ECHOCARDIOGRAPHIC ASSESSMENT OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC KIDNEY DISEASE SEEN AT THE JOS UNIVERSITY TEACHING HOSPITAL

Artu Ishishen John[1]*, Akpagher Shawon Fredrick[2]
[1]Department of Internal Medicine, Jos University Teaching Hospital (JUTH)
[2]Department of Medicine and Surgery University of Jos

***Corresponding author:** *Artu Ishishen John. Department of Internal Medicine (Cardiology Unit), Jos University Teaching Hospital (JUTH) Email: ishishenr2@gmail.com*

ABSTRACT

Background: Pulmonary hypertension (PH) is common in patients with chronic kidney disease (CKD) and is an independent predictor of mortality. It is a major public health issue that can lead to renal failure, heart disease, and early mortality. This study aims to assess the prevalence of pulmonary hypertension in patients with chronic kidney disease seen at JUTH.

Methods: A hospital-based cross-sectional study was conducted where 69 CKD patients were selected using a convenience sampling technique. The mean pulmonary arterial pressure (mPAP) of CKD patients was determined using transthoracic echocardiography. Chi-square and ANOVA were used to test for a significant difference in the prevalence of PH in different stages of CKD and levels of PAP based on severity in CKD patients respectively.

Results: Out of the 69 participants, 18 (26.1%) had elevated mPAP that was >24mmHg, of which 16 (23.3%) were mildly elevated with an mPAP of 29.6 mmHg, 1(1.4%) were moderately elevated with mPAP of 46.0 mmHg, and 1(1.4%) also had severely elevated PAP with a mean value of 58.0 mmHg. Most of the CKD patients were in stage 5 – 13(18.8%) while a few were in stage 2 and stage 3 representing 1 (1.4%) each.

Conclusion: Patients with CKD frequently experience pulmonary hypertension, and this rises as renal failure worsens. Therefore, echocardiography is advised for assessing pulmonary pressures in CKD patients in stage 3 and above, and for subsequent monitoring of the disease progression and response to treatment.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health issue that can lead to renal failure, heart disease, and early mortality.[1,2] Cardiovascular disease continues to be the leading cause of morbidity and mortality in patients with CKD regardless of whether renal replacement therapy (RRT) is required.[3] Pulmonary hypertension (PH) is common in patients with CKD and is an independent predictor of mortality.[4] From several studies, the prevalence of PH ranges from 9 - 39% in individuals with stage 5 CKD, 18.8 - 68.8% in haemodialysis patients, and 0 - 42% in patients on peritoneal dialysis therapy.[5]

Several implicit mechanisms have been put forward to explain the co-existence of PH and CKD. Fibroblast growth factor 23 (FGF-23) is a marker of worsening renal function and has also

lately been intertwined as a causative factor in left heart abnormalities. For people who are genetically more likely to get left heart disease, FGF-23 may have a direct effect on pulmonary vascular remodeling. It may also have an indirect effect by promoting left heart disease, which in turn leads to pulmonary vascular remodeling. Moreover, CKD may contribute to PH through increased renin-angiotensin-aldosterone-system activation and inflammatory response, which have both been shown to be elevated in CKD and contribute to pulmonary vascular remodeling. Other risk factors for PH, such as left ventricular hypertrophy (LVH) and diastolic dysfunction, are common in patients with CKD and may predispose them to high pulmonary pressures.[6]

Pulmonary hypertension in patients with CKD may be induced and/or aggravated by left ventricular disorders and other risk factors typical of CKD. Some of these factors are volume overload, arteriovenous fistula, sleep-disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification/stiffening, and severe anemia.[5,7]

In Nigeria, the incidence of CKD is 1.6 - 12.4%8, while several hospital-based studies reported a prevalence of 2.5 - 26%.[1] However, the prevalence of PH in CKD patients in Nigeria is not known. This study aims to assess the prevalence of pulmonary hypertension in patients with chronic kidney disease at the Jos University Teaching Hospital (JUTH), Plateau State, Nigeria.

