Drug-Induced Liver Injury (DILI) related to Propylthiouracil (PTU) in hyperthyroidism with liver cirrhosis

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INTRODUCTION

Hyperthyroidism is an excessive concentration of thyroid hormone in tissues caused by increased thyroid hormone synthesis, excessive thyroid hormone release, or an endogenous or exogenous extrathyroidal source.1 The prevalence of hyperthyroidism in Indonesia ranges from 6.9% to 1.2% in the United States and 0.8% in Europe.2 There are 3 types of therapy of hyperthyroid, namely antithyroid drugs (PTU, thiamazole, and carbimazole), radioactive ablation, and surgery. However, antithyroid drugs carry a potential risk of hepatotoxicity.3

Drug-induced liver injury (DILI) is a health problem with diagnostic challenges. DILI is caused by exposure to drugs or non-infectious agents.4 The incidence of DILI in Asia was higher than in the United States and Europe.5 A prospective study from the Drug-Induced Liver Injury Network (DILIN) in Delaware in 2017 showed the incidence of DILI was 2.7/100,000 annually.6 While the 2-year prospective study from South Korea in 2012 based on hospitalization rate showed the incidence of DILI was 12/100,000.7 According to EASL, DILI is generally divided into two categories: intrinsic (direct) and idiosyncratic. Intrinsic DILI is dose-related and occurs in most (predictably) drug-exposed individuals. In addition, the onset occurs in a short time span (hours to days). Whereas idiosyncratic DILI is generally not dose-related, occurs in only a small proportion of exposed individuals (unpredictably) and exhibits latency that varies onset from days to weeks. Both types of DILI have different pathogeneses but have some similar characteristics. The organic compounds of the drug, particularly lipophilicity and drug biotransformation, are important in both types. This exposes the liver to reactive metabolites that have the potential to bind to proteins covalently, cause oxidative stress, activate signal transduction pathways and cause organelle stress, obstruct bile acid transport, and either has lethal consequences or induce adaptive responses that dampen these processes so that injury does not occur or is only mild. However, in some people with a genetic predisposition to adaptive immunity, stress can trigger innate immune responses that co-stimulate an adaptive immune response.8

Propylthiouracil (PTU) and thiamazole have been the treatment of choice for hyperthyroidism patients for the past 50 years. The presence of liver injury is a rare side effect in hyperthyroid patients with the use of these drugs.9 PTU is one of the drugs on the list that cause DILI issued by EASL.8 PTU cause liver injury with symptoms ranging from mild asymptomatic elevations of aminotransferases to life-threatening acute liver failure.3 In the following, we will present a case of a therapeutic problem in a man with liver cirrhosis, most likely related to DILI with PTU as a treatment for hyperthyroidism.

ABSTRACT

Background: Hyperthyroidism is an excessive concentration of thyroid hormone in tissues caused by increased thyroid hormone synthesis, excessive thyroid hormone release, or an endogenous or exogenous extrathyroidal source. There are 3 types of hyperthyroid therapy: antithyroid drugs (PTU, thiamazole, and carbimazole), radioactive ablation, and surgery. However, PTU is one of the drugs included in the list of medications that cause Drug-induced Liver Injury (DILI).

Case Presentation: A 36-years old male came to the IRD Dr. Sutomo General Hospital with a chief complaint of weakness for 1 month. The patient also complained of yellowing of the skin on the body, especially in the eyes, for 1 month, and the stomach was getting bigger and bloated before admission to the hospital. The patient has a history of hyperthyroidism since 6 months ago and has taken PTU for 5 months. Exophthalmos eyes, icteric eyes, ascites, and splenomegaly were found on physical examination. The laboratory results showed hyperbilirubinemia, an increase in transaminase enzymes, and hypoalbumin. In the hospital, the patient was given an infusion of albumin, tyrosol, UDCA, spironolactone, and propranolol.

