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Case Report

Idiopathic Pulmonary Arterial Hypertension Newly Diagnosed in Pregnancy with Anemia and Threatened Preterm Labor

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ABSTRACT

Background: Pulmonary hypertension (PH) is a rare cardiovascular disorder that leads to right heart failure (RHF). Although most PH occurs secondary to congenital heart disease (CHD), PH can occur primarily due to pulmonary arterial vasculature abnormalities, known as Idiopathic pulmonary arterial hypertension (IPAH). In addition, the physiologic changes during pregnancy can potentially lead to worsening PAH and confer a poor prognosis. Therefore, when the mother refuses termination, a multidisciplinary team should manage the pregnancy and delivery to improve maternal and fetal outcomes.
Objectives: This case report aimed to describe the importance of early diagnosis and treatment in PAH.
Case reports: We reported a case of a 24-year-old woman with idiopathic pulmonary arterial hypertension (IPAH) that was newly diagnosed at 25 weeks of pregnancy and previously misdiagnosed with patent ductus arteriosus (PDA). This pregnancy was complicated with anemia and threatened preterm labor. Sildenafil was used as a vasodilator to reduce the symptoms of PAH. Unfortunately, the pregnancy was terminated at 29 weeks because of PPROM after considering giving lung maturation and neuroprotectant to the fetus. The patient was discharged without complication, but the baby died after eight days of intensive care due to HMD II, which led to respiratory failure.
Conclusion: PAH in pregnancy is a life-threatening condition if untreated. Continuous treatments can help control the symptoms and avoid further complications for both mother and baby.

1. Introduction

Pulmonary hypertension (PH) is a rare heart defect and can be fatal, causing maternal and fetal death. The most frequent causes of PH during pregnancy (64%) are congenital heart diseases (CHD) such as ventricular septal defect (VSD), atrial septal defect (ASD), or patent ductus arteriosus (PDA).[1] The incidence of pregnancy with PH is scarce for approximately 1.1:100,000 women (Obican et al., 2014). PH group 1 or known as primary Pulmonary arterial hypertension (PAH), is a condition that is rarely found, with an average survival rate of only 2.8 years if not treated.[2] Therefore, a woman with PH is not advised to get pregnant. The physician should offer termination when pregnancy occurs. Nevertheless, some mothers cannot accept the decision to terminate the pregnancy and choose to continue their pregnancy.[3]

Physiological changes that occur in pregnancy can aggravate the burden on the heart, especially in PAH conditions. The condition of anemia can also worsen the work of the heart in pregnant women with PAHs. Iron deficiency is one of the most frequent causes of anemia in pregnancy and also affects the pathogenesis of PAHs. Iron deficiency due to malnutrition underlies cardio-intestinal syndrome, which can worsen hypoxic conditions in pregnant women with PAHs.[4] Both anemia and decreased CO due to PH can increase morbidity in the mother and fetus. Pregnant women with PH and anemia require intensive, multidisciplinary treatment during pregnancy and childbirth.[2]

We will report cases of pregnancy with Idiopathic Pulmonary Arterial Hypertension (IPAH), which was newly diagnosed during pregnancy. The PAH condition is exacerbated by anemia in pregnancy which causes symptoms of acute shortness of breath and causes complications of preterm labor. Pregnancy management with PAH is carried out by a multidisciplinary team at Dr. Saiful Anwar Hospital Malang so that it can add insight to handling pregnancy cases with PAH. However, establishing a diagnosis that is not easy can lead to misdiagnosis and increase the risk of complications that occur in the mother and fetus. Therefore, the management of pregnancy with PAH is complicated and makes it a big challenge.

