Usefulness of Combining NT-proBNP Level and Right Atrial Diameter for Simple and Early Noninvasive Detection of Pulmonary Hypertension Among Adult Patients with Atrial Septal Defect

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ABSTRACT

Background: *Atrial septal defect developed pulmonary hypertension (ASD-PH) at first diagnosis due to late presentation are common in Indonesia. Transthoracic echocardiogram (TTE) is a common tool to detect ASD-PH, before proceeding to invasive procedure. The NT-proBNP measurement to screen ASD-PH is not yet considered the standard approach, especially in limited resource conditions. The objective of this study is to assess the value of NT-proBNP, along with simple TTE parameter, to screen PH among adults with ASD.* ***Methods:*** *This was a cross-sectional study. The subjects were adult ASD-PH patients from the COHARD-PH registry (n=357). Right heart catheterization (RHC) was performed to diagnose PH. Blood sample was withdrawn during RHC for NT-proBNP measurement. The TTE was performed as standard procedure and its regular parameters were assessed, along with NT-proBNP, to detect PH.* ***Results:*** *Two parameters significantly predicted PH, namely NT-proBNP and right atrial (RA) diameter. The cut-off of NT-proBNP to detect PH was ≥140 pg/mL. The cut-off of RA diameter to detect PH was ≥46.0 mm. The combined values of NT-proBNP level ≥140 pg/mL and RA diameter ≥46.0 mm yielded 46.6% sensitivity, 91.8% specificity, 54.3% accuracy, 96.5% positive predictive value and 26.2% negative predictive value to detect PH, which were better than single value.* ***Conclusion:*** *NT-proBNP level ≥140 pg/mL represented PH in adult ASD patients. The NT-proBNP level ≥140 pg/mL and RA diameter ≥46.0 mm had a pre-test probability measures to triage patients needing more invasive procedure and also to determine when and if to start the PH-specific treatment.*

Keywords**:** *atrial septal defect, N-terminal pro-BNP, pulmonary arterial hypertension, diagnostic test.*

INTRODUCTION

In developed countries, registries of congenital heart disease (CHD) in adults associated with pulmonary hypertension (PH) are dominated by heart congenital systemic-to-pulmonary shunt defects.[1,2] In this context, its prevalence is much higher in developing countries due to PH complication as a late diagnosis and uncorrected systemic-to-pulmonary shunting.[3-5] Adult patients with undetected and delayed diagnosis of CHD seek medical advice mostly due to complaints related to PH such as dyspnea, easily fatigued, dizziness, presyncope and chest discomfort.[5,6] The most common CHD with overlooked diagnosis is atrial septal defect (ASD), which accounts for the most common uncorrected CHD in adults.[3,5,6]

In ASD patients, PH is a result of protracted hypercirculation and overloaded blood volume in the pulmonary circulation. Its consequences are represented by: endothelial dysfunction, pulmonary vascular remodeling, increased pulmonary artery pressure and augmented pulmonary vascular resistance.[7] The current guideline compels the utilization of right heart catheterization (RHC) to diagnose the hemodynamics of PH and guidance to confirm pulmonary artery hypertension (PAH), by directly measuring mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP).[8] The precise values of mPAP ≥20 mmHg, PVR >3 Wood Units and PCWP ≤15 mmHg are determined for a confirmation of PAH diagnosis.[8,9] In ASD, the values of RHC are not only used for PAH diagnosis, but also for selecting patients suitable for defect closure as a definitive therapeutic choice which should have been done as early as possible in childhood.[6]

In Indonesia, due to their late presentation at cardiologist visit, the majority of adult patients with ASD have already developed PH at initial diagnosis.[5] Moreover, the number of hospitals which can provide RHC and heart defect correction are limited. The chest-X ray, electrocardiogram and transthoracic echocardiogram (TTE) are the most common tools to detect suspicion of PH due to ASD (ASD-PH), before proceeding to RHC. The current guideline on diagnosis and management of pulmonary hypertension by Indonesian Heart Association includes the TTE as a first diagnostic tool to detect PH and the use of biomarker, NT-proBNP, as a prognostic component of PAH. Although TTE measurements are widespread, the use of NT-proBNP as a diagnostic tool to help screen for ASD-PH is not yet considered a standard approach. Currently, in PAH patients the use of NT-proBNP is recommended only as prognostic value.[8,9] Therefore, the diagnostic role of NT-proBNP for ASD-PAH needs to be further investigated, especially in the settings with limited resources and scarce facilities for more advanced procedures, such as RHC and surgical closure. Consequently, we conducted a study to assess the sensitivity, specificity, accuracy and predictive value of circulating level of NT-proBNP in early and non invasive detection of the PH presence among adult patients with ASD.