Conclusion: It has been reported that a man, 36 years old, has an underlying disease of liver cirrhosis. The patient has habitual risk factors for consuming alcohol. The patient had received PTU therapy for 1 month and came to the hospital suspected of DILI. Based on these cases, it is necessary to be vigilant about administering medications to patients with underlying diseases.

Keywords: Hyperthyroid, DILI, PTU.

CASE DESCRIPTION

A patient complained of weakness 1 month before admission to the hospital. In addition, nausea and vomiting were also followed for 3 days before being admitted to the hospital. The patient also felt the stomach was getting bigger and bloated about 1 month ago. The patient also has decreased appetite. The patient complained of yellowing of the skin on the body, especially in the eyes, 1 month before admission to the hospital. The patient sometimes feels itching on the skin. The patient currently has no complaints of palpitations or chest pain. The patient often feels hot and constantly sweats profusely. The patient does not know whether there is weight loss or not. The patient has had a history of hyperthyroidism since 6 months ago and has taken PTU 3x100 mg for 5 months. Because the patient felt that his stomach was getting bigger and his skin was turning yellow, the patient returned to the DKT Kediri Hospital for treatment and received Thyrozol 2x10 mg and UDCA 1x500 mg. 2 weeks later the patient came back to the DKT Kediri Hospital with complaints of getting weaker. He was treated for 5 days, then finally referred to Dr. Soetomo Hospital because the patient lives at home with his wife and children. The patient is a farmer. The patient had a history of drinking alcohol for the last 5 years. The patient has tattoos on his body.

On physical examination, the patient was comatosens, blood pressure 105/54 mmHg, pulse 105, lifting strength, respiratory rate 20x/minute, regular, axillar temperature 36.5 C, and oxygen saturation 99% without oxygen support. The head and neck examination revealed exophthalmos eyes, anemic conjunctiva, and icteric sclera, with no subconjunctival bleeding, cyanosis, and dyspnea. There was no increase in jugular venous pressure and enlarged lymph nodes. Thoracic examination showed a symmetrical chest shape, no lagging chest breath movements, and intercostal or supraclavicular retractions. On chest auscultation, vesicular breath sounds were found in both hemithorax and no crackles or wheezing in both lung fields—Lung-liver border at ICS 6 midclavicular line dextra. On cardiac examination, S1 and S2 were single and regular; no heart murmurs, gallop rhythm or pericardial friction were found. On abdominal examination, the abdomen was distended, collateral veins, shifting dullness (+), the liver was not palpable, and an enlarged S3H2 spleen. There is no tenderness in the epigastric region. Examination of acral extremities warm, dry yellow, capillary refill time less than 2 seconds. There is pitting edema (+) and palmar erythema in the lower extremities.

A clinical laboratory examination was done on the 1st day of hospitalization (Table 1). We also did the X-ray chest radiography and USG on the same day (4/11/2020). From the X-ray chest radiography, the results were no abnormality on the cor and pulmo. From the USG, the results were: Liver: intercostal liver size +/- 11.9 cm, the intensity of echo-parenchyma appears to increase roughly with irregular edges and blunt angles, IHBD/EHBD widening does not appear, vena porta caliber +/- 0.9 cm with PV velocity +/- 14.8 – 16.1 cm/s, vena hepatica appeared normal, no mass/nodule/cyst was seen. Spleen: enlarged size +/- 14.2 cm, the intensity of echo-parenchyma looks normal homogeneous, no mass/nodule/cyst visible, caliber v/splenic +/- 0.8 cm. Pancreas: normal size, parenchymal echo intensity looks normal and homogeneous, no visible mass/nodule/cyst. Examination impression: a parenchymal liver disease with slightly decreased portal vein velocity. There is no visible biliary tract dilation, splenomegaly, GB sludge, ascites, or pancreas/kidney/bladder abnormalities.

