma, dysgeusia, myalgia, sore throat, fatigue, diarrhea, and other diseases, (Klopfenstein, et. al., 2020). The three patients had the same test to diagnose the Covid-19, by using a real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay from nasopharyngeal and oropharyngeal swab. The next differences were the treatment. Each patient got a different kind of nasal irrigation. The first patient got treatment and regular nasal irrigation with saline nasal irrigation. The second patient got nasal irrigation with saline nasal irrigation and intranasal steroid, and the third patient with treatment and regular nasal saline spray. The last result of the differences on the three patients above was the duration of their recovery. It was found that the first patient felt better for their smell disorder in 5 days, while and the second patient assumed in 1 week, the third patient in 4 days. The different symptoms that had been recovered by different treatments cause different durations on the recovery time, but this is still debatable because there is no exact finding that showed certain treatment has certain results for the patient.

The recommendation in doing nasal irrigation as the additioal treatment for people to avoid or even to decrease the risk of Covid-19 because nasal irrigation can remove antigens, inflammatory mediators, and microorganisms such as bacteria and viruses, (Casale, et. al., 2020). The other treatment for reduces the risk of Covid-19 are saline nasal irrigation (SNI), nasal spray, antimicrobial mouthwashes (gargling), and stuff (Casale, et. al., 2020; Burton, et. al., 2020). According to the previous research, this kind of treatment can be used, but it did not recommend as the main treatment in anosmia recovery, especially in Covid-19. *Perhimpunan Dokter Spesialis Telinga Hidung Tenggorok Bedah Kepala Leher* (PERHATI-KL) in Management Guidelines in the Field THT-KL during Covid-19 pandemic book stated in the basic principle that suit with the management of cases of anosmia caused by other viral infections, namely a combination of nasal washing using 0.9% NaCl solution, intranasal corticosteroids, topical decongestants, and zinc preparations, (Hediyanti, et al., 2020). Rhinological Society explained that certain oral medicine and nasal steroids could not be given to the patient as one of its treatments. Therefore, if there were patients with sudden anosmia, it was better to do test for Covid-19 than do treatment first because it could be the potential individuals with Covid-19 (Krajewska, et al., 2020). The limitation of the study was the patients did not do more check-ups to know the function of the olfactory such as used sniffing tests.

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CONCLUSION

Anosmia or losing olfactory function or smell disorder can distract people's healthy and in this situation, it may be one symptom of Covid-19. Besides, there is still no exact proof that it could be the only symptom that measures Covid-19. One and another patient has a different symptom; even some people are positive Covid-19 without symptom. Some Covid-19 patients do not get anosmia but get other symptoms such as fever, cough, flu, runny nose, and etc. This case series may help people get information about anosmia related to Covid-19 cases that happended and may be the information for the reader and the health worker to be more aware of getting at patient recovery.

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Case Report

Palpebral non-hodgkin lymphoma with non-specific reactive hepatitis

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ABSTRACT

Extranodal Non-Hodgkin Lymphoma (NHL) remains an odd issue and something to discuss. Clinical evidence and guidelines on the treatment have not yet been broadly published and accessible. Here, we present a case of a thirty-eight years old woman complaining of mass on both lower lids of the eyes. The CT Scan examination showed enhancing solid masses on right-sided and left-sided palpebra inferior that press bulb oculi, suspected as bilateral malignant masses of bilateral palpebra inferior. Laboratory data revealed the surge of liver function marker. The patient was eventually diagnosed with Non-Hodgkin Lymphoma (NHL) of palpebra inferior B cell type high-grade stadium II E. Although there are still ongoing research and development of definitive treatments, R-CHOP a regiment given to this patient has shown complete favorable result with dosage adjustment due to the surge of basal liver function. The regiment was considered safe since no adverse effects reported

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INTRODUCTION

Extranodal Non-Hodgkin Lymphoma (NHL) is a complex and rare case; approximately 30% of NHL are extranodal lymphoma. Extra-nodal NHL can arise from any organ, including palpebra, NHL of palpebra 1-10% of NHL cases. Mean-age diagnosed NHL of palpebra 15 years old and 70 years old (Eckardt, Lemound, Rana, & Gellrich, 2013; Nanthakwang et al., 2019; Vannata & Zucca, 2015)

Extranodal Non-Hodgkin Lymphoma is mainly diagnosed at the advanced stage. The condition of patients was associated with immune-compromised, progressive disease or bulky disease, often relapses, poor prognosis, and rare incomplete response (Vannata & Zucca, 2015). NHL of palpebra was commonly a bulky disease and often partial response, relapses, or recurrent (Svendsen et al., 2017).