METHODS

This was a cross-sectional design study. The variable tested for this study was the cut-off level of NT-proBNP for diagnostic power of the presence of PH in adults with ASD. We enrolled patients with diagnosis of PH already confirmed by RHC as a gold standard. The studied population was represented by adult patients in hospital with uncorrected ASD, who were mostly symptomatics.[5]

The subjects of this study were patients registered into the COngenital HeARt Diseases in adult and Pulmonary Hypertension (COHARD-PH) registry. The COHARD-PH registry is a single-center, observational, and prospective registry which enrolls adult patients with CHD and CHD-associated PH in Dr. Sardjito Hospital, Jogjakarta, Indonesia.[5] The subjects selected for this study fulfilled the inclusion and exclusion criteria as follows. Inclusion criteria were: (1) patients diagnosed with ASD, (2) patients evaluated by RHC, and (3) patients in whom NT-proBNP circulating levels was obtained. Exclusion criteria were: (1) patients who underwent a previous ASD closure procedure, (2) patients with other congenital defects or multiple septal defects, (3) patients with significant valve diseases other than tricuspid or pulmonal valves

regurgitation, (4) patients with component of post-capillary PH by RHC (i.e. mean left atrial pressure (mLAP) or PCWP >15 mmHg) and (5) the incomplete haemodynamic result of RHC.

The sample size estimation was determined from formula to calculate the accuracy index by receiver operating characteristics (ROC) curve.[10] The minimal sample size requirement was 114 for each case and control.[10]

All subjects signed an informed consent form as part of the inclusion in the COHARD-PH registry and its subsequent studies. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by Medical and Health Research Ethical Committee of Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Indonesia (Ref. no. KE/FK/0738/EC/2020 and KE/FK/1189/EC/2021).

Data Collection

The demographics, clinical characteristics, laboratory data and echocardiograms were retrieved from the COHARD-PH registry database. The data were collected from the index of ASD diagnosis, i.e. during TTE and transoesophageal echocardiography (TOE) examinations (G.E Vivid 7 (G.E Healthcare, U.S.A), G.E Vivid S6 (G.E Healthcare, U.S.A) or Phillips HD 15 (Philips N.V, The Netherlands)). The measurement of defect diameter, right atrial (RA) diameter (minor dimension), right ventricle (RV) diameter (maximal minor dimension), tricuspid annular plane systolic excursion (TAPSE) and left ventricle ejection fraction (LVEF) were performed based on standard procedures.[11] The image acquisitions were conducted by experienced sonographers. The validation and confirmation of TTE and TOE results were performed by cardiologist consultants as described previously.[5,12]

The results of RHC data were retrieved from the COHARD-PH registry database. During RHC, the hemodynamic measurements and calculations were determined by indirect Fick methods, as previously described.[5] The PH diagnosis in this study was determined as mPAP ≥20 mmHg and PCWP or mLAP ≤15 mmHg by RHC, at any calculated PVR index.

The blood sample was collected from each patient during RHC by venipuncture from peripheral veins (for hemoglobin and hematocrit measurement by hemocytometer) and from inferior vena cava (for NT-proBNP measurement by electrochemiluminescence immunoassay (ElecsysProBNP II) and a Cobas e immunoassay analyzer (Roche Diagnostics, Germany). These measurements were performed in our hospital's central laboratory.[5]

Statistical Analysis

The presentation of numerical data was in mean and standard deviation (SD) (for normal distribution of numerical data) or median and interquartile range (IQR) (for non-normal distribution of numerical data). The Kolmogorov-Smirnov test was applied as determination of normal and non-normal numerical data distribution. The presentation of categorical data was in percentage. The Student T test or Mann-Whitney test was used to compare numerical data. The chi-squared test was used to compare categorical data. Univariate and multivariable analyses were performed with logistic regression tests to analyze the independent predictors for PH. A correlation test was performed with either Pearson (for normal distribution of numerical data) or Spearman test (for non-normal distribution of numerical data). An ROC curve was constructed to analyze the area under the curve (AUC) and to determine the best cut-off point for accuracy of the diagnostic test for PH. The diagnostic tests were performed using the determined cut-off value. A p value <0.05 was considered statistically significant.