From the data above, the patient was assessed as hyperthyroid, hypokalemia, hypo albumin, suspect liver cirrhosis dd DILI dd acute on chronic liver disease. The planning diagnosis is a complete blood count, urinalysis, endoscopy, and fibroscan evaluations. The planned treatment is diet H 2100 kcal/day with extra fruits and vegetables. Infusion of KCI premix 50% 500 cc/24 hours, infusion of Albumin 20% 100 cc/4 hours, injection of Vit K 1 ampoule/ 8 hours, injection of metoclopramide 10 mg/ 8 hours, thyroid 10 mg/12 hours, spironolactone 100 mg/24 hours, UDCA 250 mg/8 hours, KSR 600 mg/ 8 hours, and Propanolol 20 mg/8 hours.

Table 1. Clinical Laboratory Results (4th November 2020).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reference Range</th>
<th>Results</th>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>11-14.7</td>
<td>10</td>
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<td>White Blood Cell (μL)</td>
<td>3370-10000</td>
<td>8900</td>
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<tr>
<td>Neutrophyl (%)</td>
<td>39.8-70.5</td>
<td>72.2</td>
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<tr>
<td>Lymphocyte (%)</td>
<td>23.1-49.9</td>
<td>13.9</td>
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<tr>
<td>Platelet (μL)</td>
<td>150.000-450.000</td>
<td>139.000</td>
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<tr>
<td>Sodium (Na)(mmol/L)</td>
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<td>129</td>
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<tr>
<td>Potassium (K)(mmol/L)</td>
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<tr>
<td>Chloride (Cl) (mmol/L)</td>
<td>98-107</td>
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<td>SGOT (U/L)</td>
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<tr>
<td>SGPT (U/L)</td>
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</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4-5.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Blood Urea Nitrogen (mg/dL)</td>
<td>7-20</td>
<td>7</td>
</tr>
<tr>
<td>Creatinin (mg/dL)</td>
<td>0.5-1.2</td>
<td>0.6</td>
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<tr>
<td>Direct Bilirubin (mg/dL)</td>
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<td>Total Bilirubin (mg/dL)</td>
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<tr>
<td>HIV</td>
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<td>Glucose (mg/dL)</td>
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<td>PPT (seconds)</td>
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<td>APTT (seconds)</td>
<td>26-38</td>
<td>63.2</td>
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<tr>
<td>TSH (IU/mL)</td>
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<tr>
<td>FT4 (ng/dL)</td>
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<td>1.06</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>&lt;0.05</td>
<td>0.69</td>
</tr>
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</table>

On cardiac examination, S1 and S2 were
History of illness
The patient complained of nausea on the second day of treatment (6th November 2020). The patient still complained of swelling in the legs. The patient's appetite was good. We also did the clinical laboratory examination (Table 2), which showed hypoalbumin. Therefore, the patient was given an infusion of Albumin 20% 100 cc in 4 hours. On the third day of treatment (7th November 2020), the patient complained of nausea and leg swelling. We also did the clinical laboratory examination, as seen in Table 2, which showed the patient had no complaints of weakness, nausea, and vomiting. The final assessment of this patient was hyperthyroidism + DILI ec PTU (improved). The patient was discharged that day and scheduled for a follow-up. The patient was given Spironolactone 1x30 mg, UDCA 1x250 mg, Thyrozol 2x10 mg, and Propranolol 3x10 mg.

Two months after discharge from the hospital (7th January 2021), the patient went to the hepatic polyclinic. The patient has no complaints. From the physical examination, the blood pressure was 110/80 mmHg, pulse was 80x/minute, breathing was 18x/minute, the axillary temperature was 36.5 C, and SpO2 was 98% without O2 support. We also did the clinical laboratory examination evaluation, as shown in Table 2.

We did the clinical laboratory examination on the eighth day of treatment (12th November 2020), as seen in Table 2. The patient had no complaints of weakness, nausea, and vomiting. The final assessment of this patient was hyperthyroidism + DILI ec PTU (improved). The patient was discharged that day and scheduled for a follow-up. The patient was given Spironolactone 1x30 mg, UDCA 1x250 mg, Thyrozol 2x10 mg, and Propranolol 3x10 mg.

