Major Depressive Disorder in a Patient with Systemic Lupus Erythematous, Pulmonary Hypertension, and Hypercoagulation: A Case Report

Muhammad Yamin[1], Edward Faisal[2], Rudi Putranto[2], Hamzah Shatri[2]*

[1] Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Division of Psychosomatic and Palliative Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Hamzah Shatri, MD., PhD. Division of Psychosomatic and Palliative Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: hshatri@yahoo.com.

ABSTRACT

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes, which are considered periods of 2 weeks of depressive moods featuring impaired neurovegetative functioning, psychomotor activity, and cognition, as well as suicidal thoughts. Major depressive disorder is commonly associated with other medical conditions, especially chronic and systemic medical illnesses. Cardiovascular diseases are among the most related, especially pulmonary hypertension, a cardiovascular disorder that results in increased pulmonary circulation pressure—with an average resting pulmonary arterial pressure of at least 25 mmHg—and which the WHO has associated with several other conditions, including connective tissue diseases such as scleroderma and systemic lupus erythematosus (SLE). The patient in this case is a 39-year-old woman diagnosed with major depressive disorder and SLE-associated pulmonary artery hypertension, which has been associated with hypercoagulable states, as observed in this instance. The complicated associations between these problems require collaboration between disciplines to establish optimal treatment integrity, with palliative care necessary to improve this patient's quality of life.

Keywords: *Depressive disorder, Pulmonary Hypertension (PH), Systemic Lupus Erythematous (SLE), Hypercoagulation.*

INTRODUCTION

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes[1] and is usually associated with other medical conditions, especially chronic and systemic conditions. The overlapping clinical conditions of physical comorbidities, the neurovegetative symptoms associated with major depressive disorder, and the emotional response to physical illness complicate accurate diagnosis and provision of appropriate treatment for depression in a person with a medical illness.[2,3] Major depressive disorder is frequently observed to be a chronic condition, occurs two to three times more often among women than men, and features a prevalence of approximately 2–4% in the community. Prevalence increases by 5–10% among outpatients in primary care and by 10–14% among medical inpatients. These statistics indicate an association between physical illness and major depressive disorder.

Psychological disorders, such as depression

and anxiety, are often observed in patients with cardiovascular diseases.[4,5] Such psychological factors have also been implicated in increases in hospitalization and mortality rates among patients with cardiovascular disease, as well as decreases in their quality of life. A study comparing patients with heart disease who were not depressed with those who were depressed indicated that the latter group was more likely to be admitted as patients within the next 3 months. Additionally, the latter group was almost 50% more likely to die during the following year (29% compared to 20%).[4]

Heart failure is especially associated with decreased quality of life, describing the final stage of various cardiovascular diseases, including pulmonary hypertension (PH), which commonly causes right heart failure and has been defined as an increase in pulmonary circulation pressure, quantified as a mean resting pulmonary artery pressure of at least 25 mmHg.[6] The WHO has classified PH into five main groups: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to pulmonary disease or chronic hypoxia, PH due to chronic thromboembolic disease, and a miscellaneous group.[7–9] Women are more likely to experience PAH, with data indicating 65–80% predominance in their favor.

The first WHO classification group, PAH, can be idiopathic (Idiopathic Pulmonary Arterial Hypertension, IPAH), inherited (Heritable Pulmonary Arterial Hypertension, HPAH), related to drugs or toxins (Drug and Toxin Pulmonary Arterial Hypertension, DTPAH), or associated with other conditions (Associated Pulmonary Arterial Hypertension, APAH), such as connective tissue diseases including scleroderma and systemic lupus erythematosus (SLE). The prevalence of PAH among those with SLE has been estimated as 0.5–17.5%.[10] An autoimmune disease with varying clinical features, SLE can manifest as one of several autoantibodies or as the formation and deposition of immune complexes, among other immune processes. These complex clinical features and pathogenesis make SLE difficult to diagnose quickly.[11]

Notably, medical comorbidities may slow the remission of major depressive disorder, meaning a prompt diagnosis leading to multidisciplinary and collaborative treatment is needed to improve patient quality of life.