MATERIALS AND METHODS

Study area: The study was conducted at the medical outpatient clinic and inpatient ward of Jos University Teaching Hospital (JUTH) Jos. Jos is the capital of Plateau State in North-central Nigeria. It is about 1250m (4100 feet) above sea level with an average monthly temperature between 21oC and 25oC (69oF and 77oF). The cold weather and highland resort make it a center for tourist attraction.

Study design: The study was a hospital-based cross-sectional study carried out over 8 months.

Study population: Patients aged 18 years and older diagnosed with CKD attending the Nephrology clinic, or those on admission at the medical wards of JUTH who met the inclusion criteria constituted the study population.

Inclusion criteria: Adults (Aged 18 years and older) born to parents with Nigerian nationality.
Patients diagnosed with CKD in JUTH, defined as evidence of renal damage or eGFR less than 60ml/min/1.73m^2 for three months and above assessed using the CKD-EPI formula.

Exclusion criteria: Patients with renal disease on known pulmonary arterial hypertension medications like prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, or appetite-inhibitive medications history (e.g., fenfluramine, dexamphetamine), patients with heart failure, patients who have positive HIV results as obtained from their case notes, patients with a history of chronic lung diseases (Chronic obstructive pulmonary disease, pulmonary tuberculosis, lung fibrosis).

Sample size determination: The sample size was determined using Cochran's formula[9]

$$N = \frac{Z^2(P)Q}{d^2}$$

$$N = \frac{(1.96)^2(0.049)(1-0.049)}{(0.05)^2} = 70$$

The sample size for this research was composed of 70 CKD patients.

Sampling technique: A convenience sampling method was adopted in selecting patients who met the inclusion criteria above. This non-probability technique allowed the recruitment of CKD patients who were available and willing to be recruited consecutively.

Materials: A questionnaire, scanning gel, Tissue papers, Stadiometer, weighing scale, Mercury Sphygmomanometer (Accoson brand), Littman

stethoscope, Portable (2D) GE echocardiography Machine with 3.5mHz transducer probe (Vivid e, weight 4.9kg, serial number 514327wx6, 2016 May).

Study procedure: The purpose of the study was explained to each patient in the language they best understood. Consenting patients were required to sign a consent form or append their thumbprint where appropriate. Participate and were at liberty to withdraw from the study at any stage without consequences. An interviewer-administered questionnaire was completed for each patient, from which data on socio-demographic characteristics, medical history, and other parameters were obtained.

Blood pressure measurement: The blood pressure (BP) was taken after a 5-minute rest to eliminate anxiety10 using standard protocols for the auscultatory method.

Investigations: Electrocardiography was done for each patient. The CKD-epi formula was used to calculate eGFR which determined the stage of CKD as defined below. Patients were stratified into Groups 1-4 as CKD Stages 1-4, and Group 5 for those who were in Stage 5 and not on haemodialysis.

"Glomerular filtration rate: Glomerular filtration rate (GFR) is a test that measures the level of kidney function and determines the stage of kidney disease. It is the best overall index of kidney function that measures the kidney's ability to filter toxins or waste from the blood. Normal GFR varies according to age, sex, and body size and declines with age. The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2021) to estimate GFR11 which was adopted for this study.

Determination of Chronic kidney disease: Either of the following had to be present for 3 months and above to be CKD:

GFR less than 60 ml/min/1.73.

Albumin-to-creatinine ratio (ACR) ?30 mg/g or other markers of kidney damage.

