JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 52, Number 3, 2020; 235-242
http://dx.doi.org/10.19106/JMedSci005203202005

Association between serum soluble ST2 level and right ventricle systolic function on pulmonary hypertension due to atrial septal defect

Firandi Saputra, Anggoro Budi Hartopo*, Hariadi Hariawan, Dyah Wulan Anggrahini, Lucia Kris Dinarti

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesi

Submitted : 2020-03-04
Accepted : 2020-07-04

ABSTRACT

Pulmonary hypertension (PH) due to atrial septal defect (ASD) may cause a decline in right ventricle (RV) function. Soluble ST2 isa prognostic biomarker for left ventricle dysfunction. However, its role in RV function has not been investigated. This study aimed to investigate the association between serum soluble ST2 with RV systolic function in patients with ASD–associated PH. This was a cross sectional study. Subjects were patients participated in the COHARD-PH registry performed in Dr. Sardjito General Hospital, Yogyakarta Indonesia. The patients with ASD and PH confirmed by right heart catheterization (RHC) were enrolled in this study. The soluble ST2 level was measured in the serum collected from pulmonary artery during RHC. Right ventricle systolic function was determined by transthoracic echocardiography using peak systolic velocity of tricuspid annulus (S') parameter. This study was performed in 32 adults with uncorrected ASD. They predominantly females [n=29 (90.6%)] with median age of 31(22.5-44.0) years old. Mean ASD diameter was 2.69±0.53 cm. Median mean pulmonary artery pressure (mPAP) 45.0 (36.25-70.0) mmHg. Median soluble ST2 level was 23.28 ng/mL. There were no significant correlations between soluble ST2 level with S'value (r=0.071; p=0.35), with mPAP (r=0.043; p=0.815), with pulmonary vasculer resistance (PVR) (r=0.025; p=0.893) and with right ventricle (RV) diameter (r=0.200; p=0.273). Soluble ST2 level was found higher in subject with RV dysfunction but not statistically significant. In conclusion, serum soluble ST2 level did not associate with RV systolic function, measured by S', in adult ASD-associated PH.

ABSTRAK

Hipertensi paru (HP) akibat defek septum atrium (DSA) dapat menyebabkan penurunan fungsi ventrikel kanan. ST2 terlarut adalah biomarka prognostik untuk disfungsi ventrikel kiri, namun perannya pada fungsi ventrikel kanan belum diteliti. Tujuan penelitian ini adalah menyelidiki hubungan antara ST2 terlarut serum dengan fungsi sistolik ventrikel kanan pada pasien HP-yang terkait DSA. Penelitian ini merupakan penelitian potong lintang. Subjek adalah partisipan register COHARD-PH yang dilakukan di RSUP Dr. Sardjito, Yogyakarta, Indonesia. Pasien dengan DSA dan HP yang dikonfirmasi dengan penyadapan jantung kanan diikutkan dalam penelitian ini. Kadar ST2 terlarut diukur dari serum yang diambil dari arteri paru selama penyadapan jantung kanan. Fungsi sistolik ventrikel kanan ditentukan dengan pemeriksaan ekhokardiografi transthoraks menggunakan parameter kecepatan puncak sistolik dari anulus trikuspid (S'). Penelitian ini dilakukan pada 32 pasien DSA dewasa yang tidak dikoreksi. Sebagian subjek adalah wanita [n=29 (90,6%)] dengan median umurnya 31(22,5-44,0) tahun. Rerata diameter DSA adalah 2,69±0,53 cm. Median tekanan rerata arteri paru adalah (mPAP) 45,0 (36,25-70,0)mmHg. Median kadar ST2 terlarut adalah 23,28 ng/mL. Tidak terdapat korelasi signifikan antara kadar ST2 terlarut dengan nilai S' (r=0.071; p=0.35), dengan rerata tekanan arteri paru (mPAP) (r=0,043; p=0,815), dengan tahanan vaskular paru (PVR) (r=0,025; p=0,893) dan dengan diameter ventrikel kanan (RV) (r=0,200; p=0,273). Kadar ST2 terlarut lebih tinggi pada subjek dengan disfungsi RV, namun tidak bermakna secara statistik. Dapat disimpulkan, kadar ST2 terlarut serum tidak berhubungan dengan fungsi sistolik ventrikel kanan, yang diukur dengan S', pada pasien HP-terkait DSA dewasa.