RESULTS

From July 2012 until December 2020, 910 consecutive adult patients with ASD included in the COHARD-PH registry were enrolled into the study. Among them, 620 had undergone RHC procedure. As many as 436 patients had NT-proBNP measurement during the RHC procedure. After being selected based on inclusion and exclusion criteria, 357 subjects were considered eligible to be included in this study. Seventy-nine subjects were excluded due to incomplete RHC results. **Figure 1** showed the flow-chart of subjects' enrollment and selection

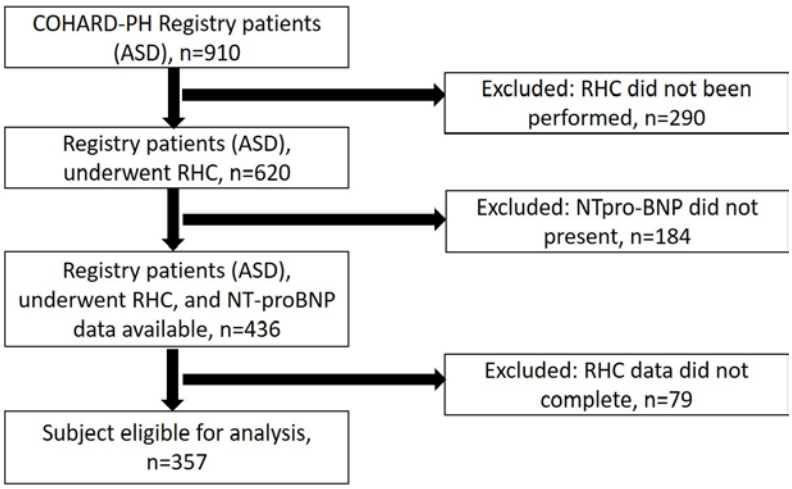

Figure 1. The flow-chart of enrollment and selection of subjects from the COHARD-PH registry.

from the COHARD-PH registry.

The majority of subjects were females (82.7%) with ages in their mid-thirties. The mean ASD diameter was 2.4±0.8 cm. Most subjects had already developed PH (82.9%), based on the criteria. Subjects with ASD-PH had significantly older ages, less bodyweight, less oxygen saturation, with higher hemoglobin and hematocrit levels. From TTE result, they had larger septal defect diameter, greater RA and RV diameters, lower TAPSE and higher LVEF. The NT-proBNP level was significantly higher in subjects with ASD-PH compared to ASD patients with no PH. **Table 1** shows the demographic, clinical, laboratory, echocardiogram and hemodynamic characteristics of all subjects and their comparisons based on the presence of PH.

Among variables that were associated with PH in the univariate analysis, only NT-proBNP level (adjusted OR 1.004, 95% CI: 1.001-1.006,

Table 1. The demographic, clinical, laboratory, structural (TTE) and hemodynamic (RHC) characteristics of all subjects and their comparison based on the presence of PH.