1. Stage 1: Normal renal function with eGFR ? 90ml/min/1.73
2. Stage 2: Mild renal impairment with eGFR 60 - 89ml/min/1.73
3. Stage 3: Moderate renal impairment with eGFR 30 - 59ml/min/1.73
4. Stage 4: Severe renal impairment with eGFR 15 - 29ml/min/1.73
5. Stage 5: End-stage renal disease with eGFR < 15ml/min/1.73

Echocardiography: Doppler echocardiography which is an accepted screening tool for pulmonary hypertension and the surrogate of choice for establishing a relationship between pulmonary hypertension and adverse outcomes in ESRD patients12 was used to determine pulmonary arterial pressures in this study. The sensitivity and specificity of echocardiography to diagnose PH are modest at 83% and 72% respectively. A transthoracic echocardiography using a portable (2D) GE echocardiography machine with a 3.5mHz transducer probe (Vivid e, weight 4.9kg, serial number 514327wx6, 2016 May) was performed by the researcher for each patient, with the researcher bearing the cost. The procedure was carried out with the subjects lying in left lateral or recumbent positions. Several images were obtained from the apical four-chamber view, short-axis view, long-axis view, and subcostal views. Five readings for the maximum tricuspid systolic jet were obtained for each participant in the parasternal or apical window using the continuous wave Doppler, and the average value was taken as TRVmax. For the few patients without tricuspid regurgitation, peak pulmonary regurgitation (PR) Doppler velocity was measured and inputted into Bernoulli's equation (4V2) which was added to the estimated right atrial pressure (RAP) to get pulmonary arterial systolic pressure (PASP). Right atrial pressure (RAP) was estimated from the inferior vena cava (IVC) size and its variation with respiration. Pulmonary artery systolic pressure (PASP) was extrapolated from the modified Bernoulli's equation: PASP or Right ventricular systolic pressure (RVSP) = 4 × (tricuspid regurgitant velocity)2 + estimated right atrial

pressure. Mean Pulmonary Arterial Pressure was calculated using the Chemla formula (0.61x PASP + 2 mmHg). The severity of pulmonary hypertension using mean PAP was categorized into mild (25-40 mmHg), moderate (41-55mmHg), and severe (>55 mmHg).13

Statistical analysis: The chi-square test was used to test for a significant difference in the prevalence of PH in different stages of CKD using echocardiography, while ANOVA was used to test for significant differences in the levels of PAP based on severity in patients with CKD, all at 95% C.I with SPSS version 26.0 utilized.

Ethical clearance: Ethical approval for the study was obtained from the JUTH Health Research Ethics Committee with an approval number JUTH/DCS/REC/127/XXXI/2487.

RESULTS

Table 1: Distribution of mean pulmonary arterial pressures among patients with chronic kidney disease.

Reference range (mmHg)	No. Observed	**Mean PAP (mmHg)**	F	p-value
Normal (0-24)	51	10.41±0.76	54.634	0.001
Mild (25-40)	16	29.62±0.84		
Moderate (41-55)	1	46.00±0.01		
Severe (>55)	1	58.00±0.01		
TOTAL	**69**			

Result is significant were p<0.05; values are Mean±SD

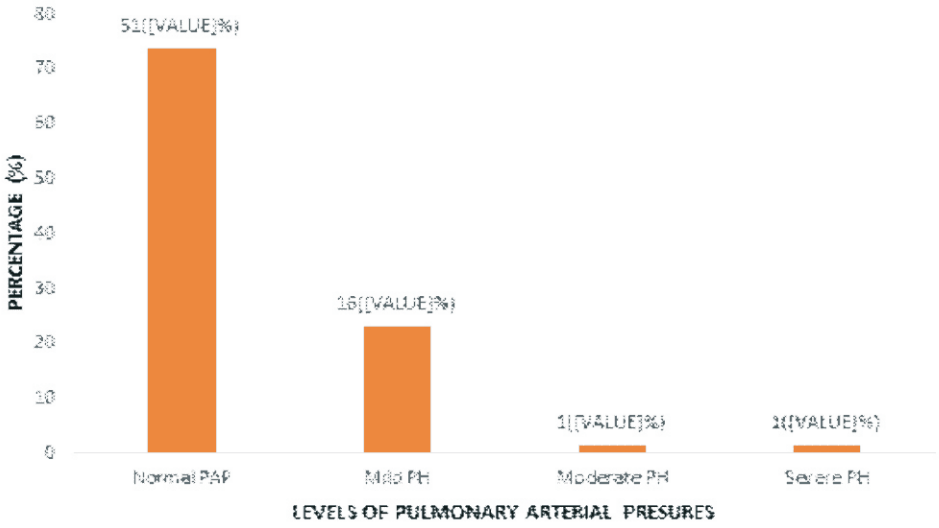
Table 1 above shows the distribution of pulmonary arterial pressures among CKD patients, which shows a significant difference in the levels of severity of PAP at (p<0.05). *Out of the 69 participants in this study, 18(26.1%) had elevated PAP >24mmHg. Out of which*16(23.3%) were mildly elevated with a mean PAP of (29.62mmHg), 1(1.4%) was moderately elevated with a PAP of (46.00mmHg), and 1(1.4%) had severely elevated PAP with a value of (58.00mmHg), (percentages are shown in Fig 1).