CASE ILLUSTRATION

A 39-year-old female patient presented to the emergency department complaining of shortness of breath since a week before the visit. The tightness was induced by activity, and the patient felt better in a sitting position. The patient also complained of a cough, a fever, and edema in both arms and legs. Urine volume had decreased since the previous month. Although the patient was initially suspected of having contracted COVID-19, two PCR swab examinations returned negative results. The patient had routinely visited the Cardiology Division, where she had been diagnosed with hypertension and given medication therapy in the form of digoxin, candesartan, beraprost, rivaroxaban, and furosemide. Additionally, the patient was in a hypercoagulable state and was routinely visiting the hematology and oncology clinic, where she received heparin as medication. The patient had no history of other chronic diseases.

The patient had been divorced from her husband 10 years earlier and had a 16-year-old daughter. The patient was living with her parents, daughter, brother, sister, brother-in-law, and nephew and was no longer working following 10 years of employment at a travel agency. She had decided to stop working to focus on caring for her child, feeling that she had grown distant from her daughter, who she reported as tending to ignore her, never wanting to talk or communicate with her. This led the patient to feel neglected. The patient felt that her daughter was much closer to her younger siblings and parents, which had made the patient feel very sad for many years. The patient had tried to talk to her daughter, but the child was unresponsive. Attempts to communicate this to her family left the patient feeling rejected. Additionally, the patient had no friends to talk to, feeling that, for more than 5 years, she had been sad, helpless, useless, and listless. Still, she had been able to move forward and did not have suicidal thoughts.

The consciousness of the patient on arrival was compos mentis. Her blood pressure was

97/77 mmHg, her heart rate was 81 BPM, her respiratory rate was recorded as 30 times per minute, her body temperature was 36.5° C, and her O_2 saturation was 98% with 10 liters of oxygen per minute (via simple mask). The patient could be categorized as having grade II obesity (BMI: 42.98 kg/m^2). A physical examination revealed marked pallor of the skin and conjunctiva and pitting edema at both lower extremities. There were wounds in the buttocks and breast folds. Physical examinations of the heart, lungs, abdomen, and other areas were not remarkable.

As mentioned, the patient's mental status was recorded as compos mentis (E4V5M6), and her appearance was described as that of an obese woman lying down with short breath and requiring assistance with self-care functions. She was in a calm psychomotor state and cried when telling the story of her daughter. The patient was cooperative. She could speak and answer spontaneously, fluently, and clearly. The patient was in a hypothimic mood with limited affect and presented coherent thoughts with a sense of helplessness, worthlessness, and preoccupation with her daughter. Her perception was good.

Laboratory investigations showed microcytic hypochromic anemia (Hb 7 g/dL), leukocytosis, neutrophilia, hyponatremia (128), hypokalemia (3.3), hypochlorite (95.8), hypocalcemia (1.0), normal T4, increased TSH, normal cortisol levels, increased bilirubin (total: 7.91, director: 5.56, indirect: 2.35), hypoalbuminemia (2.65), hyperglobulinemia (4.65), increased LDH levels (253), and increased D-Dimer (7730). The antinuclear antibody (ANA) profile examination results were positive, showing decreased C3 (78). Radiological findings showed cardiomegaly with minimal right-sided perihilar, paracardial infiltrates, and right side superior mediastinal enlargement. Meanwhile, CT angiography revealed dilatation of the pulmonary arteries, dilatation of the right atrium and right ventricle, and bilateral pleural effusions, features consistent with PH. Echocardiography showed normal left ventricular systolic (ejection fraction of 58.1%) and diastolic functions with diminished right ventricle systolic function (TAPSE: 9.8). The tricuspid valve was severely regurgitated, and transesophageal echocardiography showed atrial septal aneurysm with PFO and right heart dilatation, most likely indicating PH. Cardiology catheterization indicated IPAH.

The medical problems present in the patient's comprehensive multiaxial diagnosis were (i) axis I: dysthymia; (ii) axis II: histrionic personality; (iii) axis III: PH, SLE, hypercoagulation, anemia, pneumonia, subclinical hypothyroidism, obesity, obstructive jaundice; (iv) axis IV: underlying medical conditions, poor child and family relationships; and (v) axis V: a Global Assessment of 40 points for functional score. Psychosocial problems were bad relationships with family members, a sense of worthlessness, and preoccupation with past mistakes.