Characteristics	Total (n=357)	ASD, no PH (n=61)	ASD-PH (n=296)	*P* value
Age (years) [mean±SD]	34.7±12.1	30.7±10.7	35.5±12.2	0.005
Female sex, n (%)	292 (82.7)	53 (86.9)	239 (81.8)	0.344
Body weight (kg) [mean±SD]	47.9±10.4	50.9±9.3	47.4±10.5	0.014
Body mass index [mean±SD]	19.9±7.1	20.5±3.0	19.8±7.7	0.445
Oxygen saturation (%)[mean±SD]	95.4±5.0	98.3±0.9	94.9±5.3	<0.001
Hemoglobin (g/dL) [mean±SD]	14.1±2.1	13.2±1.9	14.3±2.1	<0.001
Hematocrit (%) [mean±SD]	42.3±6.2	39.7±5.2	42.8±6.3	<0.001
NT-proBNP (pg/mL) [median(IQR)]	383.8 (147.1-1309.0)	109.1(55.2-197.3)	606.1 (177.5-1706.3)	<0.001
Defect diameter (cm) [mean±SD]	2.4±0.8	2.1±0.9	2.5±0.8	<0.001
RA diameter (mm) [mean±SD]	45.8±6.7	42.0±5.6	46.6±6.6	<0.001
RV diameter (mm) [mean±SD]	43.2±6.8	38.7±5.5	44.1±6.8	<0.001
TAPSE (mm) [mean±SD]	25.1±5.3	27.3±4.5	24.6±5.4	<0.001
Left ventricle EF (%)[mean±SD]	69.8±8.7	67.5±7.8	70.2±8.8	0.026
mPAP (mmHg) [median(IQR)]	36.0 (22.0-56.0)	16.0(14.5-18.0)	43.0 (27.0-59.8)	<0.001
PVRi (Wood Unit.m^2)[median(IQR)]	3.5(1.5-13.4)	1.3(1.0-2.0)	5.8 (2.2-17.3)	<0.001
mRAP(mmHg) [median(IQR)]	8.0(5.0-11.0)	5.0(3.0-8.0)	9.0(6.0-11.0)	<0.001
mLAP (mmHg) [median(IQR)]	9.0 (6.0-11.0)	6.0(5.0-9.0)	9.5 (7.0-12.0)	<0.001
Aorta saturation (%)[mean±SD]	91.8±7.6	96.2±4.2	90.9±7.9	<0.001

TTE: transthoracal echocardiogram; RHC: right heart catheterization; ASD: atrial septal defect, PH: pulmonary hypertension, SD: standard deviation, RA: right atrial, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion, EF: ejection fraction, mPAP: mean pulmonary artery pressure, PVRi: pulmonary vascular resistance index, mRAP: mean right atrial pressure, mLAP: mean left atrial pressure

p=0.008) and RA diameter (adjusted OR 1.13, 95% CI: 1.01-1.28, *p*=0.028) were independently associated with PH diagnostic criteria. **Table 2** shows the results of the univariate analysis of covariables and multivariable logistic regression analysis which indicated that only NT-proBNP level and RA diameter were significantly and independently associated with PH.

The ROC curve to determine the accuracy and cut-off point of NT-proBNP level to detect PH among patients with ASD is shown in **Figure 2**. The AUC of NT-proBNP was 84.4% (95%CI: 80.1%-88.8%, *p*<0.001) to predict PH. The best cut-off of NT-proBNP level to detect PH was ≥140 pg/mL. The NT-proBNP level ≥140 pg/mL had a sensitivity of 85.1%, a specificity of 62.3% and accuracy of 81.2%. Its positive predictive value was 91.6%, positive likelihood ratio was 2.26, negative predictive value of 46.3% and negative likelihood ratio was 0.24 to detect PH. **Table 3** indicates the results of the diagnostic tests with NT-proBNP level ≥140 pg/mL to detect PH.

The ROC curve to determine the accuracy and cut-off point of RA diameter to detect PH among patients with ASD was demonstrated in **Figure 3**. The AUC of RA diameter was 69.9% (95%CI: 63.2%-76.1%, *p*<0.001) to predict PH. The cut-off value of RA diameter to detect PH was determined at ≥46.0 mm. This value had a sensitivity of 51.0%, a specificity of 78.7% and accuracy of 55.7%. Its positive predictive value was 92.1%, positive likelihood ratio was 2.40, negative predictive value of 52.2% and negative likelihood ratio was 0.62 to detect PH. **Table 4** indicates the results of the diagnostic tests with RA diameter of ≥46.0 mm to detect PH.

Table 2. The results of the univariate and multivariable analyses of covariables associated with ASD-PH.