Table 2: Prevalence of Pulmonary Hypertension in different stages of chronic kidney disease using echocardiography.

CKD Stages	Freq.	High PP (%)	Normal PP (%)	PAP (mmHg)	X^2	p-value
Stage I	5	**-**	5(100.0)	7.0±0.01	9.217	0.050
Stage II	8	1(12.5)	7(87.5)	11.12±2.74		
Stage III	15	1(6.7)	14(93.3)	14.06±2.29		
Stage IV	9	3(33.3)	6(66.7)	15.42±3.29		
Stage V	32	13(40.6)	19(59.4)	19.93±2.30		
TOTAL	**69**	**18(26.1)**	**51(73.9)**			

The result is significant (p<0.05) at 95% C. I

Table 2 above shows the proportion of PH in different stages of CKD, 18(26.1%) of CKD patients had PH while 51(73.9%) had normal pulmonary pressures. Most CKD patients with PH were in stage 5, while the least was in stage 3 1(6.7), none was observed in stage 1. In all participants, PH was present in 13(40.6%) of patients. A significant difference was observations at ($p<0.05$)



PAP = Pulmonary arterial pressure, PH = Pulmonary hypertension

Figure 1. Percentage distribution of mean pulmonary arterial pressures among patients with chronic kidney disease.

Figure 1 above is a bar chart that shows the distribution of mean pulmonary arterial pressures depicting the degree of pulmonary hypertension severity. The majority of CKD patients had normal pulmonary pressures 73.9%, while 23.2% had mild pulmonary hypertension, and about 1% had moderate and severe PH each.

DISCUSSION

There is a varying prevalence of PH among CKD patients worldwide. In this study, a cut-off value for PH was taken as mPAP greater than or equal to 25mmHg, measured using echocardiography according to the European Society of Cardiology (ESC) and European Respiratory Society (ERS) 2015 guidelines on diagnosis and treatment of PH. However, the Sixth World Symposium on Pulmonary Hypertension (6th WSPH) in 2018 proposed a new haemodynamic threshold of mPAP >20 mmHg as this is widely accepted now following a large cohort study which established increased mortality and risk for hospitalization for mPAP 21 to 24 mmHg.[15]

The overall prevalence of PH among CKD patients found in this study was 26.1%. This prevalence value is comparable to the 25% reported by Issa et. al. and slightly lower than the 32% reported by Abdelwhab et. al. in Stage 5 CKD patients in the United States and Egypt, respectively, even though this study included stage 1 to 5 CKD patients. Moreover, a concordant prevalence of 22% and 27% were reported by Selvaraj and Reque respectively in 2017. Whereas, Jared et al. in the US reported a discordant prevalence of 68% among CKD patients, this high prevalence could be explained by the increased sensitivity of right heart catheterization used to determine pulmonary pressure values when compared to

echocardiography. Furthermore, patients in CKD stage 2 and below were excluded, and probably, patients with other conditions that affect pulmonary pressures could have been included since it was a retrospective study thereby leading to a higher prevalence value. Other reasons for variable prevalence estimates for PH might be explained by different definitions of PH by different researchers. Secondly, different levels of volume excess could also skew the prevalence. Thirdly, some patients with CKD who did not have echocardiographic data were excluded from most studies.