Pharmacological therapy and supportive psychotherapy validating empathy, along with psychoeducation and cognitive behavioral therapy (CBT) were planned for this patient. Medical therapy was also prescribed based on the patient's acute conditions of shortness of breath, dysthymia, poor perfusion, hypercoagulation, edema, and electrolyte disturbances. The patient was hospitalized at intensive care for circulatory failure, electrolytes, administration of anticoagulation to prevent thrombus formation and embolism, and administration of pharmacological therapy to treat the cause. The patient was to receive endothelin receptor antagonist drugs (namely, ambrisentan, bosentan, and macitentan).

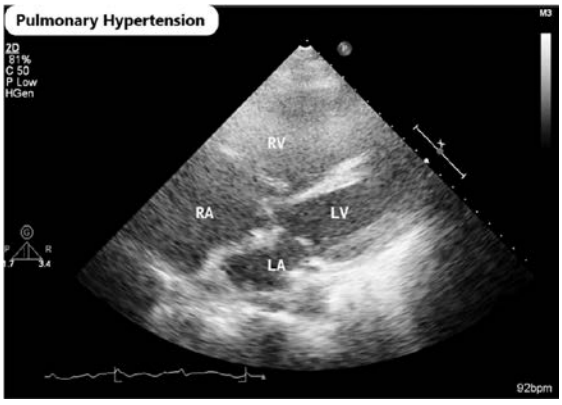

Figure 1.

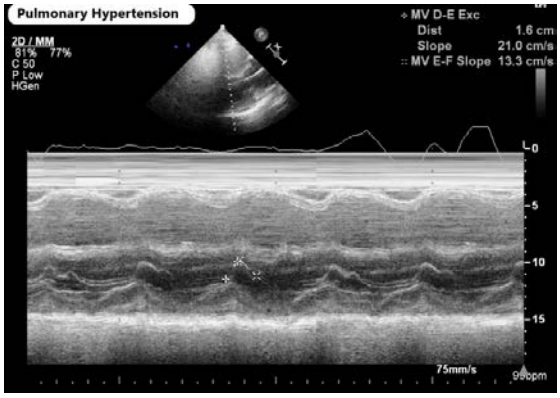

Figure 2.

DISCUSSION

Major depressive disorder is characterized by the presence of single or repeated major depressive episodes, which are considered periods of 2 weeks of depressive moods featuring impaired neurovegetative functioning (e.g., appetite, weight loss, sleep disturbances), psychomotor activity (e.g., loss of energy and interest, agitation, or retardation), and cognition (feelings of worthlessness, hopelessness, and guilt), as well as anxiety and suicidal thoughts.[1]

In this case, the patient was examined for mental status. Symptoms matched the criteria for major depressive disorder. The patient had experienced depressive moods for periods of 2 weeks for more than five years. Neurovegetative dysfunction was found in the form of decreased appetite and changes in sleeping patterns. Psychomotor activity disorders included loss of energy and interest. Additionally, impaired cognitive functioning was observed in the form of feeling worthless[1,12,13] to her family. The patient had divorced her husband 10 years earlier, almost certainly one of the stressors for the patient. Additionally, the patient's daughter was a teenager, and the patient and her daughter were living with her parents, daughter, brother, sister, brother-in-law, and nephew. The patient was no longer working, having worked for 10 years at a travel agency before deciding to stop working to focus on caring for her child. According to the patient, she had recently become less close to her daughter. All of these factors had acted as stressors for the patient, leading to poor decisions. Additionally, because she was not working and all her daily needs were paid for by her parents, her sense of worthlessness increased.

Major depressive disorder is usually associated with other medical illnesses, especially chronic and systemic medical conditions. The overlapping physical and neurovegetative symptoms of major depressive disorder and the initial normative emotional response to physical illness increase the challenge of making an accurate diagnosis. These factors also affect decisions on the appropriate treatment for major depressive disorder in a person with a medical illness.[2] Comorbidities challenge therapeutic approaches, increasing hospitalization and mortality rates, as well as decreasing quality of life.[14]

One of the medical diseases identified in this patient was PH, which, increases pulmonary circulation pressure.[4] Specifically, the patient was observed to have PAH, which is characterized by molecular and pathological changes in pulmonary circulation that primarily result in progressive vascular remodeling of the pulmonary arteries, increased pulmonary vascular resistance, and, ultimately, right heart failure and death. These changes are caused by several inflammatory, metabolic, and cellular changes that eventually promote occlusive lesions, in-situ thrombosis, and plexiform lesions. There is pro-thrombotic pathobiological evidence indicating an increased hypercoagulable state in PAH patients.[15]