According to many case reports, there is no specific treatment for NHL of the palpebra. Triple modalities (surgery, chemotherapy, and radiotherapy) were commonly used for treating NHL of palpebra (Shikino & Ikusaka, 2019; Svendsen et al., 2017). Our case will discuss the diagnostic approach and modalities of therapy from NHL of the palpebra.

CASE

Thirty-eight years old female, married, having two children, lived in Lamongan, East Java. She came with masses on the bilateral palpebra inferior. The first mass was on the right-sided palpebra inferior, which appeared two years ago during her second pregnancy at five months of gestational age. Mass became larger, solid, and grew bilaterally. There was no tenderness, no pus and blood, and discolorization. Right-sided palpebra inferior mass looked like bekel ball, and left-sided mass palpebra inferior looked like a nut. The patient did not have abnormal vision and movement of orbital muscles and destruction structure around orbital. After giving birth, mass was still there, and the patient did not have weight loss and fever without unknown origin.

The patient visited Ngimbang Hospital, Lamongan, in February 2019 since the mass became larger then she was referred to Dr. Soetomo General Hospital in March 2019. CT Scan result showed enhancing solid mass on the right and left sides of inferior palpebra, pressing bulb oculi to be posterior, showed a suspicious bilateral malignant mass of palpebra inferior, showed no extended intra-ocular lesion to the left or right side, and bilateral submandibular lymphadenopathy bilateral as well. (Figure 1).

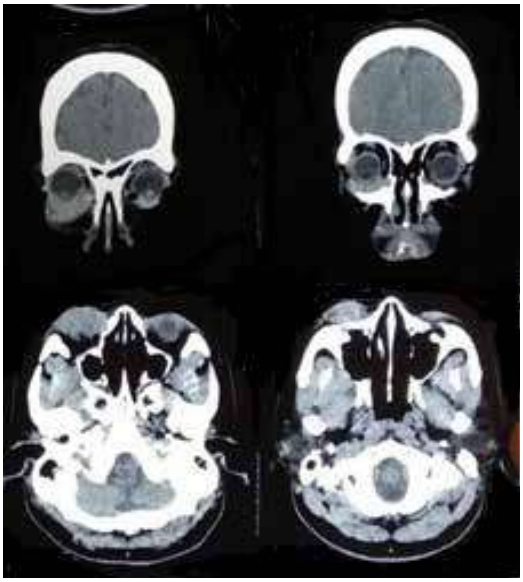

Figure 1. CT-Scan Orbital. Enhancing solid mass size +/- 3,2x1,9x1,75 cm on right-sided inferior palpebra and +/- 2,6 x 0,8 x 1,2 cm on left-sided inferior palpebra, pressing bulb occuli to posterior, suspicious bilateral malignant mass of inferior palpebra, no extended intraocular lesion to left and right sides, submandibular lymphadenopathy.

Liver function marker showed AST/ALT 65/110, negative HbsAg negative, negative anti HCV, negative IgM anti HAV, and normal AFP (3.3 mg/ml). Abdominal ultrasound showed parenchymal liver disease. In the meantime, the result of Fibroscan F2 from the right-sided palpebra inferior showed a suspicious