The proportion of patients with PH in stage 5 CKD was 40.6% (table 2) which was higher than 13.5% for stages 1 to 4 combined. This supports the assertion that as renal disease advances there is a corresponding increase in the prevalence of PH. The reasons for this could be due to the multifactorial causes of elevated pulmonary pressures such as vascular stiffening/calcifications, anaemia, fluid overload, LVH et cetera, which are more prominent in advanced stages of CKD. Other studies have shown slightly lower prevalence such as 37.5% reported by Zhilian Li et. al in China, and 13.4% by Yigla[22] in Israel. Similarly, Bozbas et al in Turkey reported a 6% rate of PH in stage 5 CKD patients receiving peritoneal dialysis. This decline in prevalence might be due to their study's use of a higher PASP cut value of 45mmHg and above to define PH as compared to the 2015 ESC guideline that suggested a cut value of 35mmHg which could account for the discrepancy.

The chronic kidney disease patients in stage 5 had a higher mean pulmonary arterial pressure of 19.93mmHg compared to other CKD stages. This is concordant with studies done by Abdelwhab et al. in 2008,[17] Yigla in 2009, and Pabst in 2012. This may be accounted for by the increased fluid overload, severe anaemia, worsening uraemia, and vascular calcifications seen in end-stage renal disease (ESRD) enhancing the development of elevated pulmonary pressures. Severe anaemia, a recognized cardiovascular risk factor in CKD, has been shown to have an impact on the pulmonary circulation. Low haemoglobin levels can exacerbate hypoxia brought on by concurrent diseases, which can lead to PH. High levels of circulating free fatty acids and long-chain acylcarnitines in ESRD, as well as invivo myocardial triglyceride accumulation, could cause considerably elevated pulmonary pressures according to several studies.

The high prevalence of elevated mean pulmonary pressure beyond the threshold of normal in this study increases the pulmonary hypertension burden in CKD patients. Pulmonary hypertension is associated with debilitating symptoms and reduced life expectancy, especially among CKD patients irrespective of the cause. The low index of suspicion, late diagnosis, and ineffective treatment of PH in CKD patients are the main drivers of poor survival and high mortality. The use of a relatively available and affordable tool like echocardiography in the determination of PH during routine evaluation of CKD patients is invaluable in mitigating the negative consequences of PH.

CONCLUSION

Even though, right heart catheterization which is the gold standard for diagnosing PH was not used in this study due to its non-availability, echocardiography used in this study has been shown to still deliver clinically useful or comparable results.[25] Patients with CKD frequently experience pulmonary hypertension (PH), and the prevalence rises as the disease worsens to end-stage renal failure. It is recommended that CKD patients in stage 3 and above should have an assessment of pulmonary pressures using echocardiography and subsequent monitoring of disease progression and response to therapy.