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DISCUSSION

Hyperthyroidism is an inappropriate increase in the synthesis and/or secretion of thyroid hormones from the thyroid gland. The most common cause of hyperthyroidism is Graves’ disease, an autoimmune condition with loss of immunotolerance, causing thyrotropin receptor antibodies (TRAb) to form, bind and then stimulate TSH. Subsequently, it can affect the metabolic activity of the thyroid gland and cause hyperthyroidism. Clinical manifestations of hyperthyroidism include symptoms of weight loss, fatigue, heat intolerance, weakness, diarrhea, sleeping difficulty, hyperactivity of the thyroid gland and cause hyperthyroidism. Symptoms of hyperthyroidism include symptoms of weight loss, fatigue, heat intolerance, weakness, diarrhea, sleeping difficulty, hyperactivity of the thyroid gland and cause hyperthyroidism.

The thyroid gland. The most common cause of hyperthyroidism is Graves’ disease, an autoimmune condition with loss of immunotolerance, causing thyrotropin receptor antibodies (TRAb) to form, bind and then stimulate TSH. PTU and Methimazole are two antithyroid agents often used in various countries. PTU is a thioamide derivative widely used for treating hyperthyroidism, which exerts its pharmacological effects through two different mechanisms. PTU inhibits the reaction catalyzed by the thyroid peroxidase enzyme, which is expressed in the thyroid follicle and inhibits the organification of iodine and the 5′-deiodinase enzyme, which is responsible for the peripheral conversion of T4 to the active T3 moiety. Methimazole inhibits thyroid hormone production by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin, which is an important step in the synthesis of T3 and T4. Side effects of thyroid medication are fever, arthralgia, agranulocytosis and hepatotoxicity.

In this case, based on history and physical examination, the patient was diagnosed as hyperthyroid. The therapy that has been given to this patient is PTU 3x100 mg. The patient took PTU for 5 months. However, in this case, there is also suspicion of DILI because of jaundice, abdominal ascites, and abnormalities of liver function that occur after drug administration. And the drug consumed and suspected to be related to DILI is PTU.

DILI is divided into two categories: direct hepatotoxicity and idiosyncratic. The current hypothesis for DILI is the “hapten/prohapten Hypothesis.” A drug is converted into a reactive metabolite, which in some people with susceptible HLA haplotypes, can activate the adaptive immune system through neoantigen or molecular mimicry. Hepatocytes may undergo cellular stress and activation of stress response pathways due to the reactive metabolite, such as endoplasmic reticulum (ER) and mitochondrial stress. Under normal circumstances, the liver produces many reactive metabolites during metabolism, but the liver microenvironment triggers an immune tolerance state that either stops or reverses toxicity, known as adaptation.

In rare instances, due to defective adaptation, the mild liver injury might develop into severe idiosyncratic DILI and acute liver failure. Drugs associated with intrinsic and idiosyncratic DILI was mentioned in the previous study. Based on the table released by EASL in 2019, PTU is included in the category of drugs related to idiosyncratic DILI.

In patients with abnormalities in liver function tests with no apparent cause, a careful history should be taken first. The history should include drug dose, route of administration, previous administration, alcohol consumption, and underlying chronic liver disease. In addition, patients should be examined for fever, rash, or jaundice. Acute liver injury is often detected and confirmed by biochemical blood tests, namely Serum Glutamic Oxaaloacetate Transaminase / SGOT, Serum Glutamic Pyruvic Transaminase / SGPT, Bilirubin and albumin. The case definition for DILI includes one of the following limits: 1) ≥5 Upper Limit of Normal/ULN of SGOT; 2) ≥2 ULN of gamma-glutamyltransferase (GGT) in the absence of bone pathology in elevated alkaline phosphatase/ALP values; or 3) ≥3 x ULN of SGOT and a simultaneous increase in total bilirubin concentration exceeding 2 x ULN.