Covariables associated with ASD-PH	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years)	1.04 (1.01-1.07)	0.005	1.04 (0.99-1.08)	0.100
Bodyweight (kg)	0.97 (0.94-0.99)	0.016	1.00 (0.96-1.05)	0.863
Oxygen saturation (%)	0.54 (0.39-0.75)	<0.001	0.72(0.49-1.04)	0.076
Hemoglobin (g/dL)	1.33 (1.14-1.55)	0.003	1.66 (0.77-3.59)	0.200
Hematocrit (%)	1.10 (1.04-1.16)	0.001	0.86(0.66-1.11)	0.271
NT-proBNP (pg/mL)	1.005 (1.003-1.007)	0.019	1.004 (1.001-1.006)	0.008
Defect diameter (cm)	1.92 (1.32-2.77)	0.001	1.81 (0.98-3.37)	0.060
RA diameter (mm)	1.13 (1.07-1.19)	<0.001	1.13 (1.01-1.28)	0.038
RV diameter (mm)	1.15 (1.09-1.22)	<0.001	1.08 (0.97-1.19)	0.160
TAPSE (mm)	0.91 (0.86-0.96)	<0.001	0.95 (0.86-1.05)	0.344
Left ventricle EF	1.04 (1.01-1.06)	0.028	1.03 (0.97-1.08)	0.321

ASD: atrial septal defect, PH: pulmonary hypertension, RA: right atrial, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion, EF: ejection fraction

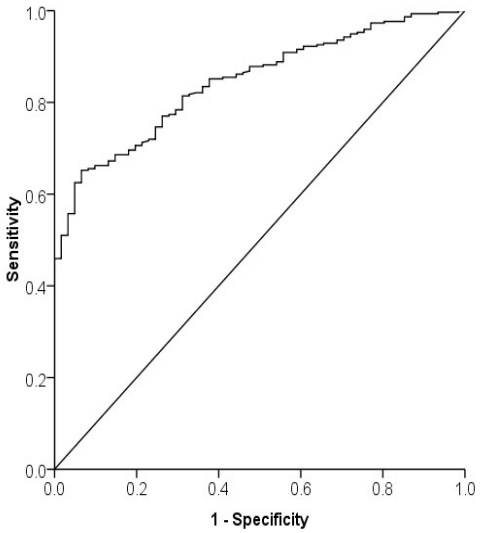

Figure 2. The ROC curve and AUC of NT-proBNP (84.4%, 95%CI: 80.1%-88.8%, p<0.001) performance to detect the presence of PH among ASD patients.

Table 3. The results of the diagnostic tests with NT-proBNP cut-off value of ≥140.0 pg/mL to detect ASD- PH.

	ASD-PH (n=296)	ASD-No PH (n=61)
NTproBNP ≥ 140.0 pg/mL (n=275)	252 (85.1)	23 (37.7)
NTproBNP < 140.0 pg/mL (n=82)	44 (14.9)	38 (62.3)
Sensitivity: 252/296=85.1%	Accuracy: 290/357 = 81.2%	
Specificity: 38/61=62.3%	Prevalence: 296/357 = 82.9%	
Positive predictive value: 252/275=91.6%		
Negative predictive value: 38/82=46.3%		
Positive likelihood ratio: 85.1/ (23/61) =2.26		
Negative likelihood ratio: 14.9/ (38/61) =0.24		

The combined values of NT-proBNP level ≥140 pg/mL and RA diameter ≥46.0 mm yielded a sensitivity of 46.6%, a specificity of 91.8% and accuracy of 54.3%. Its positive predictive value was 96.5%, positive likelihood ratio was 5.7, negative predictive value of 26.2% and negative likelihood ratio was 0.58 to detect PH. **Table 5** indicates the results of the diagnostic tests with the combined values of NT-proBNP level ≥140 pg/mL and RA diameter ≥46.0 mm to detect PH.

NT-proBNP level showed a significant positive correlation with both mPAP and PVRi in all ASD subjects (r value=0.639, p<0.001 and r value=0.587, p<0.001, respectively) and in ASD-PH subjects (r value=0.517, p<0.001 and r value=0.515, p<0.001, respectively). The NT-proBNP level had significant negative correlations with aorta saturation in ASD subjects (r value=-0.543, p<0.001) and in ASD-PH subjects (r value=-0.451, p<0.001). **Table 6** shows the correlation test results between NT-proBNP levels and hemodynamic parameters by RHC.