REFERENCES

1. Chukwuonye II, Ogah OS, Anyabolu EN, Ohagwu KA, Nwabuko OC, Onwuchekwa U, Chukwuonye ME, Obi EC, Oviasu E. Prevalence of chronic kidney disease in Nigeria: systematic review of population-based studies. Int J Nephrol Renovasc Dis. 2018;11:165-172.
2. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving Global Outcomes (KDIGO)z. Kidney Int. 2005;67(6):2089–20100.
3. Walther CP, Nambi V, Hanania NA, Navaneethan SD. Diagnosis and management of pulmonary hypertension in patients with CKD. Am J Kidney Dis [Internet]. 2020;75(6):935–945. Available from: https://doi.org/10.1053/j.ajkd.2019.12.005
4. Pabst S, Hammerstingl C, Hundt F, Gerhardt T, Grohe C, Nickenig G, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. PLoS One. 2012;7(4): e35310.
5. Bolignano D, Rastelli S, Agarwal R, Fliser D, Massy Z, Ortiz A, Wiecek A, Martinez-Castelao A, Covic A, Goldsmith D, Suleymanlar G, Lindholm B, Parati G, Sicari R, Gargani L, Mallamaci F, London G, Zoccali C. Pulmonary hypertension in CKD. Am J Kidney Dis. 2013;61(4):612-22.
6. Navaneethan SD, Roy J, Tao K, Brecklin CS, Chen J, Deo R, et al. Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. J Am Soc Nephrol. 2016;27(3):877–86.
7. Zhang Q, Wang L, Zeng H, Lv Y, Huang Y. Epidemiology and risk factors in CKD patients with pulmonary hypertension: a retrospective study. BMC Nephrol. 2018;19(1):70.
8. Odubanjo MO, Oluwasola AO, Kadiri S. The epidemiology of end-stage renal disease in Nigeria: the way forward. Int Urol Nephrol. 2011;43(3):785-92.
9. Ahmad H, Halim H. Determining sample size for research activities. Selangor Business Review. 2017; 2(1):20-34.
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289(19):2560-2572.
11. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis. 2022;79(2):268-288.e1.
12. Gazda AJ, Aponte MM, De Golovine A, Edwards A, Pai A, Akkanti BH. A crossroads at the understanding of pulmonary hypertension in end-stage renal disease. Heart & Lung: The Journal of Cardiopulmonary and Acute Care. 202;50(1):232-233.
13. Mehra P, Mehta V, Sukhija R, Sinha AK, Gupta M, Girish MP, Aronow WS. Pulmonary hypertension in left heart disease. Arch Med Sci. 2019;15(1):262-273.
14. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart

and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
15. Anderson JJ, Lau EM. Pulmonary Hypertension Definition, Classification, and Epidemiology in Asia. JACC Asia. 2022 ;2(5):538-546.
16. Issa N, Krowka MJ, Griffin MD, Hickson LJ, Stegall MD, Cosio FG. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. Transplantation. 2008;86(10):1384–1388.
17. Abdelwhab S, Elshinnawy S. Pulmonary hypertension in chronic renal failure patients. Am J Nephrol. 2008;28(6):990–997.
18. Selvaraj S, Shah SJ, Ommerborn MJ, Clark CR, Hall ME, Mentz RJ, et al. Pulmonary hypertension is associated with a higher risk of heart failure hospitalization and mortality in patients with chronic kidney disease: The Jackson Heart Study. Circ Hear Fail. 2017;10(6): e003940.
19. Reque J, Garcia-Prieto A, Linares T, Vega A, Abad S, Panizo N, et al. Pulmonary hypertension is associated with mortality and cardiovascular events in chronic kidney disease patients. Am J Nephrol. 2017;45(2):107–114
20. O'Leary JM, Assad TR, Xu M, Birdwell KA, Farber-Eger E, Wells QS, Hemnes AR, Brittain EL. Pulmonary hypertension in patients with chronic kidney disease: invasive hemodynamic etiology and outcomes. Pulm Circ. 2017;7(3):674-683.
21. Li Z, Liang X, Liu S, Ye Z, Chen Y, Wang W, et al. Pulmonary hypertension: epidemiology in different CKD stages and its association with cardiovascular morbidity. PLoS One. 2014;9(12): e114392.
22. Yigla M, Fruchter O, Aharonson D, Yanay N, Reisner SA, Lewin M, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney Int. 2009;75(9):969–975.
23. Bozbas SS, Akcay S, Altin C, Bozbas H, Karacaglar E, Kanyilmaz S, et al. Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation. Transplant Proc. 2009; 41(7):2753-2756.
24. Van Loon RL, Bartelds B, Wagener FA, Affara N, Mohaupt S, Wijnberg H et al. Erythropoietin Attenuates Pulmonary Vascular Remodeling in Experimental Pulmonary Arterial Hypertension through Interplay between Endothelial Progenitor Cells and Heme Oxygenase. Front Pediatr. 2015; 3:71
25. Homma A, Anzueto A, Peters JI, Susanto I, Sako E, Zabalgoitia M, Bryan CL, Levine SM. Pulmonary artery systolic pressures estimated by echocardiogram vs cardiac catheterization in patients awaiting lung transplantation. The Journal of heart and lung transplantation. 2001;20(8):833-9.