

The Effect of Pulmonary Hypertension on Mortality of Heart Failure Patients in a Nigerian Population

*Ogbomo A, **Obasohan AO

* Department of Medicine, *University of Benin Teaching Hospital/ **University of Benin, Benin City, Edo State, Nigeria

ABSTRACT

Background: Pulmonary hypertension has become increasingly recognized as a contributory cause of death in patients with heart failure. This study examines the effect of pulmonary hypertension on the survival of heart failure patients, both intra-hospital and follow-up for one year.

Methods: A descriptive cross-sectional study in which one hundred and fifty patients admitted for heart failure were recruited.

Results: A total of 31 (22.67%) patients admitted for heart failure died within one year of presentation. Among those that died, 22 (71%) had pulmonary hypertension, while 9 (29%) did not have pulmonary hypertension. The one-year mortality rate was 27.2% and 13.0% in heart failure patients with and without pulmonary hypertension respectively. Also, the intra-hospital mortality was 12.3% and 5.8% in heart failure patients with and without pulmonary hypertension respectively.

Conclusion: This study shows a high one-year mortality rate among patients with heart failure; with intra-hospital mortality rate of 10%. There is therefore need for better management strategies to help reduce mortality in heart failure patients.

Correspondence

Dr Aisosa Ogbomo

Department of Medicine

University of Benin Teaching Hospital
Benin City, Edo state.

Email: aisosa.ogbomo@yahoo.com

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INTRODUCTION

Pulmonary hypertension has become increasingly recognized as a contributory cause of death in patients with heart failure especially when associated with right ventricular dysfunction (Vonk Noordegraaf & Galile, 2011) This is partly due to evidence from the ESCAPE TRIAL(The ESCAPE Investigators and ESCAPE Study Co-ordinators, 2005) and other studies that Doppler echo estimation of pulmonary hypertension has a good correlation with right heart catheterization findings (Balci et al., 2016; Schewel et al., 2020). This has led to increasing reports of Doppler studies of pulmonary hypertension worldwide and few reports from Nigeria and Sub-Saharan Africa (Bigna et al., 2017). Pulmonary hypertension estimates and effects vary according to the study population (Shorr et al., 2007; Davis et al., 2008), aetiology of heart failure and chronicity of the disease (Guglin et al., 2012; Choudhary et al., 2013)

which may vary worldwide and even in a large country like Nigeria.

While there are few reports of pulmonary hypertension prevalence in Nigeria and Sub-Saharan African countries there are fewer still, if any data on the effect of PH on mortality especially in the medium and long term. This study examines the effect of pulmonary hypertension on the survival of heart failure patients both intra-hospital and follow up to one year of presenting with acute decompensation.

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MATERIALS AND METHODS

This was a descriptive cross-sectional study in which one hundred and fifty (150) heart failure patients in the University of Benin Teaching

Hospital (UBTH), Benin City, Edo state, Nigeria who were consecutively admitted into the medical wards for acute decompensated heart failure.

Doppler Echo was performed within 48 hours of admission using an ALOKA PHD PROSOUND SSD 4000SV with a 3.5-5MHZ transducer. Standard two-dimensional, M-mode and Doppler images were obtained. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Complete 2D Echo examination was performed according to the recommendation of the American Society of Echocardiography (ASE) (American Heart Association, 2006).

The mean pulmonary artery pressure was derived from the right ventricular systolic pressure. In the absence of pulmonary stenosis, PASP equals right ventricular systolic pressure (RVSP). This was estimated by adding the systolic pressure gradient and the right atrial pressure. The systolic pressure gradient was measured from the tricuspid regurgitant jet by placing the Doppler beam between the two tips of the tricuspid valve leaflets. The inferior vena cava was assessed in the subcostal view to estimate the right atrial pressure. A Right atrial pressure of 5mmHg, 10mmHg and 15mmHg was assumed if the inferior vena cava was completely collapsed, partially collapsed or not collapsed respectively (Kircher et al., 1990; Rudski et al., 2010). Thereafter, MPAP was derived from PASP using the Chemla formula: $MPAP = PASP \times 0.61 + 2$ (Chemla et al., 2004).

Pulmonary hypertension was then defined as $MPAP > 25\text{mmHg}$ (Srinivas. 2006)

Consent was obtained from all participants while ethical approval was given for this study by the Research and Ethics Committee of the University of Benin Teaching Hospital, Benin City, Nigeria.