Keywords:
atrial septal defect;
pulmonary artery hypertension;
right ventricle systolic;
function;
soluble ST2;

*corresponding author: a_bhartopo@ugm.ac.id

INTRODUCTION

Atrial septal defect (ASD) is one of the most common adult congenital heart disease (CHD). It was estimated that the prevalence is about 1.6 per 1,000 birth.[1] There are three types of ASDs, among them is secundum type ASD which occurs in 75% of overall ASD cases.[1] In ASD, the chronic left-to-right shunt through septal defect gives rise to chronic volume overload in the right ventricle (RV) and blood overflow in pulmonary circulation. Eventually, pulmonary artery pressure elevates and pulmonary hypertension (PH) ensues.

Pulmonary hypertension is a vasculopathy disorder in which there is a progressive increase in pulmonary vascular resistance that lead to RV dysfunction.[2] Itis a frequent complication of CHD, especially CHD with left-to-right shunt, such as ASD. The prevalence of PHin uncorrected ASD patients is 5-10%.[3] The RV function determines the prognosis in patients with ASD-associated PH. The structure and function of RV is not only an indicator of the severity and chronicity of PH but also an indicator of severity of underlying disease. The RV dysfunction decreased life expectancy of ASD-associated PH.[4]

Several clinical conditions associated with myocardial strains, such as volume or pressure overload, dilatation of the heart chamber, valvular heart disease, or increased pulmonary artery pressure, increase soluble suppression of tumorigenicity-2 (ST2) levels.[5] Recent studies have focused on the role of soluble ST2 on left heart failure. There is only a few studies investigate the soluble ST2 level in right heart failure induced by PH. A study found that circulating soluble ST2 level increased in PH patients and was associated with RV dilatation as well as systolic dysfunction.[6] Soluble ST2 level not only reflects left ventricular function but also the degree of right heart failure, as occurs in patients with PH.[6,7] However, the association of soluble ST2 level with RV systolic function in ASD-associated PH has not yet confirmed. This study aimed to investigate the association between soluble ST2 level from pulmonary artery and RV systolic function in adult ASD-associated PH patients.

MATERIALS AND METHODS

Subject

The study design was cross sectional. The subjects were patients registered in the Congenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry, Yogyakarta, Indonesia whom recruited between January 2017 and April 2018 period.[8] The inclusion criteria of this study were1) adult (≥ 18 years old) uncorrected secundum ASD; 2) patients had been undergone right heart catheterization (RHC) and confirmed PAH, and 3) patients had sinus rhythm in electrocardiogram. The exclusion criteria of this study were 1) patients with history of myocardial infarction; 2) patients with impaired left ventricular systolic function; 3) patients have significant valve diseases; 4) patients have lung diseases (asthma bronchial, chronic obstructive and restrictive lung diseases, and post lung tuberculosis); 5) patients with diabetes mellitus; 6) patients with chronic renal disease, and 7) patients with a history of malignancy.

Protocol of study

The diagnosis of ASD and probability of PH was screened by transthoracic echocardiography (TTE) and/or transoesophageal echocardiography (TOE). The TTE and TEE were performed by experienced sonographers and the results were confirmed by cardiologist consultants using the VIVID7 Echo machine (G.E, USA). The echocardiographic data was stored digitally in the form of discs to be analyzed offline from workstation computers using Echo-Pac (G.E, USA)

software by cardiologist consultants. The parameters analyzed were ASD diameter, right atrium (RA) diameter, RV diameter, transvalvular gradient (TVG) and tricuspid regurgitation (TR) severity. The RV systolic function was measured from apical 4-chamber view with Tissue Doppler mode to analyze peak systolic velocity of tricuspid annulus (S') parameter. The RV systolic dysfunction was determined if the S' value <10cm/second.