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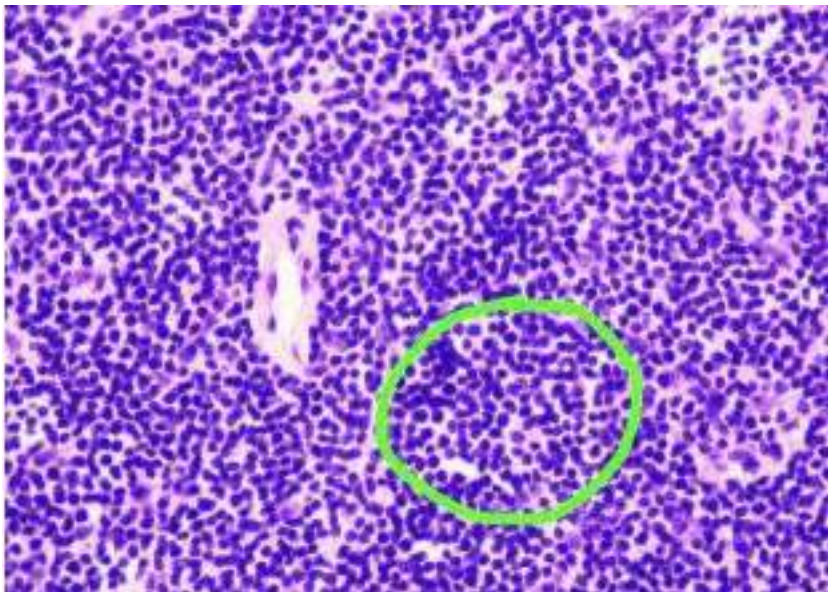

Figure 2. Histopathology of NHL biopsy specimen taken from right palpebra.

lymphoid tumor with Non-Hodgkin Lymphoma (NHL) and inflammatory pseudotumor as differential diagnosis. (Figure 2). IHC result showed positive CD 20 positive, negative CD 3, Ki 67 proliferation index 40%, Non-Hodgkin Lymphoma, B cell type high grade.

The patient was diagnosed with NHL of palpebra inferior B cell type high-grade Stadium II EA. Chemotherapy using regiment R-CHOP was performed every three weeks and six cycles. After the first chemotherapy, we started adjusting the dose due to the surge of AST/ALT level to 109/152. Dosage was not modified until six cycles finished.

The fourth cycle and sixth cycle chemotherapy evaluation showed complete response with ADE grade 0 without significant increase of AST/ALT level (82/93). No abnormality of vision, orbital muscle movement, and destruction structure around orbital during and after sixth cycle chemotherapy. The patient didn't undergo radiotherapy. CT-Scan evaluation after six months of chemotherapy showed no relapse or recurrence of the palpebral mass.

DISCUSSION

Palpebral NHL is one of extranodal NHL; it is a rare and aggressive form of lymphoma. Palpebral NHL is lymphoma that infiltrates the pre-septal tissue, which includes the skin, subcutaneous, and/or orbicularis oculi muscle. Palpebral NHL is also part of ocular adnexal lymphoma (OAL). Since the palpebra is made up of skin, there is also a palpebral lymphoma in the form of cutaneous lymphoma. Palpebral NHL affects mainly 52% of men and 48% of women with 56% of B-cell origin and 44% of T-cell origin. Patients diagnosed with palpebral LNH were mainly at the age between 15 and 70 years. The most common type of B-cell lymphoma was extranodal marginal zone lymphoma (MALT) (14%) and diffused large B-cell lymphoma (9%). Palpebral LNH is part of the ocular adnexal lymphoma (OAL) in only about 8% of cases. Most cases occur in Asia and Europe (Eckardt et al., 2013; Nanthakwang et al., 2019; Priego, Majos, Climent, & Muntane, 2012; Svendsen et al., 2017).

History taking from the patients revealed a record of a lump that enlarged slowly with or without visual disturbances. Visual

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disturbances are caused by a pressing mass in the orbital area. History of visual disturbances, worsening quality of visual fields, and restricted orbital muscle motion suggest that primary lymphoma may not come from the palpebra but the orbit or systemic disease. Past medical history of patients with autoimmune diseases such as Sjörgen Syndrome, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), autoimmune thyroid disease enhances the risk of palpebral NHL development. Besides, a history of HIV / AIDS which bring patients to an immunosuppressive state also increases the risk of developing palpebral NHL (Borghi et al., 2013; Eckardt et al., 2013; Hahn et al., 2001; Mbulaiteye, Parkin, & Rabkin, 2003; Nutting, Shah-Desai, Rose, Norton, & Plowman, 2006; Priego et al., 2012; Svendsen et al., 2017).