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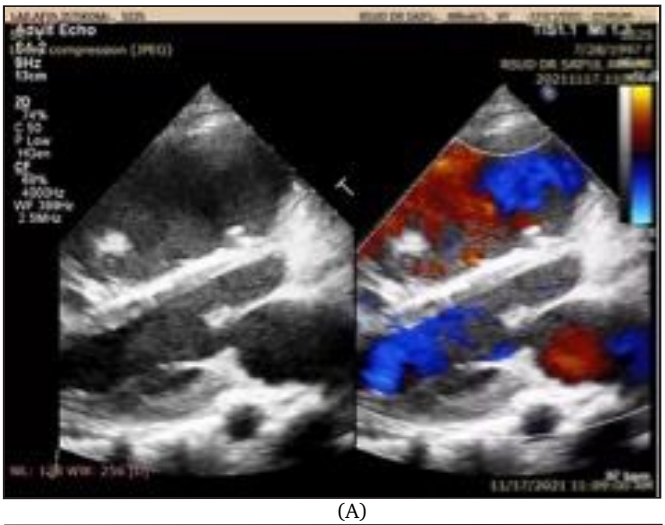

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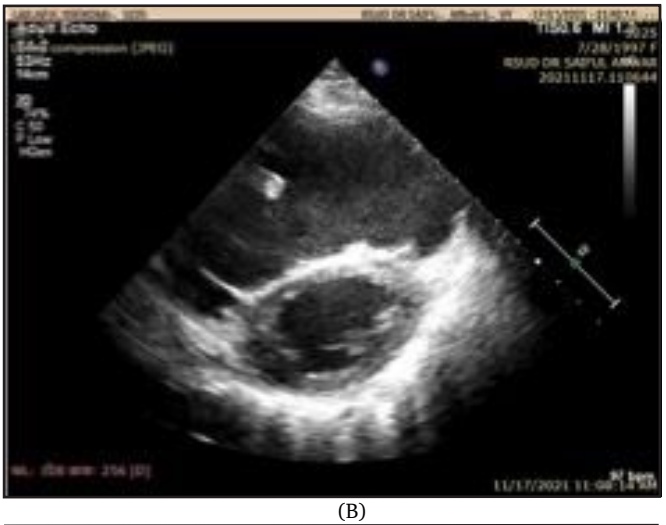

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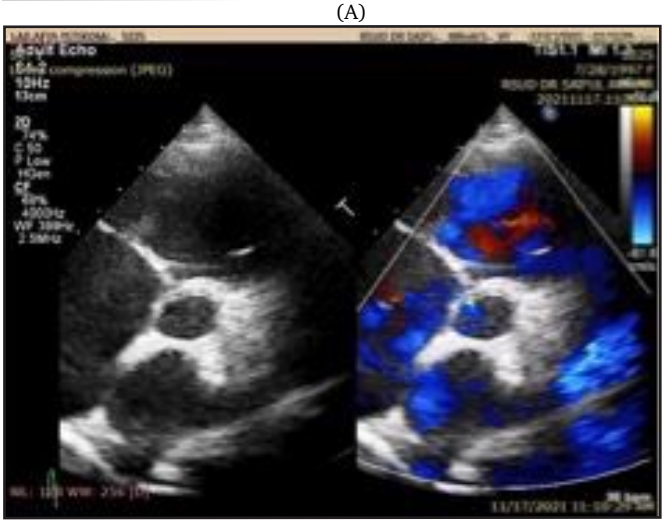

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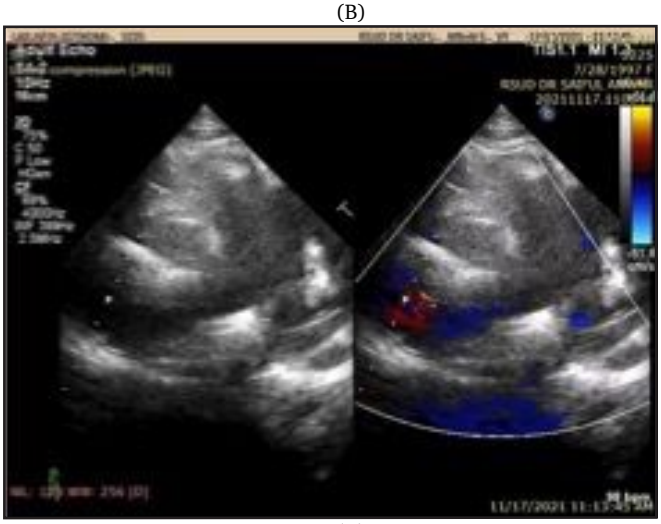