The hemodynamic assessment was performed with RHC examination using right femoral vein access. The parameters assessed include mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), flow ratio (FR), mean aortic pressure (mAoP) and right ventricle systolic pressure (RVSP). The diagnosis of PH was based on mPAP value ≥25 mmHg and pulmonary artery wedge pressure (PAWP) value ≤15 mmHg.[9]

Blood samples for measurement of circulating ST2 level were with drawn by catheter placed in the pulmonary artery during RHC. The 2 mL blood volume were inserted into EDTA tube and centrifuged at 4,000 rpm for 10 min at 25°C. The supernatan was pipetted and aliquoted in a polypropylene tube. The tube was stored at -80°C freezer until analyzed. The sample was thawed once just before it was analyzed. The circulating ST2 levels were measured with a cassette-based immunofluorescence imaging method (cartridge) using the principle of lateral flow immunoassay technology. This test used ASPECT-PLUS™ ST2 Test tapes and was analyzed with an ASPECT READER™ (Critical Diagnostics, USA) tool like previously described.[10] The measured sST2 was expressed in concentration (ng/mL).

All participants in this study were given an informed consent. The ethics committee of Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia had approved the study protocol.

Statistical analysis

Statistics analysis was performed with SPSS software version 16.0 (SPSS Inc., Chicago, IL). For continuous data, the data normality test was performed by Saphiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (SD), not normally distributed data were presented in the median and interquartile range (Q1-Q3). Categorical variables were presented in proportion. Pearson correlation test was performed to determine the correlation coefficient between two normally distributed variables, while Spearman correlation test for data with not normal distribution. The mean difference between the two groups was analyzed using the student-t or Mann Whitney test. A p value <0.05 was considered statistically significant.

RESULTS

A total of 32 subjects were enrolled in this study. The characteristics of the subjects are presented in TABLE 1. The majority of the subjects were females (90.6%) with a median age of 31 (22.5-44.0) years old. From RHC examination, median mPAP was 45.0 (36.25-70.0) mmHg and mean mAoP equal to 102.0 ± 14.75 mmHg. The mean FR was 2.69± 2.01, median PVR was 5.25 (1.88-12.68) Wood unit and mean RVSP was 80.63± 29.32 mmHg. The median value of serum ST2 level from pulmonary artery was 23.28 (18.80-33.55)ng/mL.

From the echocardiography examination, the mean diameter of ASD defect was 2.69 ± 0.53 cm, the median RA diameter was 4.70 ± 0.55cm, the meanRV diameter was 4.74 ± 0.54 cm, and the mean TVG was 68.84 ± 32.45mmHg. The degree of TR varied in the subjects, with 10 subjects had mild degree (31.3%), moderate degree in 11 (34.4%) subjects, and severe degree in 11 (34.4%) subjects.

TABLE 1. The characteristics of adult secundum atrial septal defect-associated pulmonary hypertension

Characteristics	Total (n=32)
Gender [n (%)]	
• Male	2 (9.4)
• Females	29 (90.6)
Age [media (Q1-Q3) year]	31 (22.5-44.0)
Body Surface Are (mean ± SD year)	1.40 ± 0.16
Echocardiography parameter	
• ASD defect diameter (mean ± SD cm)	2.69 ± 0.53
• RA diameter (mean ± SD cm)	4.83 ± 0.55
• RV diameter (mean ± SD cm)	4.74 ± 0.50
• S' (mean ± SD cm/s)	13.72 ± 3.69
• TVG (mean ± SD mmHg)	68.84 ± 32.45
• TR severity [n (%)]	
• Mild	10 (31.3)
• Moderate	11 (34.4)
• Severe	11 (34.4)
• LV ejection fraction (mean ± SD %)	73.94 ± 7.80
Hemodynamic parameter by RHC	
• mPAP [median (Q1-Q3) mmHg]	45.0 (36.25-70.0)
• mAoP(mean ± SD mmHg)	102.0 ± 14.75
• FR (mean ± SD)	2.69 ± 2.01
• PVR [median (Q1-Q3) Woods unit]	5.25 (1.88-12.68)
• RVSP (median ± SD mmHg)	80.63 ± 29.32
PH-targeted therapy	
• Seldenafil [n (%)]	11 (34.4)
• Beraprost [n (%)]	5 (15.6)
Serum sST2 (ng/mL); median (Q1-Q3)	23.28 (18.80-33.55)