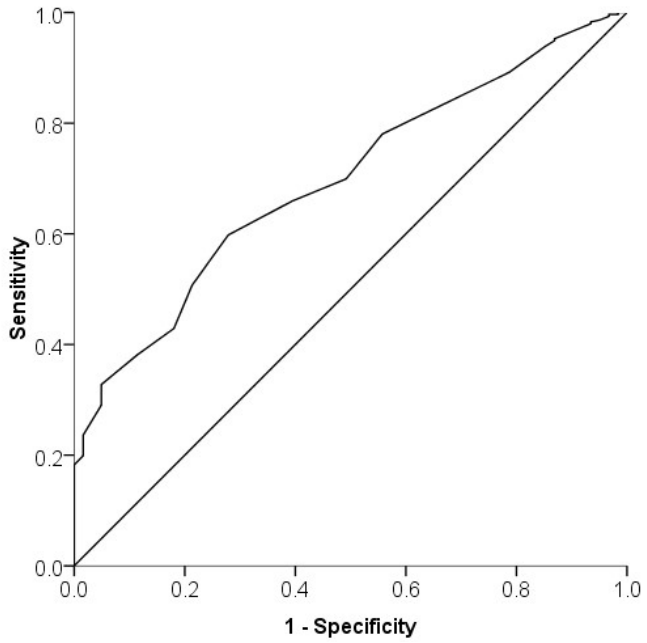

Figure 3. The ROC curve and AUC of RA diameter (69.6%, 95%CI: 63.2%-76.1%, p<0.001) performance to detect the presence of PH among ASD patients

Table 4. The results of the diagnostic tests with RA diameter cut-off value of ≥46.0 mm to detect ASD-PH

	ASD-PH (n=296)	ASD-No PH (n=61)
RA diameter ≥ 46.0 mm (n=164)	151 (51.0)	13 (21.3)
RA diameter < 46.0 mm (n=193)	65 (49.0)	48 (78.7)
Sensitivity: 151/296 = 51.0%	Accuracy: 199/357 = 55.7%	
Specificity: 48/61 = 78.7%	Prevalence: 296/357 = 82.9%	
Positive predictive value: 151/164 = 92.1%		
Negative predictive value: 48/92 = 52.2 %		
Positive likelihood ratio: 51.0/21.3 = 2.4		
Negative likelihood ratio: 49.0/78.7 = 0.62		

Table 5. The results of the diagnostic tests of NT-proBNP ≥140 pg/mL and RA diameter ≥46.0 mm todetect ASD-PH.

	ASD-PH (n=296)	ASD-No PH (n=61)
NT-proBNP ≥ 140 pg/mL and RA diameter ≥ 46.0 mm (n=143)	138 (46.6)	5 (8.2)
No both values (n=214)	158 (53.4)	56 (91.8)
Sensitivity: 138/296 = 46.6%	Accuracy: 194/357 = 54.3%	
Specificity: 56/61 = 91.8%	Prevalence: 296/357 = 82.9%	
Positive predictive value: 138/143 = 96.5%		
Negative predictive value: 56/214 = 26.2%		
Positive likelihood ratio: 46.6/8.2 = 5.7		
Negative likelihood ratio: 53.4/91.8 = 0.58		

Table 6. The correlation between NT-proBNP level with hemodynamic parameters measured by RHC in all subjects and in ASD-PH subjects.

Variables*	All subjects		ASD-PH	
	r value	*P*value	r value	*P*value
mPAP	0.636	<0.001	0.517	<0.001
PVRi	0.587	<0.001	0.515	<0.001
mRAP	0.082	0.128	-0.056	0.342
mLAP	0.045	0.399	-0.095	0.105
Aorta saturation	-0.543	<0.001	-0.451	<0.001

* Spearman correlation test
RHC: right heart catheterization; mPAP: mean pulmonary artery pressure, PVRi: pulmonary vascular resistance index, mRAP: mean right atrial pressure, mLAP: mean left atrial pressure

DISCUSSION

Our study results revealed that NT-proBNP level ≥140 pg/mL demonstrated a diagnostic value to detect the presence of PH within adult patients with ASD. The NT-proBNP for this prediction effect showed a sensitivity of 85.1% and a specificity of 62.3%. These values represented the ability of NT-proBNP ≥140 pg/mL to screen for early detection of PH within adult patients with ASD and ruling-out PH among those with NT-proBNP level <140 pg/mL, and selecting those with NT-proBNP level ≥140 pg/mL for PH and further PAH confirmation with invasive procedure, i.e. RHC. The NT-proBNP level ≥140 pg/mL showed 91.6% positive predictive value, which indicated its excellent ability to detect PH in adult patients with ASD coming to hospital, in which the prevalence of PH is more than 80%. This ability was also supported by the 2.26 positive likelihood ratio of this cut-off value to detect PH among adult patients with ASD.