Patients were split into two groups of heart failure with pulmonary hypertension and heart failure without pulmonary hypertension for data analysis. Data obtained was entered into and analyzed using the International Business Machines Statistical Product and Service Solutions (IBM-SPSS) version 23.0. Categorical data were compared using the chi-square test while continuous data were analyzed using the t-test and Pearson's correlation co-efficient where applicable. A multiple linear regression was also done for significant correlates. The Kaplan Meier method was used to determine differences in the survival between patients with and without pulmonary hypertension. A p-value ≤ 0.05 was considered significant for all statistical comparisons.

RESULTS

There was a total of 150 subjects of which females were 82 (54.7%) and males 68 (45.3%). The mean age of the study population was 58.4 ± 17.2 years. Pulmonary hypertension was present in 54 (65%) females and 27 (39.7%) males ($p = 0.0001$).

The mean cardiac output was also found to be significantly lower in patients with PH, compared to those without PH ($p=0.022$). There was no statistically significant difference between the mean left ventricular internal diameter, thickness of the left ventricular wall and stroke volume.

In the total sample population, there was a significant positive correlation between mean pulmonary artery pressure (MPAP) and the left atrial diameter in the total population, patients with PH and patients without PH ($r=0.301$, $p<0.001$; $r= 0.454$, $p<0.001$ and $r= 0.30$, $p= 0.012$). Similarly, a significant positive correlation was found between MPAP and the left ventricular internal diameter in diastole and systole in the total population and pulmonary hypertension ($r= 0.18$, $p=0.028$ and $r=0.32$, $p=0.003$). There was no significant correlation between MPAP and left ventricular internal diameter in those without PH. ($r= -0.09$, $p= 0.986$).

Thirty-one (22.67%) patients admitted for heart failure died within one year after presentation. The mean age was $57.4 (\pm 16.6)$ years for those who died and $58.7 (\pm 17.5)$ years for those who were alive. Out of those that died 22 (71%) had PH, while 9 (29.0%) did not have PH. This suggests that patients with PH had a higher mortality within one year of presentation ($p= 0.033$ OR-2.49, CI: 0.99-6.40).

Assessment of 2D/ M-MODE right ventricular echocardiographic parameters in this study that tricuspid annular plane excursion (TAPSE) was significantly lower in patients with PH. It was 1.9 ± 0.1 and 2.67 ± 0.4 for patients with and without PH respectively ($p = 0.029$). However, the right ventricular internal diameter was significantly wider in patients with PH. Also, the inferior vena cava (IVC) diameter was wider in subjects with PH. The mean IVC diameter was $1.8 \pm 0.4\text{cm}$ and $1.25 \pm 0.44\text{cm}$ for subjects with and without PH respectively ($p < 0.001$). Furthermore, a positive correlation between TAPSE and the mean pulmonary artery pressure in the total population and patients with PH ($r = -0.21$, $p=0.012$; $r=-0.55$, $p<0.001$).

The one-year mortality rate was 27.2% and 13.0% in heart failure patients with and without pulmonary hypertension respectively. Also, the intra-hospital mortality was 12.3% and 5.8% in heart failure patients with and without pulmonary hypertension respectively.

The survival distribution curve showed that eighty seven percent of patients without pulmonary hypertension and 72.8% of patients with pulmonary hypertension survived up to 365days. The overall survival rate was 79.3%. The mean survival in patients without pulmonary hypertension (331.00 ± 11.59 days) was higher than that of patients with pulmonary hypertension (298.71±13.54). The overall mean study survival duration was 313.56 ± 9.14 days.

A log rank test was run using the Kaplan Meier method to determine if there were differences in the survival distribution for the two groups of heart failure patients. Log rank comparison showed a statistically significant difference in survival

distribution for patients who had pulmonary hypertension when compared to those without pulmonary hypertension ($\chi^2 = 4.31$; $df = 1$; $p = 0.038$).

The mean duration of hospital stay was 13.8±6.4days in patients who died within one year and 10.3±4.9days for patients who were alive. The mean duration of hospital stay was significantly higher among the patients that died within one year compared to patients who were alive ($p=0.001$). Similarly, the mean duration of hospital stay was also significantly longer in patients with PH compared to patients without PH ($p=0.022$; $p=0.016$ respectively).