ASD: atrial septal defect, RA: right atrium, RV: right ventricle, TVG: tricuspid valve gradient; TR: tricuspid regurgitation, LV: left ventricle, mPAP: mean pulmonary artery pressure, mAoP: mean aortic pressure, FR: flow ratio, PVR: pulmonary vascular resistance;RVSP: right ventricle systolic pressure, PH: pulmonary hypertension

From Spearman correlation test, it was found that serum ST2 level did not correlate with S' value (r = 0.071; p = 0.35) (FIGURE1). In addition, the serum ST2 level did not correlate with age (r =0.098; p =0.054), defect diameter (r =0.010; p =0.955), RA diameter (r =0.041; p =0.823), RV diameter (r =0.025; p =0.893), FR (r =0.025; p =0.893), PVR (r =-0.025; p =0.273), TVG (r =-0.041; p =0.824), and RVSP (r =-0.024; p =0.262).

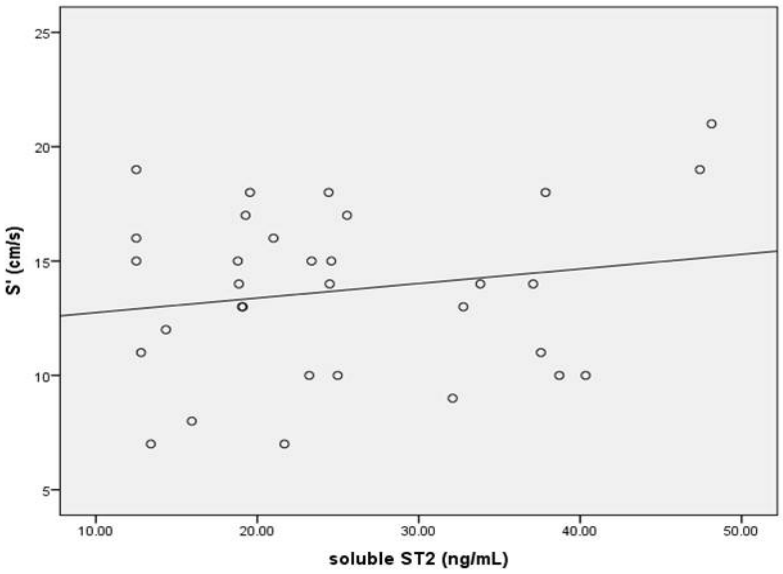

FIGURE 1. The scatter-plot of correlation between soluble ST2 and S' value (r = 0.071; p = 0.35).

The analysis was performed by categorizing subjects into 2 group, i.e. subjects with RV dysfunction and subject with normal RV function. The RV dysfunction was defined by value S' <10cm/sec. There was significant difference between these 2 groups in term of mean RVSP (99.71±33.42vs. 75.28±26.36 mmHg; p=0.050), median mPAP (72.0(34–91) vs. 43.0 (30–79) mmHg; p=0.032), and median PVR (30.19(3.1–56.28)vs. 5.31 (2.37–12.64) Wood unit; p=0.034), respectively. Serum ST2 level was higher in subjects with RV dysfunction as compared with subjects with normal RV function but statistically not significant (median: 24.97 (21.68-38.7)ng/mL vs. 21 (17.36-33.28) ng/mL; (p=0.284) (TABLE 2).

TABLE 2. The comparison of characteristic of adult secundum atrial septal defect-associated pulmonarybased on the presence of right ventricle systolic dysfunction

Characteristics	Right ventricledysfunction (n=7)	Normal right ventricle function (n=25)	p
Age (years)	25 (21-41)	34 (23-45.5)	0.373*
Echocardiography Parameter			
• Defect diameter (mean ± SD cm)	2.64± 0.66	2.67±0.50	0.887
• RV diameter (mean ± SD cm)	4.87± 0.54	4.71±0.49	0.466
Hemodynamic parameter by RHC			
• RVSP (mean ± SD mmHg)	99.71±33.42	75.28±26.36	0.050
• mPAP(mean ± SD mmHg)	72.0(34-91)	43.0(30-79)	0.032*
• PVR [median (Q1-Q3) Woods unit]	30.19 (3.1–56.28)	5.31 (2.37–12.64)	0.034*
• FR (mean ± SD)	1.54±0.50	3.0±2.0	0.088
Serum sST2 (mean ± SD ng/mL)	24.97 (21.68-38.70)	21.0(17.36-33.28)	0.284*