By combining the values of NT-proBNP level ≥140 pg/mL and RA diameter ≥46.0 mm, obtained at TTE evaluation, the specificity was increasing (91.8%), which denoted it had more power with the combined values to identify adult patients with ASD as having PH. These combined values also had increasing positive predictive value and positive likelihood ratio, further supporting its role in detecting PH among adult patients with ASD coming to hospital where there is a high prevalence of PH. The use of the RA diameter parameter measured by TTE as a complement to the NT-proBNP level has an added benefit since it is an already standardized measurement and easily non-invasively be

obtained by any echocardiograph-dedicated machine.[11] Furthermore, these measured parameters are already approved by Indonesian guideline. As a screening tool, this measurement meets the requirements regarding expediency and availability. The TTE findings can be used to examine the hemodynamic consequences of ASD-related shunting, such as RA dilation, RV dilation, RV function, tricuspid annular dilation and tricuspid regurgitation, as an estimation of the presence of PAH or severity of PH.

In developing countries with limited resources or scarce facilities then we propose the triage of adult patients with ASD combining the NT-proBNP level and RA diameter non invasive evaluation to decide the urgent need to perform more advanced and invasive procedures, such as RHC (**Figure 4**). Adult ASD with NT-proBNP value <140 pg/mL can be ruled-out for the presence of PAH. In these patients, there is less urgency to perform RHC, however the RHC would be eventually still required to correct the defect and measure hemodynamic parameters, especially in secundum ASD suitable for non-surgery closure. Patients with NT-proBNP ≥140 pg/mL represent those with high probability of PAH, and by adding the measurement of RA diameter, those with RA diameter ≥46.0 mm indicate the most urgent cohort of patients needing to undergo RHC to measure hemodynamic parameters and determine correctability criteria. The semi-urgent status for RHC is indicated in adult ASD patients with both NT-proBNP ≥140 pg/mL and RA diameter <46.0 mm. By producing this triage, the scheduling of RHC for adult patients with ASD visiting the hospitals can be more efficiently performed. Those with NT-proBNP ≥140 pg/mL may also benefit from PAH-specific medication before undergoing the RHC procedure, if any World Health Organization (WHO) functional class was indicated.

Large ASD is associated with increased morbidity and mortality overtime if left uncorrected, from 0.6% and 0.7%/year in the first two decades of life until 4.5%/ year in the fourth decade of life.[13] The most common morbidities and mortality are related with PH and right heart failure.[13] Adult patients with ASD usually have a prolonged asymptomatic presentation or insidious obscured symptom courses which go undetected.[5] The delayed symptoms most often arise in the third or fourth decades of life.[14] At early phase of the disease, most symptoms occur during physical exertion which relate to the decrease in cardiac output because of the interatrial shunting.[13] Overtime, the severity of symptoms increases and patients seek medical help. Our registry indicated that the prevalence of PH and PAH among symptomatic adults with ASD was 82.9% by RHC examination.[5]

The RHC is important to evaluate the pulmonary pressures and direction of the shunt flow in ASD with PH and to guide the decision of appropriateness of defect closure, particularly in adult patients with ASD. The combination of clinical signs, WHO functional capacity, TTE/TOE parameters, and RHC hemodynamic results determines the recommendation of defect closure.[14] Therefore, through PH screening among adult patients with ASD with easy, comfortable and non-invasive tools, the selection of who will get the most urgent working up by more invasive procedures can be timelier and more efficiently executed. For patients with ASD-PH, the urgency to undergo RHC for diagnostic, therapeutic and prognostic purposes are applicable in the current guidelines.[8,16] For adult ASD patients without PH, the RHC is needed for therapeutic purposes to close the defect. In this scenario, adult patients with ASD