The next step is to evaluate the results of laboratory tests relevant to liver biochemistry. A useful determination for treatment is to determine the R-value, which is calculated as follows: R-value = Serum (ALT/ALT ULN) (ALP/ALP ULN). This figure is used to categorize the pattern of injury into 3 types: hepatocellular (R > 5), mixed (R = 2–5), and cholestatic (R < 2).
CASE REPORT

gender, malnutrition, obesity, diabetes mellitus, and comorbid diseases, including underlying liver disease. Age may confer susceptibility to DILI in drug-specific ways. A reduction in kidney function in the elderly would increase drug concentration in the liver. Associated with patients with chronic liver disease, it is hypothesized that this population is at a higher risk of DILI. The spectrum of chronic liver disease includes inflammation, fibrosis, and cirrhosis. When cirrhosis is diagnosed, it is important to differentiate between compensated and decompensated diseases. The clinical manifestations of decompensated cirrhosis are ascites, gastrointestinal bleeding, encephalopathy, and jaundice. An ultrasound can be carried out to help establish the diagnosis of liver cirrhosis. Measurements with Fibroscan can also be used to assess the degree of liver fibrosis. In addition to fibroscan, liver biopsy is the gold standard for assessing the degree of necro-inflammation and fibrosis. However, liver biopsy has its limitations, which are pain and bleeding.

In this case, the patient had a risk factor for the underlying disease associated with DILI, namely liver cirrhosis. The ultrasound and fibroscan investigations showed that the patient had liver cirrhosis.

The second is environmental factors. Environmental factors include smoking, alcohol consumption, and infection. Alcohol consumption is one of the criteria for the RUCAM causality assessment instrument, although no specific level of consumption has been determined. Alcohol is a CYP2E1 inducer and is essential in forming N-acetyl-p-benzoquinone imine, the reactive metabolite responsible for the hepatotoxicity of acetylaminoephene. In this patient, there are risk factors for consuming alcohol for a long time which can be a cause of chronic liver disease and risk factors for DILI.

Third are factors related to drugs. Drug dose plays an important role in intrinsic DILI, which occurs in patients with a drug overdose. However, the threshold dose may vary between individuals. This is exemplified in the case of DILI, where the patient tolerates the drug at a lower initial concentration but develops DILI when a dose increase is required (still within the recommended daily dose range) for better pharmacological effect. In addition to the dose, the drug's metabolism in the liver is believed to influence the potential hepatotoxicity of the drug. Most drugs require some form of biotransformation to be removed and often to produce the active pharmaceutical ingredient. This process usually requires the formation of reactive metabolites that can cause covalently bound haptns and/or cellular stress in a susceptible cellular environment that can elicit or stimulate the development of an adaptive immune response that results in DILI.

DILI caused by PTU can be so severe that it can lead to liver failure. Routine monitoring of liver biochemistry is recommended to allow the termination of PTU in cases of suspected liver injury. The form of liver injury caused by Methimazole is mainly of the cholestatic type, whereas liver injury caused by PTU is of the hepatocellular type. PTU-related hepatotoxicity manifests as acute allergic hepatitis with laboratory evidence of hepatocellular damage, including significantly increased aminotransferase levels and submassive or massive hepatic necrosis on biopsy. Liver biopsy remains the gold standard for diagnosing PTU-induced liver injury, but the diagnosis is often inferred from the course of time after the initiation of PTU therapy. PTU has been reported to cause histologic changes, including portal and periportal inflammation with eosinophilic, lymphocytic, and plasmacytic infiltrates in various combinations, chronic active hepatitis, and submassive or massive hepatic necrosis. A hypothesis has been proposed as an explanation for PTU-induced hepatopathy in which there is more or less inhibition of glucuronol transferase, reduced bile acid synthesis, and increased oxygen consumption by hepatocytes. To establish the diagnosis of DILI, there are several important things; first is DILI can resemble all types of disease and currently, the diagnosis of DILI is carried out by exclusion because there are no biological markers or specific examinations that can confirm the diagnosis of DILI; we should explore all clinical and biochemical data related to liver injury to determine the pattern of liver injury; third is medical conditions that necessitate the use of drugs that can cause liver dysfunction and can complicate the diagnosis of DILI and last, because several drugs are generally given together, synergistic interactions between drugs can occur and raise the question of which drug is causing DILI. The RUCAM (Roussel-Uclaf Causality Assessment Method) method can be used to determine causality in DILI. Scores were grouped into probability levels of “excluded” (score ≤ 0), “unlikely” (1–2), “possible” (3–5), “probable” (6–8), and “highly probable” > 8. The following is a table to see the possible causes. In this patient, a score of 7 was obtained, which means that the presence of drug-induced liver injury from PTU is “probable” because there are still three data that have not been examined.