Table 1: Demographic and cardiac variables

	PH PRESENT n=81	PH ABSENT n=69	T	P-value
Mean Age (years)	59.50± 16.60	56.85 ± 18.50	0.83	0.48
BMI (Kg/m ²)	22.89 ± 5.95	25.71 ± 5.18	4.48	<0.02
Weight (Kg)	66.74 ± 13.60	74.90±17.90	3.17	<0.02
SBP (mmHg)	124.52 ± 30.97	146.52 ± 34.76	4.098	<0.001
DBP (mmHg)	74.94 ± 26.69	92.03 ± 23.55	4.124	<0.001
EF (%)	35.20 ± 35.30	44.00 ± 29.50	1.64	0.10
FS	22.45 ± 15.10	22.73 ± 9.99	0.13	0.893
CO (L/min)	4.94 ± 2.18	4.30 ± 2.16	1.80	0.022

Table 2: Pulmonary hypertension and mortality

		PH PRESENT n=81 n(%)	PH ABSENT n=69 n(%)	χ^2	P
Intra-hospital mortality	Yes	10 (12.3)	4 (5.8)	1.89	0.169
	No	71 (87.7)	65 (94.2)		
Mortality in 6months	Yes	16 (19.8)	6 (8.7)	3.64	0.056
	No	65 (80.2)	63 (91.3)		
Mortality within 1year	Yes	22 (27.2)	9 (13.0)	4.53	0.033*
	No	59 (72.8)	60 (87.0)		

*OR (CI): 2.49 (0.99 – 6.40)

Table 3: zD/M-mode right ventricular echocardiographic parameters in study population

	PH PRESENT n=81 Mean (SD)	PH ABSENT n=69 Mean (SD)	T	P
RVAW**	0.60 ± 0.30	0.50 ± 0.30		0.164
RVID**	2.90 ± 1.00	2.60 ± 1.15		0.015**
TAPSE**	1.70± 0.83	2.19 ± 0.95		<0.001

Table 4: Right ventricular function versus pulmonary hypertension

		PH PRESENT n=81 n(%)	PH ABSENT n=69 n(%)	TOTAL n=150 n(%)	χ^2	P
RVSD	Present	43 (59.7)	29 (40.2)	72 (48%)	10.50	0.001*
	Absent	26 (33.3)	52 (66.7)	78 (52%)		
RVDD	Present	51 (63.0)	30 (37.0)	81 (54%)	5.69	0.017*
	Absent	30 (43.5)	39 (56.5)	69 (46%)		

Table 5: Pulmonary hypertension versus NYHA FC

NYHA		PH PRESENT n(%)	PH ABSENT n(%)	TOTAL	χ^2	P
CLASS 3	3	22 (47.8)	24 (52.2)	46 (100)	1.02	0.313
CLASS 4	4	59 (56.7)	45 (43.3)	104 (100)		
TOTAL		81 (54.0)	69 (46.0)	150 (100)		