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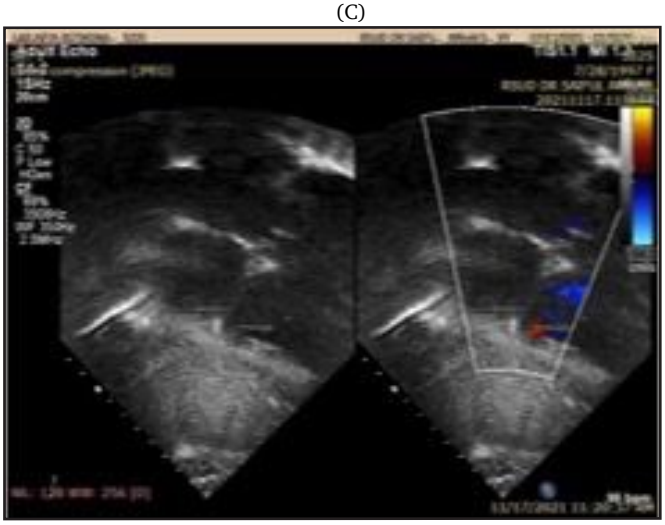

(E)

Figure 1. Echocardiographic of idiopathic pulmonary arterial hypertension

A. Parasternal Long Axial image: RV dimension enlarged with LV geometric change; B. LV D-shaped in Parasternal short Axis (PSAx) image; C. PSAx- great artery level shows there is no interatrial shunt; D. Pulmonary Artery Enlargement; E. There is no interatrial shunt from sub-costal view

2. Case Report

A 24-years-old woman, primigravid, was referred to our emergency department by an Obstetrician at a private hospital with a chief complaint of shortness of breath after two times of PRC transfusions. The patient was hospitalized for two days and diagnosed with threatened preterm labor and anemia. The patient felt a frequent uterine contraction at 25 weeks of gestation, a day before being hospitalized. The hemoglobin level at visiting that private hospital was 7.4 gr/dL. Patient planned for dexamethasone-induced fetal lung maturation and PRC transfusion twice a day. After the second transfusion, the patient felt dyspnoea and palpitation. The patient was consulted by the Cardiologist and given digoxin 1x0,25 mg. The patient was diagnosed with ASD based on clinical appearance and electrocardiograph examination. After 24 hours of observation, the patient did not get better. Because lack of facilities, the Obstetrician referred the patient to our hospital.

The patient did antenatal care with the midwife and never came to Obstetrician. She did a triple elimination test in Public Medical Centre Jatisari, and the results were non-reactive. On admission, the patient's vital sign was blood pressure of 120/81 mmHg, heart rate of 107 bpm, respiratory rate of 28 breaths/min, pulse oxygenation of 99% on nasal cannula three L/min, and temperature of 36.2°C. Head and neck examination found conjunctiva anemia and JVP +1. Cor examination found murmur systolic 3/6 continuous at ICS II left parasternal line. The abdominal examination determined the fundal height of 18 cm, single intrauterine baby head below, fetal heart rate of 147 bpm,

and uterine contraction (+). In addition, we found two cm cervical dilatation, 50% effacement, head presentation at Hodge I, and no amniotic fluid leakage from the vaginal examination.

Her hemoglobin level at admission was 8.5 mg/dL. Patient has hypercoagulability condition that showed from increased D-dimer 1.32 mg/L FEU (normal range < 0.5 mg/L FEU) and fibrinogen 502 mg/dL (normal range 154.3-397.9 mg/dL). The patient was hospitalized in the Obstetrics High Care Unit for preterm delivery observation. Her shortness of breath was due to suspect congenital heart disease with a high probability of PH. The transfusion was continued with one PRC daily. Tocolytic ketoprofen suppositories were given to relieve uterine contraction. Treatment of pulmonary hypertension with oral sildenafil 20 mg daily improved the shortness of breath.