A patient with NHL palpebra came complaining of a solid and painless mass. The superior palpebrae were more frequently affected; most cases were unilateral mass with a similar ratio of the right and left palpebrae (51% vs. 49%) rather than bilateral. The constitutional symptoms at the time of diagnosis of palpebral NHL are uncommon, but they indicate a poor prognosis if they emerged. Physical examination may reveal palpebral swelling and prolapse with single or multiple lymphadenopathies. Palpebral masses may be accompanied by ulcers that cause a secondary infection. Eye examination of palpebral NHL may be accompanied by disturbance of orbital muscle movement and intraocular pressure increase due to mass pressure. Visual field disturbance indicates a systemic lymphoma. The role of an ophthalmologist when performing intraocular and extraocular evaluations is vital before beginning the following diagnostic steps (Eckardt et al., 2013; Marcus, Sweetenham, & Williams, 2014; Svendsen et al., 2017).

We used CT-Scan, MRI, or PET scan to evaluate the extension of the mass to the orbital, lacrimal gland, and intracranial. CT-scan shows a well-defined mass adhering to the surrounding orbital structure with a homogeneous and heterogeneous density. Homogeneous densities describe no bone destruction, while heterogeneous densities describe one and indicate high-grade lymphoma. CT scan could assist in the biopsy process with a CT-guided biopsy if there were an extension to the orbit or structures around the orbit. MRI evaluation helps determine intraconal or extraconal involvement of the LNH palpebra. If intraconal was involved, the radiological differential diagnosis could be meningioma, glioma, or cavernoma; while the differential diagnosis of extraconal involvement could be pseudotumor inflammation, tumor of the lacrimal gland, thyroid orbitopathy, or metastases. A PET-Scan examination is used to figure out the extent of involvement of the affected lymph nodes. This radiological examination helps the ophthalmologist to determine the location of the biopsy and evaluate the complete resection if needed. It also aids the interventional radiologist in planning radiotherapy (Amit, Purwar, Agarwal, & Kanchan, 2012; Pfeffer et al., 2004; Priego et al., 2012).

A palpebral biopsy was performed to obtain pathological specimens as a diagnostic tool. The anatomical pathology of palpebral NHL shows large lymphoid cells with a nucleus doubled in size of normal lymphocyte nuclei and no Reed Stenberg cells. These pathologic features can be differentially diagnosed with pseudotumor inflammation, which is the most common feature on a biopsy of a palpebral mass. The IHC examination will be beneficial in determining the mass of B-cell or T-cell lymphoma. IHC that were determined are CD3, CD5, CD 10, CD20, CD23 CD43, CD 79a, bcl-6 and Ki67. The Ann-Arbor system is used in LNH staging (Marcus et al., 2014;

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Vallinayagan, Krishnamoorthy, Vijayakumar, & Suryawanashi, 2017; Wali & Al-Mujaini, 2010).

The standard of therapy for palpebral NHL is currently still unclear. Palpebral NHL is a rare case, and there is no yet prospective randomized clinical trial available. Complete excision is performed on solitary low-grade lymphoma and combined with chemotherapy or radiotherapy. Two cases of palpebral NHL in the form of ocular adnexal lymphoma showed satisfying results with surgery alone. Unfortunately, surgery alone showed a high relapse rate in other types of palpebral LNH, and long-term post-operative monitoring without adjuvant chemotherapy is unknown. The role of a craniomaxillofacial surgeon is undoubtedly needed in a multidisciplinary team if the palpebral NHL is to dissect the orbits and the structures around the orbit (Marcus et al., 2014; Nola et al., 2004; Svendsen et al., 2017).

Chemotherapy on palpebral NHL is used for high-grade tumors with or without radiotherapy. Since the rituximab era began after 2006, there had been an improvement in the prognosis of patients with palpebral LNH (Chihara et al., 2019; Olsen et al., 2019; Svendsen et al., 2017). The first-line chemotherapy regimen used to treat palpebral LNH is primarily CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); if CD20 is positive, we use R-CHOP (Rituximab, cyclophosphamide, doxorubicin/ epirubicin, vincristine, prednisone) every 21 days for 6-8 cycle. The dosage of Rituximab is 375 mg / m2, cyclophosphamide 750 mg / m2, Doxorubicin 50 mg / m2, and Vincristine 1.4 mg / m2, Prednisone oral 50 mg / m2 per day for 5 days (Skeel & Khleif, 2011).