Various approaches have been used to assess the severity of DILI. The Drug-Induced Liver Injury Network (DILIN) has suggested a 4-point severity rating of mild, moderate, severe, and fatal in assessing suspected DILI. Since different hospitalization criteria may be followed in different countries, the International DILI Expert Working Group proposed a modified four-point scale. Based on the severity scale of the International DILI Expert Working Group, in this case, the patient had severe DILI with an SGOT value of 259 U/L and a total bilirubin of 18.74 mg/dL. An important step in managing suspected DILI is discontinuing the agent involved. In most DILIs, spontaneous recovery occurs without needing special treatment. Spontaneous recovery after discontinuing the offending drug is an important criterion in causality assessment. There is generally complete or near complete resolution within days to weeks. However, sustained or worsening injury may occur after the offending agent is discontinued. At the same time, the severity of the liver injury should be assessed. In addition to drug discontinuation, there are several therapies for DILI, namely cholestyramine, carnitine, N-acetylcysteine, and UDCA. In this case, the patient had discontinued the PTU drug associated with DILI and the patient was given UDCA. After anti-
hyperthyroid therapy was replaced with thiazole, there was an improvement in clinical, complaints and laboratory parameters. This study has several limitations. First, in evaluating suspicion of DILI, it is necessary to carry out an Anti Smooth Muscle Antibody (ASMA) test to rule out suspicion of autoimmune hepatitis. However, this patient did not undergo an ASMA test due to limited laboratory equipment at the hospital. So that in this patient, the presence of autoimmune hepatitis still cannot be ruled out. Liver biopsy, which is the gold standard for diagnosing PTU-induced liver injury, is also not performed due to patient resistance, so the diagnosis is often inferred from the course of time after initiation of PTU therapy. Thus, an explanation to patients regarding liver biopsy needs to be emphasized in establishing the diagnosis of DILI. Therefore, in diagnosing and managing a disease, it is important to carry out a comprehensive examination and provide therapy as early and as best as possible so that the patient does not have to stay in the hospital for a long time.

CONCLUSION
It has been reported that a man, 36 years old, has an underlying disease of liver cirrhosis. The patient has habitual risk factors for consuming alcohol. The patient had received PTU therapy for 1 month and came to the hospital suspected of DILI. Based on the RUCAM score search, a score of 7 was obtained, which means “possible,” with a mixed type injury pattern and a severe degree. After discontinuation of the drug, the patient’s condition improved. Based on these cases, it is necessary to be vigilant about administering medications to patients with underlying diseases.

CONFLICT OF INTEREST
The authors declare that there is no competing interest regarding the manuscript.

ETHICAL CONSIDERATION
This research was conducted based on the ethical conduct of research from the Ethics Committee of the Medical Faculty, Airlangga University/Dr. Soetomo General Hospital, Surabaya.

FUNDING
The authors are responsible for the study’s funding without the involvement of grants, scholarships, or any other funding resource.

AUTHOR CONTRIBUTION
All authors contributed equally to the study from the conceptual framework, data gathering, and data analysis until the study’s results were interpreted upon publication.

ACKNOWLEDGMENTS
The authors would like to thank Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga and Dr. Soetomo Hospital, Surabaya.

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