In diagnosing PAH, findings from medical history, physical examination, radiographs, and electrocardiography (ECG) may reveal PH and right ventricular dysfunction. Physical examination of PH may reveal a systolic ejection murmur. Meanwhile, right ventricular failure causes systemic venous congestion, with signs including a high-pitched systolic murmur due to tricuspid regurgitation, as well as hepatomegaly, ascites, and peripheral edema. Echocardiography with Doppler can be used to initially screen to estimate pulmonary artery pressure and assess ventricular function. Right-sided cardiac catheterization is recommended as a confirmatory test for PH and can also be useful for assessing the reversibility of PAH using vasodilation therapy. Meanwhile, PAH patients should be screened clinically for possible nocturnal desaturation and obstructive sleep apnea. The complete blood

count, biochemical markers, prothrombin time, and activated partial thromboplastin time should all be checked as soon as possible, and an arterial blood gas analysis should be performed to rule out hypoxemia.[10,16]

Collagen-vascular disease screening can be performed by measuring the ANA, rheumatoid factor, and antineutrophil cytoplasmic antibody levels. Liver function tests, albumin, international normalized ratio, and platelet count may indicate either or both possible liver disease and portal hypertension. Brain natriuretic peptide (BNP from NT-proBNP) should be performed on patients as indicated. For patients at risk of HPAH, screening for gene mutations such as BMPR2 may also be considered. Ferum examination can also indicate patients at risk of PAH, with studies having found a prevalence of iron deficiency among patients with PAH. Meanwhile, histopathological lesions for patients with PAH are plexiform lesions, comprising medial hypertrophy, eccentric or concentric laminar intimal proliferation and fibrosis, fibrinoid degeneration, and thrombotic lesions.

In this case, the patient's medical history indicated severe symptoms in the form of shortness of breath and swelling, with TEE and cardiac catheterization confirming the presence of PH, good left heart systolic and diastolic functions (ejection fraction of 58%), and diminished right ventricular systolic function with tricuspid valve regurgitation. The laboratory test found an increased dimer value, prompting the diagnosis of a hypercoagulable state. That shortness of breath did not improve rapidly through acute management suggests the possibility of micro embolism associated with hypercoagulation.

Hypercoagulation is common in PH cases, with studies showing that PAH patients have increased plasma fibrinopeptide A and D-dimer levels, increased fibrinogen levels, and decreased fibrinolytic responses, especially in patients with IPAH. Fibrinopeptide A is produced when thrombin cleaves fibrinogen, indicating increased plasma thrombin activity. The procoagulant activity and fibrinolytic function of the pulmonary artery endothelium are also altered. This dysfunction is demonstrated by elevated levels of von Willebrand factor and plasminogen activator inhibitor type-1 in the plasma of PAH patients. Additionally, the pressure of blood flow to the vessel wall produces a thrombogenic surface, resulting in thrombotic lesions. In-situ thrombosis can be caused by abnormalities in some or all of the coagulation cascade, endothelial cells, and platelets. Tissue factor expression may be a major contributor to in-situ thrombosis formation, with tissue factor binding to factor VII to catalyze the activation of factor X, promoting thrombin formation and fibrin clot formation. Tissue factor expression is sensitive to changes in blood flow, hypoxia, growth factors—such as platelet-derived growth factors—and chemokines. Thromboxane A2, which stimulates activation of new platelets and increases platelet aggregation, increases in PAH patients, corresponding to a decrease in prostacyclin metabolites. Increased platelet production, activation, and aggregation can initiate a vicious cycle contributing to thrombosis.[15]

An assessment of the possibility of autoimmune disease was also performed for this patient, which is appropriate because group 1 PH can be associated with autoimmune disorders or connective tissue. The ANA profile results were positive, and the patient was diagnosed with SLE. Although the patient's symptoms did not show the abnormal clinical presentation related to SLE, autoimmune diseases with a broad clinical spectrum are known to impact specific target organs or systems. Autoimmune diseases also significantly undermine patients' quality of life.[17,18] Accordingly, this patient was classified as having WHO Group 1 PH related to autoimmune disease, commonly known as APAH.[10,11]