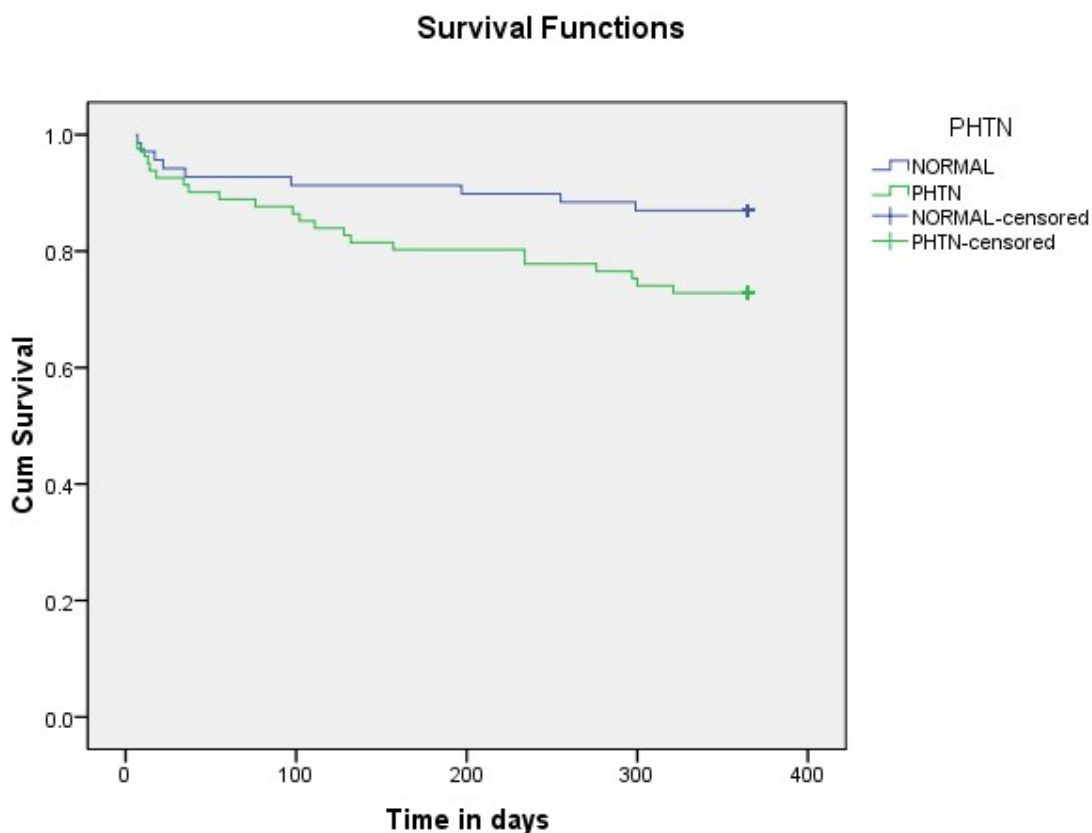


Figure 1: Kaplan Meier Survival Distribution Curve in Patients with Pulmonary Hypertension and Patients without Pulmonary Hypertension

DISCUSSION

This study has shown a severe adverse effect of pulmonary hypertension on the mortality of heart failure patients presenting in acute decompensation. It showed a high intra-hospital mortality of 12.3% in those with pulmonary hypertension versus 6% amongst those without pulmonary hypertension (average 9.3%). This progressively increased through 6 months to one year follow up, such that, at one year, 27.5% of heart failure patients with pulmonary hypertension had died compared to 13% in those without pulmonary hypertension (average 20.7%). Thus, the presence of pulmonary hypertension doubled the mortality rate of both intra-hospital and one year follow up.

The average of 9% intra-hospital mortality in this study is in agreement with previous studies which ranged between 5 and 10% (Marius et al., 2017) but lower than 14% obtained by Karaye et al in Kano, Nigeria (Karaye et al.,2013) This may be reflective of the proportion of pulmonary hypertension cases in his collection, which was 62.3%, compared to 54% in this study.

This study has gone further to assess one year mortality amongst Nigerians, which was double in those with pulmonary hypertension (27.5% vs 10%) but an average of 20.6% for all heart failure patients.

Although this study does not address the mechanism for increased mortality, pulmonary hypertension was associated with right ventricular dysfunction, both systolic measured by TAPSE and

diastolic function. Right ventricular dysfunction in pulmonary hypertension has been well described as a major contributor to mortality in patients with pulmonary hypertension, both in the ESCAPE trial and other studies (The ESCAPE Investigators and ESCAPE Study Co-ordinators, 2005).

It did not appear that the pulmonary hypertension was necessarily due to worsened left ventricular function as the mean ejection fraction did not differ significantly between the groups, though lower in those with pulmonary hypertension.

Similarly, the New York Heart Association functional class was also not different amongst the groups. Other probable mechanisms often given for increased mortality include release of inflammatory cytokines in heart failure. There was also marked prolongation of days on admission amongst those with pulmonary hypertension compared to those without. This shows that they may have been more ill and the duration of admission correlated with mortality.

The patients with pulmonary hypertension had lower mean weight and body mass index, which may suggest more cardiac cachexia. A higher BMI has been known to be a protective factor against PH (Poms et al., 2013). The obesity paradox is suggested to play a role in this as there are postulates of a more favourable outcome of longer survival for PH patients with an elevated BMI (Arena & Lavie, 2010). A sufficiently higher metabolic reserve in the face of increased catabolism and systemic inflammatory response that occurs in PH is one of many explanations for the better mortality outcomes in obese patients with PH (Lawlor et al., 2006; Poms et al., 2013).

However, other studies show that right ventricular function may be normal even in the face of poor outcomes in heart failure patients with PH (Bursi et al., 2012; Melenovsky et al., 2014). and that patients with worse LV function had worse pulmonary artery pressures in addition to no significance found in intra-hospital mortality between the two groups with Amadi et al, (2016) showing no significant difference in left heart echocardiographic parameters in heart failure patients with vs. without pulmonary hypertension although significant correlations were observed.

Pulmonary hypertension caused by heart failure on histology is difficult to determine as histology is usually of very little diagnostic significance as there is usually chronic passive congestion with haemosiderin-laden macrophages – a feature present in both heart failure patients with and without pulmonary hypertension post-mortem alongside the similar intima media abnormalities also noted in both groups of patients making it

difficult to pinpoint PH as the cause of mortality (Tuder et al., 2007).

CONCLUSION

PH is a life-threatening disease especially in the face of it co-existing with heart failure as evidenced by the high mortality rate observed in this study. Our study findings show a high one-year mortality rate in our environment with higher intra-hospital mortality rate of 10%. Survival rates are important in assessing the contributions and gains acquired from the adapted treatment/management methods in our local settings for managing heart failure with PH. There is therefore need for better management strategies and patient care to help reduce mortality.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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