Echocardiographic evaluation was done after three days of hospitalization by a senior Cardiologist (Figure 1). Dilatation of the pulmonary artery was consistent with the prior echocardiogram with a diameter of MPA 3.26 cm, RPA 1.61 cm, and LPA 2.12 cm. The intracardiac shunt did not detect either an atrium or ventricle. Dilatation of the right heart, including atrium (RA length 7.25 cm and RA width 6.14 cm) and ventricle (RVDB 5.99 cm, RV mid 5.77 cm), were found. Moderate pulmonary regurgitation and moderate to severe tricuspid regurgitation were consistent with a high probability of pulmonary hypertension. Additional laboratory workup was done for lung disease, thromboembolic, and autoimmune disorders. The patient was counseled about her idiopathic pulmonary arterial hypertension and refused to terminate the pregnancy. A multidisciplinary team, including Obstetrician, Cardiologist, Pulmonologist, Anaesthesiologist, and Neonatologist, collaborated for comprehensive management. The patient showed improvement in symptoms and was discarded from the hospital after ten days of hospitalization.

Unfortunately, after two weeks of being discarded from the hospital, the patient got a water break. The patient visited the obstetrics outpatient unit at 28 weeks of gestation. Vital sign examination was blood pressure of 113/70 mmHg, heart rate of 101 bpm, respiratory rate of 20 breaths/min, pulse oxygenation of 98% on room air, and temperature of 36.3°C. Amniotic fluid flow was visible at the uterine external os on sterile speculum examination. The patient was planned for hospitalization, and antenatal dexamethasone 6 mg twice a day for two days was given for lung maturation of the fetus. Neuroprotectant with MgSO4 20% 4 gr IV slowly bolus continued with syringe MgSO4 40% 10 gr 1 gr/hours was given 24 hours before termination.

At 29 weeks of pregnancy, the patient delivered a male infant with Apgar scores of 6 in the first minute and 9 in the 5th minute by cesarean section under low-dose spinal anesthesia block (SAB). The infant's birth weight was 1126 gr, and birth length was 37 cm. Mechanic contraceptive with IUD T380A was inserted into the uterus post-placental delivery. A preventive B Lynch procedure was done to minimize the risk of hemorrhagic post-partum. The postoperative observation was done in the intensive care unit. The patient condition post-operation was good, without any complaints. The patient was allowed to pump her breast milk because her condition was not a complication. The patient was discarded three days after the cesarean section. Unfortunately, her baby died after eight days of intensive care due to HMD II, which led to respiratory failure.

3. Discussion

PH generally occurs secondary due to underlying medical conditions such as heart and lung disease. Primary PH is less common and is included in a condition called pulmonary arterial hypertension (PAH). Our patient has been diagnosed with idiopathic pulmonary arterial hypertension (IPAH). Primary PH is very rare and often idiopathic, with a life expectancy between 2.8-5 years, especially in young patients. PH can occur in connective tissue diseases such as lupus or systemic sclerosis.[1] This patient showed an ANA test examination result was negative. Clinical findings did not show any criteria consistent with the American College of Rheumatology (ACR) for lupus and systemic sclerosis.[5]

Based on the WHO functional class, this case is included in WHO FC II, characterized by mild physical activity limitations but no complaints when the patient is resting.[2] The patient is suspected of having an Atrial Septal Defect (ASD) due to the presence of RBBB images and "crochetage" signs on all three inferior leads on the electrocardiogram. Crochetage signs obtained in all inferior leads showed 100% specificity, 73.1% sensitivity, and 69% PPV to ASD diagnosis.[6] Nevertheless, the transthoracic echocardiogram did not indicate the presence of intracardiac shunt in these patients.

Pregnancy with a PAH is contraindicated because it causes serious heart failure that could result in morbidity and mortality.[7] Pregnancy causes physiological changes in all body organs, including the cardiovascular system. The volume of blood plasma increases by approximately 6-8L by the time of approaching labor.[8] Hormonal changes in pregnancy, progesterone, and estrogen, also play a role in causing a decrease in systemic vascular resistance (SVR) by up to 40%.[9] The physiologic process in pregnancy causes an increase in the heart size by up to 30% to increase cardiac output up to 30-50%, especially in the first trimester of pregnancy. Mothers with IPAH have idiopathic dilatation of the pulmonary artery as compensation for the high pressure. In this condition, the heart cannot increase CO and potentially cause right heart failure.[3] Physiological pregnancy hypercoagulability conditions increase the risk of thromboembolism which can worsen the condition of the patient with PAH.[7]