The causes of major depressive disorder are multifactorial, including biological, genetic, environmental, and psychosocial factors. Major depressive disorder was previously thought to be primarily due to abnormalities in neurotransmitters, particularly serotonin, norepinephrine, and dopamine. Although the real correlation of major depressive disorder with cardiovascular disease in terms of physio pathological mechanisms of depression is not fully known, some similarities have been found, including high levels of catecholamines,

cortisol, and inflammatory cytokines (IL-6, IL-1β, TNF-α), which also substantially impact the clinical and prognostic significance of depression. These conditions can increase hospitalization and mortality rates. Meanwhile, anxiety can negatively affect breathing quality and cause panic attacks and chest pain, ultimately worsening symptoms. Anxiety can also correlate with the dysfunction of the hypothalamic-pituitary-adrenal axis, which is commonly observed in cardiovascular disease.[19] Major depressive disorder negatively impacts patient quality of life and functional status, decreases physical activity levels, and worsens survival rates.[20] In this case, the patient exhibited symptoms such as helplessness, decreased appetite, and hopelessness, which were absolutely closely related to her cardiovascular disease, with the condition exacerbated by her patient's social conditions, particularly her relationship with her family.

In this case, the patient required proper treatment in the form of continued palliation. Palliative care is an interdisciplinary service and a comprehensive approach to care, with the purpose of improving quality of life and alleviating pain for patients with severe disease, regardless of prognosis. Core aspects of palliative care interventions include expert assessment of pain and other physical symptoms, psychosocial care, identification of treatment goals, and support for complex care and decision making. The optimal time to integrate primary or patient-specific palliative care varies according to the patient's needs rather than the prognosis. Additionally, palliative therapy focuses on how a clinician should assess and reduce emotional stress in a patient and their family.[21] Families should be invited to discuss and collaborate to create a positive atmosphere for improving the patient's quality of life.

Pain management and making a long-term treatment plan is also required. In this case, pharmacotherapy, in the form of serotonin selective reuptake inhibitors (SSRI) class drugs, was provided in combination with CBT therapy. A few days after the follow-up visit, the patient began to accept her condition and build relationships with her daughter and family. The combination of pharmacotherapy and psychotherapy is more effective than independent treatment for depressed patients with cardiovascular disease. The first choice of SSRIs followed convention, with SSRIs usually administered with consideration of the effectiveness and tolerability of the class as a whole. Nonetheless, other classes and atypical antidepressants have also shown treatment efficacy.

The choice and type of psychotherapy can be selected according to patient needs, with CBT and interpersonal therapy most commonly used to treat major depressive disorder.[1] A structured therapy based on a cognitive-behavioral model, CBT is based on the notion that cognition affects emotions, which in turn influence behavior. This process can modify thought cycles, emotions, and behaviors that worsen moods, with CBT treatment interventions focusing on modifying cognition and behavior to improve mood. The cognitive aspects of CBT can identify and challenge negatively biased thoughts that promote major depressive episodes, with CBT involving providing evidence to support and refute this thinking and reshaping perspectives to demonstrate that a problem is not so big or complex. Furthermore, CBT techniques seek to reinforce healthy or prosocial behavior. In patients with a medical illness, this may include a focus on scheduling, problem-solving, and prioritization, which can help patients develop a sense of reasonable control over their lives.

Pharmacological management for the patient's PH was also provided. Treatment options vary. For example, diuretics are often useful for PAH patients with signs of congestion on the right side of the heart, as evidenced by lower limb edema, ascites, liver congestion, or raised jugular veins. Digoxin is mainly used to treat PAH patients with atrial tachyarrhythmias and require inotropic properties. Meanwhile, endothelin receptor antagonists (i.e., ambrisentan, bosentan, and macitentan) activate the endothelin system, causing an increase in endothelin-1 vasoconstrictor levels among PAH patients. That is, the drugs act as antagonists in this pathway. Meanwhile, regarding phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil) and guanylate cyclase stimulators (riociguat), cyclic

guanosine monophosphate (cGMP) causes vasodilation via the nitric oxide/cGMP pathway, with PDE-5 decreasing cGMP and PDE-5 inhibitors prevent such degradation. Regarding prostacyclin analogs (beraprost, epoprostenol, iloprost, treprostinil) and prostacyclin receptor agonists (selexipag), prostacyclins are potent vasodilators, with dysregulation of prostacyclin synthesis metabolism having been identified in PAH patients.