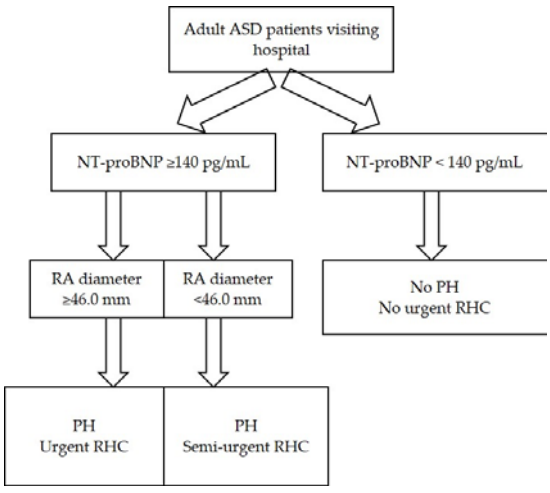

Figure 4. The triage scheme for urgency of invasive procedure by RHC among adult ASD by using NT-proBNP level and proceed by RA diameter

without PH can undergo RHC with less urgency.

The utility of NT-proBNP to triage, diagnose and risk stratify acute and chronic heart failure has been established.[17] Besides LV, NT-proBNP is an established biological indicator of RV strain and overload.[17,18] Its circulating level correlates with cardiac and pulmonary hemodynamics in PH patients.[19] In ASD patients, NT-proBNP was associated with RV dysfunction which improves after ASD closure.[20] The level of NT-proBNP has been validated as a prognostic and therapeutic response biological marker in patients with PAH.[21, 22] The European Society of Cardiology/ European Respiratory Society guidelines use the NT-proBNP threshold levels of 300 pg/ mL and 1400 pg/mL and categorize the risks as low (<5%), intermediate (5%–10%), or high (>10%) of 1-year mortality in PAH, of which also being adopted by Indonesian guideline.[8] While the adaptation of these prognostic and therapeutic markers has been widely accepted in patients with PAH, including ASD, the broader utilization of NT-proBNP as a diagnostic marker of PAH in ASD patients is not yet confirmed. This is because ASD has the hemodynamic consequences of pulmonary chronic vascular overflow and right atrial/ventricle chronic volume overload before resulting in PH and PAH. These long-term routes make it demanding to determine the timeliest point of PH diagnosis. The measurement of NT-proBNP level in adult patients with ASD can determine which patients experience PH and which had not. Our study, which included subjects coming to hospitals due to the symptoms they felt, showed that the NT-proBNP level identified and distinguished those who had already developed PH. Prompt decisions for invasive procedures and initiation of therapy in adult ASD patients with levels above the upper cut-off of NT-proBNP may avoid further RV failure, and thereby reducing early morbidity and mortality.[23]

The result of this study needs to be externally validated in the cohorts of adult ASD patients who are still frequently found in Indonesia due to the lack of screening processes in childhood. These combination of NT-proBNP level and RA diameter by TTE was a simple parameter to discriminate patients who needed more invasive procedure which will need external validation especially from district hospitals, which become the first-line treating hospitals, and also referral hospitals, which had more advanced facility to treat ASD patients with/without PH. In the future, the external validation process is important to test the usability and generability of this study finding.

This study had several notable limitations. Firstly, the sample size for control group did not meet the minimum requirement based on sample size calculation formula. Secondly, it did not exclude subjects with Eisenmenger syndrome since its current clinical and hemodynamic definitions are not clearly defined. Third, patients with corrected ASD who still developed PAH were excluded. Fourth, the time interval between index of ASD diagnosis by TTE and NT-proBNP level measurement during RHC varied. And lastly, this study was conducted in a single PH center in Indonesia, which needs further corroboration and externally validated by a large multicenter study.

CONCLUSION

NT-proBNP circulating level ≥140 pg/mL seems to represent PH in adult patients with ASD. The NT-proBNP level ≥140 pg/mL can be used together with RA diameter ≥46.0 mm at TTE as pre-test probability measures to triage patients needing more invasive procedures and also to determine when and if to start the PAH-specific treatment, especially in developing countries in which the adult ASD delayed presentation is high and the facility for PH and PAH diagnosis is limited and scarce.

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CONFLICT OF INTEREST

All authors had no conflict of interests regarding the manuscript.

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