Anemia in pregnancy is still a major problem for maternal health in Indonesia. Anemia in pregnancy increases the risk of premature delivery, low birth weight babies, perinatal mortality, and post-partum bleeding.[10] Anemia in pregnant women can occur physiologically as a response to an increased plasma volume with a peak at 30-34 weeks of gestation.[11] Iron deficiency is the main cause of anemia in pregnancy.[12] The incidence of iron deficiency anemia in pulmonary hypertension is quite high, around 40-60%.[13] Iron is needed for hemoglobin synthesis in erythrocytes and myoglobin in the heart muscle and skeletal muscle to facilitate the diffusion and storage of oxygen.[14] Impaired iron homeostasis contributes to pulmonary vascular endothelial dysfunction. Hemoglobin scavenger transporter CD163 is a regulator of cellular function and proliferation of pulmonary arterial endothelial cells (PAECs), and pulmonary artery smooth muscle cells (PASMCs) needed for pulmonary vascular remodeling.[13] The management of anemia and iron deficiency in pregnancy can reduce vasoconstriction of the vascular lung and improve pulmonary hypertension.[4]

Anemia can increase the risk of infection in pregnancy. The infection causes a 2.4-fold increase in the risk of early rupture of the amniotic. A decrease in hemoglobin levels causes a decrease in oxygen transport to tissues, including the membrane amnion. Hypoxia causes an increase in serum norepinephrine which induces maternal and fetal stress. The incidence of anxiety in pregnancy will increase corticotrophin-releasing hormone (CRH). Increased CRH can improve premature labor, hypertension, preeclampsia, and PROM. Iron deficiency can affect the proliferation of T and B cells and reduce phagocytic activity, cell activity, and bactericidal ability, thereby increasing the risk of infection. Infection is one of the risk factors for the onset of premature labor.[15]

The administration of medications can control pulmonary hypertension in pregnancy. Pharmacological therapy for HAP in pregnancy can be divided into four groups: prostaglandins,

phosphodiesterase five inhibitors (PDE-5), endothelin receptor antagonists, and soluble guanylate cyclase stimulators.[9] Only the PDE-5 inhibitor group is available in our hospitals. PDE5 inhibitors as monotherapy can be recommended in patients with functional class FC I or II with normal right ventricular function. Sildenafil is a PDE5 inhibitor first used in pulmonary hypertension and is more widely recommended than the newly recommended tadalafil.[16] Around 2009, PDE5 inhibitors acted on the nitric oxide (NO) pathway as competitive inhibitors against cGMP degradation. Increased cGMP concentrations lead to the activation of protein kinase G through the potassium sarcolemma canal. This process triggers conditions of intracellular hyperpolarisation and inhibition of calcium canals that cause the relaxation of smooth muscles of pulmonary blood vessels.[17] Sildenafil is safe to use in pregnancy, as reported by a meta-analysis study in the Netherlands. Sildenafil in obstetrics is used as a therapy for intrauterine growth restriction (IUGR) in preeclampsia. The administration of sildenafil also positively lowers peripheral vascular resistance and improves uteroplacental flow, which is beneficial for fetal development.[18] In this case, the patient is given therapy with sildenafil 3x20 mg. Complaints of tightness gradually improved after the patient was given therapy with sildenafil. The administration of sildenafil is continued until the KRS patient.

Pregnant women with PH have a higher risk of post-partum bleeding, premature delivery, and cesarean delivery.[19] Childbirth is recommended to be scheduled immediately after fetal lung maturation. Delivery with cesarean section is highly recommended to avoid prolonged labor and prepare for hemodynamic optimization and better anesthesia techniques. Childbirth is associated with an extra increase in CO by 30-50%, with a total increase of 80%. PAP increased from 53.5 mmHg in pre-pregnancy conditions to 72.8 mmHg at 31 ± three weeks. Increased reverse blood flow from causing hemodynamic instability in pregnancy with PAHs. A multidisciplinary team must carry out the management of pregnancy with PAH.[20] Experts consisting of obstetricians, cardiologists, anesthesiologists, pulmonologists, and neonatologists play an important role in managing this case.