Finally, the patient received anticoagulation therapy to treat hypercoagulation. According to the guidelines of the European Society of Cardiology and the European Respiratory Society 2015, anticoagulation is a class IIb recommendation, indicating that its usefulness and efficacy are not optimal but that it can be considered. Several retrospective and observational studies have demonstrated benefits for patients who have been anticoagulated using warfarin. However, research and data remain limited and divergent, likely due to the heterogeneity of PAH patients. Notably, the clinical use of anticoagulation to treat PAH patients varies widely.

A thorough assessment of patients experiencing mental health symptoms should not rule out medical or biological causes of the symptoms. Treatment of these patients involves an interdisciplinary approach, with both specific medications and multidisciplinary consultations required for patient treatment. The patient's hypercoagulable state, in association with PH, was also of concern, possibly creating micro embolism and making clinical improvement difficult to achieve. Additionally, while psychiatrists and therapists provide therapy to ensure open and direct lines of communication and enable patients to receive the best care,[19] it is also important to focus on the role of the patient's family, particularly, in this case, her child, siblings, and parents. Depression with medical comorbidities is not currently considered a distinct diagnostic entity; instead, it forms part of a symptom of an ongoing depressive disorder. Nonetheless, medical conditions can be a risk factor for depression, constituting stressors that can trigger or exacerbate depression among patients with other tendencies (and vice versa).

CONCLUSION

Major depressive disorder is characterized by 2-week periods of depressive moods featuring neurovegetative dysfunction—in the form of a decreased appetite and changes in sleeping patterns—and impaired psychomotor activity—including absences of energy and interest. Additionally, impaired cognitive functioning is observed, generally as feelings of helplessness and worthlessness. In this case, the patient was also observed to be suffering from APAH, a version of PH associated with an autoimmune disease. Pulmonary hypertension has also been closely related to hypercoagulation. Importantly, as observed in this case, psychosocial problems can clinically aggravate patients with cardiovascular disease, producing a complex relationship between the diagnoses that requires collaborative care between disciplines to establish optimal treatment integrity. Ultimately, in cases such as the one this paper has discussed, palliative care is required to improve a patient's quality of life.

REFERENCES

1. Thom R, Silbersweig DA, Boland R. Major depressive disorder in medical illness: A review of assessment, prevalence, and treatment options. American Psychosomatic Society. 2019.
2. Grobler G. Major depressive disorder. South African Journal of Psychiatry. 2013.
3. Bains N, Abdijadid N. Major depressive disorder. StatPearls. 2020.
4. Kenneth M, Gregory L. Psychological factors in heart failure: A review of literature. Arch Intern Med. 2002.
5. Bordoni, Bruno. Depression and anxiety in patients with chronic heart failure. Future Cardiol. 2018.
6. Tonelli AR, Arelli V, Minai OA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013.
7. Dhala, Atiya. Pulmonary arterial hypertension in systemic lupus erithematosus: Current status and future direction. Clinical and Developmental Immunology. 2012.
8. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. Chest. 2011.
9. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011.
10. Gomez S, Hansmannb G, Walter Kl, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of

pulmonary hypertension – web addenda. European Heart Journal. 2015.
11. Antonis F, Kostopoulou K, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. 2019.
12. Patel Raj, Gregory R. Persistent depressive disorder (dysthymia). StatPearls. 2020.
13. Uher R, Payne JL, Pavlova B, Perlis RH. Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV. Depress Anxiety. 2014.
14. Vandeleur CL, Fassassi S, Castelao E, et al. Prevalence and correlates of DSM-5 6. Medical therapy for heart failure associated with pulmonary hypertension. Circulation. 2019.
15. Isabel B, Wassim F. Hypercoagulability in pulmonary hypertension. Clin Chest Med. 2018.
16. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013.
17. Aringer M, Leuchten N, Johnson SR. New criteria for lupus. Current Rheumatology Reports. 2020.
18. Aringer M, Karen C, David D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. American College of Rheumatology. 2019.
19. Kessler RC, Ormel J, Petukhova M, et al. Development of lifetime comorbidity in the World Health Organization world mental health surveys. Arch Gen Psychiatry. 2011.
20. Heo, Seongkum, et al. Quality of life in patients with heart failure: Ask the patients. NIH Public Access. 2009.
21. Kavalierato. Palliative care in heart failure: Rationale, evidence, and future priorities. J Am Coll Cardiol. 2017.