According to the 2015 European Society for Medical Oncology (ESMO) guidelines, patients with large extranodal NHL <10 cm in size and a score of zero according to the International Prognostic Index (IPI) will receive R-CHOP chemotherapy every 21 days for six cycles with radiotherapy (Tilly et al., 2015). Meanwhile, based on the guidelines of The National Comprehensive Cancer Network (NCCN) in 2019 for stage II with bulky disease, the recommended regimen is R-CHOP 6 cycles with or without radiotherapy (Zelenetz et al., 2019).

Chemotherapy side effects are evaluated through the onset, target organs, and severity. Based on the onset of drug side effects, they are divided into acute (less than 1 hour after drug administration), early (1-48 hours after drug administration), delayed (2 days - 2 months after drug administration), and slow (2 months after drug administration). For monitoring of target organs and severity, it is divided into grades 0 to 5. Grade 0-2 means that it is quite safe, does not need therapy, grade 3 means that you need to be aware that sometimes you need therapy, grade 4 means that danger signs can occur that death needs early and adequate treatment, and grade 5 means the patient is dead. Side effects that often occur less than 1 hour or 1-24 hours cause symptoms such as nausea and vomit, febrile, hypotension, and symptoms of such as severe pain, erythema, and hematoma at the injection site of chemotherapy drugs. Symptoms that arise from the slow type of chemotherapy were fatigue, weakness, tingling, difficulty concentrating, heart problems, reduced lung capacity, kidney and urinary disorders, and liver problems (Ashariati, 2015).

Adjustment of chemotherapy doses can be considered after liver function or creatinine clearance measurement (Skeel & Khleif, 2011). A surge in AST/ALT by 2.5-10 times of expected value indicates a liver disorder that requires chemotherapy dosage adjustment. The chemotherapy dose in this situation is reduced by about 50% of the initial dose. If it increases> 10 times the normal value or Total bilirubin > 3 mg/dl, then the chemotherapy drug must be stopped (Hendrayana, Wilmer,

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Kurth, Schmidt-Wolf, & Jaehde, 2017). Chemotherapy drugs from the R-CHOP regimen that are metabolized in the liver include Cyclophosphamide, Doxorubicin / Epirubicin, and Vincristine, three chemotherapy drugs that need to be adjusted in patients with liver disorders. Adjustment of chemotherapy dose with the liver disorder can be reduced by increasing AST/ALT level and minimizing the risk of adverse reaction of chemotherapy (Chu & DeVita, 2018).

Eye evaluation after chemotherapy by an ophthalmologist is needed to see whether the reduced palpebral mass causes visual disturbances, visual field disorders, impairment of orbital movement, and disturbs the anterior and posterior eye segments, intraocular and extraocular part (Eckardt et al., 2013; Priego et al., 2012; Svendsen et al., 2017).

In palpebral NHL, the median months of disease-free survival are 15-24 months with a median recurrence rate of 2-26 months, depending on the type of histopathology. Treatment response at the early stage (stage I-II) showed a complete response. At stage III, 80% of cases showed partial response, 5% were progressive, and 31% of cases relapsed. A complete response to the histopathological type diffuse large B-cell lymphoma (DLBCL) in 70% of cases was found at stage IE, and one in nine patients experienced recurrence after being given Rituximab. Palpebral NHL B-cell type recurrence occurred in 27% of cases. The lowest recurrence rate came from histopathologic type extranodal marginal zone lymphoma (EMZL) and extramedullary plasmacytoma (EMP). The recurrence rate of DLBCL type reached 33% of cases, and one-third of cases experienced a relapse. (Svendsen et al., 2017).

CONCLUSION

We reported a case of a thirty-eight years old woman with bilateral inferior palpebral NHL B cell type high grade, stage IIEA CD 20 +, non-specific reactive hepatitis. Examination of vision, orbital muscle movement, intraocular pressure, anterior and posterior eye segments showed no abnormalities. For patients treated using R-CHOP with post-chemotherapy evaluation on the seventh day, the AST/ALT level surge was found insignificant. The dosage adjustment was made on the second chemotherapy due to the increase of AST/ALT to 1.43 times by the normal limit. Evaluation of IV chemotherapy gave a complete response with grade 1 ESO. Evaluation of 6th chemotherapy was full in response also with grade 1 ESO. Post chemotherapy eye examination showed no disturbances in vision, visual field, orbital muscle movement, and anterior and posterior eye segments were fine.

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