Post-partum bleeding can be controlled during surgery by administering oxytocin and the B-Lynch procedure. In addition, oxytocin administration as a preventive therapy for post-saline bleeding is also recommended. However, oxytocin is not allowed to be administered bolus intravenously because it can cause hypotension and reflex tachycardia.[3] The B-Lynch method has been known since 1997 as a suturing method that accommodates mechanical compression of the uterus during surgery to prevent and manage uterine atony.[21] Oxytocin administration, in this case, was given by intravenous drip at a dose of 20 IU in RL 500 cc at a rate of 28 drip/min to 12 hours postoperatively. Postoperative evaluation of this patient found a stable hemodynamic condition, no complaints of tightness were obtained, and the patient could be transferred to the HCU treatment room 24 hours after monitoring in the ICU.

The preoperative management carried out by TS Anesthesia includes the installation of a 2-lane IV line with an 18G needle, the administration of IVFD RL fluid 40 cc/hour during fasting, the fasting of 6 hours of pre-operation, the premedication of ranitidine 50 mg and metoclopramide 10 mg 1 hour of pre-operation and the installation of arterial line pre-operation. The key to managing intraoperative anesthesia in patients with pulmonary hypertension is the prevention of ischemia, especially in the right coronary artery.[22] The strategy that can be applied is to optimize the contractility of the right ventricle by keeping the preload safe and preventing an increase in afterload caused by mechanical, physiological, and pharmacological factors.[23] The installation of invasive arterial lines can be very useful for monitoring coronary perfusion pressure and analyzing diastolic pressure.[22] The administration of pharmacological agents such as norepinephrine and milrinone during surgery is recommended to maintain the perfusion of the coronary arteries. Norepinephrine is an alpha and beta-agonist that functions for inotropic augmentation while also being able to cause systemic vasoconstriction without affecting the pulmonary vascular. Meanwhile, milrinone is a phosphodiesterase III (PDE III) agent that directly affects the relaxation of smooth muscles of pulmonary blood vessels so that it can reduce vascular resistance of the lungs.[23]

Mothers with PAHs are recommended to use contraceptives to prevent unplanned pregnancies. Estrogen-containing contraceptives are not recommended because they will increase the risk of venous thromboembolism (VTE) and negatively affect pulmonary blood vessels. Estrogen also contributes to the pathogenesis of PAH in pregnant patients. Copper-containing intrauterine devices (IUDs) or progestin-releasing IUDs can be the recommended contraceptive options in PAHs.[9] In this case, the contraceptive chosen was a post-placental IUD installed during cesarean section because the patient was still of reproductive age. The IUD installation during surgery is safer because it does not manipulate the cervix so that it does not cause vasovagal reflexes that can harm the patient.

4. Conclusion

We reported cases of 24-year-old women with idiopathic pulmonary arterial hypertension newly diagnosed at 25 weeks of pregnancy with threatened preterm labor and anemia. The patient was diagnosed with a congenital heart defect PDA at the referring hospital. After going through laboratory supporting examinations and echocardiography evaluations, the patient was diagnosed with IPAH. Cardiovascular physiological changes during pregnancy and conditions of anemia compromise heart function, causing manifestations of shortness of breath. Treatment with collaboration between divisions between obstetricians, cardiologists, pulmonologists, anesthesiologists, and neonatologists, in this case, is appropriate. Termination was performed with an elective cesarean section performed to reduce the risk of perioperative mortality. The patient's current condition is good and controlled with the administration of 20 mg of sildenafil three times daily. PAH in pregnancy is a life-threatening condition if untreated. Continuous treatments can help control the symptoms and avoid further complications for both mother and baby.

5. Declarations

5.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: SH, BR. Design: SH, BR, NP, PMD, VYSP, MSR. Control/-supervision: BR, NP, PMD, VYSP, MSR. Data extraction: SH. Statistical analysis: SH, BR, NP, PMD, VYSP, MSR. Results interpretation: SH, BR, NP, PMD, VYSP, MSR. Critical review/discussion: SH, BR, NP, PMD, VYSP, MSR. Writing the article: SH, BR, NP, PMD, VYSP, MSR. All authors have critically reviewed and approved the final
draft and are responsible for the content and similarity index of the manuscript.

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