*Nonparametric data and analyze with Mann-Whitney test; RV: right ventricle; RVSP:right ventricle systolic pressure; mPAP: mean pulmonary arterial pressure; PVR:pulmonary vascular resistance; FR: flow ratio

The correlation between parameters with S' value was shown in TABLE 3. The mPAP and PVR had a significantly strong and negative correlation with S' value (r =-0.661; p <0.001) and (r =-0.568; p =0.001), respectively.

TABLE 3. The correlation between parameters and S' value

Parameters	value
Age	
• r	0.081
• p	0.330
mPAP	
• r	-0.661
• p	0.000
PVR	
• r	-0.568
• p	0.001
Defect diameter	
• r	0.028
• p	0.439
RV diameter	
• r	-0.271
• p	0.066

DISCUSSION

In this study, the serum sST2 level from pulmonary artery did not associate with RV systolic function. There was a tendency toward increased serum sST2 level from pulmonary artery in subjects with RV systolic dysfunction. The mPAP and PVR value influenced the RV systolic dysfunction. There was an inverse correlation between mPAP and PVR value with S' value, indicated the association between increased pulmonary artery pressure and resistance with reduced RV function.

In the secundum ASD population, females dominates as much as 65-75% of the population.[3] This is similar to this study in which females predominates, 90.6%. According to the registers in Europe, the mean age of ASD patients was 36 years old.[11,12] This was consistent with this study in which the median age of this study subjects was about 30 years. There is a timespan from asymptomatic to symptomatic phase of ASD due to complication PH. In the COHARD-PH registry, most patients with ASD did not diagnosed properly in childhood and consequently develop complication of PH, Eisenmenger syndrome and right heart failure.[8]

This study was the first to assess the association between serum sST2 level, taken from pulmonary artery, with S' parameter in ASD-associated PH. Previous research had shown a significant correlation between serum sST2 with RV systolic function parameters,i.e Tricuspid Annular Plane Systolic Excursion (TAPSE) and Right Ventricle Fractional Area Change (RVFAC), in the PH subjects population due to chronic obstructive pulmonary disease.[13] Other studies with PH population due to various etiologies,

found that sST2 levels were associated with RV systolic function measured by cardiac magnetic resonance imaging.[13] Our results differ from those previous studies, in which serum sST2 were not significantly correlated with RV systolic function parameters, by S' value. The serum sST2 level also did not discriminate subjects with RV dysfunction.

The difference in the results of this study compared with previous studies may be due to different RV adaptation responses in two different populations. The RV adaptive response to shunt of CHD is quite good as compared to idiopathic PAH or PH due to other causes.[4] One study found that RV dilatation and rapid decline in RV systolic function are more common in patients with idiopathic PAH or PH-associated with pulmonary disease or connective tissue disease. In contrast, the decrease in RV function occurs much more slowly in patients with ASD-associated PH.[14,15]

This study has several limitations, i.e. the subjects sample size is small and the parameter of RV systolic dysfunction is only one parameter i.e. S' by TTE. Further large study need to be performed to corroborate or contradict the result of this study. However, our result suggests that sST2 is not a good biomarker to detect RV function especially in ASD-associated PH patients. Our previous data indicated that other strained biomarker, i.e. N-terminal pro brain natriuretic peptide, is performed better in predicting PH severity, RV pressure overload and RV systolic function in adult patients with ASD.[16] Future direction needs to be addressed is to test the other potential biomarkers for RV function in patients with PH.

CONCLUSION

In conclusion, there is no association between serum sST2 levels from pulmonary artery with systolic RV function in secundum ASD-associated PH patients.

ACKNOWLEDGEMENT

Authors would like to thanksall research assistants of COHARD-PH registry. Authors express gratitude to Ms. Sri Mardilah Wuryani AMK for echocardiography examination, Mr. Farid Abdullah for blood sample analysis, and Dr. Kurniasari Endah from UBC Medical Indonesia for providing the Aspect plus ST2 reader and Aspect plus ST2 rapid test cassette.

REFERENCES

1. Post MC. Association between pulmonary hypertension and an atrial septal defect. Neth Heart J 2013; 21:331-2. https://doi.org/10.1007/s12471-013-0432-9
2. Lourenco AP, Fontoura D, Henriques-Coelho T, Leite-Moreira AF. Current pathophysiological concepts and management of pulmonary hypertension. Int J Cardiol 2012; 155:350-61. https://doi.org/10.1016/j.ijcard.2011.05.066
3. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. Circulation 2006; 114:1645-3. https://doi.org/10.1161/CIRCULATIONAHA.105.592055
4. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, Mcgoon MD, Meldrum DR, *et al.* Right ventricular function and failure. Circulation 2006; 114:1883-91. https://doi.org/10.1161/CIRCULATIONAHA.106.632208
5. Januzzi J, Peacock W, Maisel A, Chae CU, Jesse RL, Baggish AL, *et al.* Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the Pro BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. J Am Coll Cardio 2007; 50:607-13. https://doi.org/10.1016/j.jacc.2007.05.014
6. Carlomagno G, Messalli G, Melillo R, Stanziola A, Visciano C, Mercurio V, *et al.* Serum soluble ST2 and

interleukin-33 levels in patients with pulmonary arterial hypertension. Int J Cardiol 2012; 168:1545-47. https://doi.org/10.1016/j.ijcard.2012.12.031
7. Zheng Y, Yang T, He J, Chen G, Liu Z, Xiong C, *et al.* Plasma soluble ST2 levels correlate with disease severity and predict clinical worsening in patients with pulmonary arterial hypertension. Clin Cardiol 2014; 37:365–70. https://doi.org/10.1002/clc.22262
8. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD. The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. BMC Cardiovasc Disord 2020; 20(1):163. https://doi.org/10.1186/s12872-020-01434-z
9. Galie N, Humbert M, Vachiery KL, Gibbs S, Lang I, Torbicki A, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016; 37:67-119. https://doi.org/10.1183/13993003.01032-2015
10. Hartopo AB, Sukmasari I, Puspitawati I. The utility of point of care test for soluble ST2 in predicting adverse cardiac events during acute care of ST-segment elevation myocardial infarction. Cardiol Res Pract 2018; 3048941. https://doi.org/10.1155/2018/3048941
11. Engelfriet PM, Duffels MGJ, Moller T, Boersma E, Tijssen JGP, Thaulow E, *et al.* Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart 2007; 93:682-7. https://doi.org/10.1136/hrt.2006.098848
12. Beghetti M, Galiè N. Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol 2009; 53:733-40. https://doi.org/10.1016/j.jacc.2008.11.025
13. Agoston-Coldea L, Lupu S, Hicea S, Paradis A, Mocan T. Serum levels of the soluble IL-1 receptor family member ST2 and right ventricular dysfunction. Biomarkers Med 2014; 8: 95-106. https://doi.org/10.2217/bmm.13.116
14. Poels EM, Martins PA, Empel VP. Adaptive capacity of the right ventricle, why does it fail? Am J Physiol Heart 2015; 308:H803-13. https://doi.org/10.1152/ajpheart.00573.2014
15. Gorgulu S, Eren M, Uslu N, Ozer O, Nurkalem Z. The determinants of right ventricular function in patients with atrial septal defect. Int J Cardiol 2006; 111:127-30. https://doi.org/10.1016/j.ijcard.2005.07.037
16. Pratama RS, Hartopo AB, Anggrahini DW, Dewanto VC, Dinarti LK. Serum soluble suppression of tumorigenicity-2 level associates with severity of pulmonary hypertension associated with uncorrected atrial septal defect. Pulm Circ 2020; 10(2):2045894020915832. https://doi.org/10.1177/2045894020915832