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# The causes, treatment, and outcome of pulmonary hypertension in Africa: Insights from the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry

Friedrich Thienemann [a], Anastase Dzudie [b], Ana O. Mocumbi [c], Lori Blauwet [d], Mahmoud U. Sani [e], Kamilu M. Karaye [f], Okechukwu S. Ogah [g], Irina Mbanze [h], Amam Mbakwem [i], Patience Udo [j], Kemi Tibazarwa [k,l], Albertino Damasceno [h], Ashley K. Keates [m], Simon Stewart [l,m,n], Karen Sliwa [l,n,*]

[a] Institute of Infectious Diseases and Molecular Medicine and Department of Medicine, Faculty of Health Science, University of Cape Town, Cape Town, South Africa
[b] Department of Internal Medicine, Douala General Hospital and Buea Faculty of Health Sciences, Douala, Cameroon
[c] Instituto Nacional de Saúde, and Universidade Eduardo Mondlane, Maputo, Mozambique
[d] Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55902, USA
[e] Department of Medicine, Bayero University Kano & Aminu Kano Teaching Hospital, PMB 3452 Kano, Nigeria
[f] Department of Medicine, Bayero University & Aminu Kano Teaching Hospital, Kano, Nigeria
[g] Division of Cardiology, Department of Medicine, University College Hospital Ibadan, Oyo State, Nigeria
[h] Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique
[i] Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria
[j] Department of Paediatrics, University of Uyo Teaching Hospital, Uyo, Nigeria
[k] Department of Cardiovascular Medicine, Muhimbili National Hospital, Dar es Salaam, Tanzania
[l] Hatter Institute for Cardiovascular Research in Africa and Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[m] Mary MacKillop Institute for Health Research and NHMRC Centre for Research Excellence (CRE) to Reduce Inequality in Heart Disease, Australian Catholic University, Melbourne, Australia
[n] Soweto Cardiovascular Research Unit, University of the Witwatersrand, Johannesburg, South Africa

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ABSTRACT

*Background:* Epidemiology, aetiology, management and outcome data for various forms of pulmonary hypertension (PH) in Africa are scarce.
*Methods:* A prospective, multinational cohort registry of 220 consecutive patients (97% of African descent) from 9 specialist centres in 4 African countries. The antecedents, characteristics and management of newly diagnosed PH plus 6-month survival were studied.
*Results:* There were 209 adults (median age 48 years [IQR 35, 64]) and 11 children (age range 1 to 17 years). Most adults had advanced disease - 66% WHO Functional Class III-IV, median 6-minute walk test distance of 252 m (IQR 120, 350) and median right ventricular systolic pressure 58 mm Hg (IQR 49, 74). Adults comprised 16% pulmonary arterial hypertension, 69% PH due to left heart disease, 11% PH due to lung disease and/or hypoxia, 2% chronic thromboembolic pulmonary hypertension, and 2% PH with unclear multifactorial mechanism. At 6-months, 21% of adults with follow-up data had died. On an adjusted basis (independent of sub-groups) mortality was associated with increasing functional impairment ($p = 0.021$ overall - WHO Class IV versus I, OR 1.68 [95% CI 0.13, 4.36]) and presence of combined right atrial and ventricular hypertrophy (46% - OR 2.88, 95% CI 1.45, 5.72). Children commonly presented with dyspnoea, fatigue, cough, and palpitations with six and three children, respectively diagnosed with concurrent PH associated congenital heart disease and left heart disease.
*Conclusions:* These data provide new insights into PH from an African perspective, with clear opportunities to improve its prevention, treatment and outcomes.
*Trial Registration:* ClinicalTrials.gov (NCT02265887).



## 1. Introduction

Pulmonary hypertension (PH) is a devastating, progressive disease associated with increasingly debilitating symptoms and a poor prognosis due to narrowing of the pulmonary vasculature and consequential right heart failure (RHF) [1]. The epidemiological profile of PH in

* Corresponding author at: Hatter Institute for Cardiovascular Research in Africa, Cape Heart Centre, 4th floor Chris Barnard Building, Faculty of Health Sciences, University of Cape Town, Private Bag X3, Observatory 7935, South Africa.
*E-mail address:* Karen.Sliwa-Hahnle@uct.ac.za (K. Sliwa).

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Africa is largely unknown. However, recent reports suggest that its incidence is higher than in high-income countries due to a higher prevalence of antecedent risk factors and contributory diseases [2–4]. Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), rheumatic heart disease (RHD), schistosomiasis and chronic hepatitis B and C infection are endemic in Africa, as are tuberculosis, poorly controlled asthma, high levels of pollution in urban areas and high-risk occupations such as mining [5]. Secondary pathways to PH also include a lack of specialist paediatric services to diagnose and manage congenital heart disease [6], as well as highly prevalent RHD and endomyocardial fibrosis (with a potentially high burden of parasitic infections) [7,8]. Africa is also in epidemiological transition with increased prevalence of non-communicable forms of heart disease - most notably high levels of hypertensive heart disease in relatively younger individuals [9]. In these increasingly common cases there is strong potential for advanced and severe left heart failure (HF) to provoke PH and consequent RHF [10].

Based on the hypothesis that the underlying pathways to this deadly condition in Africa would be many and varied and produce a high burden of disease (relative to high-income countries), we initiated the Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry Study [11]. Herein, we present baseline and 6-month follow-up/outcome data in consecutive African patients newly diagnosed with PH, from participating centres across the African continent.

The primary aim of this study was to describe the typical disease presentation (including clinical severity and aetiological pathways) and subsequent outcomes, including 6-month mortality, from the diagnostic and therapeutic management of PH and associated morbidity in the African context.

## 2. Methods

The broad design, aims and specific methods underlying the PAPUCO registry, the largest contemporary cohort study of PH in Africa, have been described in greater detail previously [11] and prospectively registered at ClinicalTrials.gov. (NCT02265887). Wherever possible, the registry adheres to the STROBE guidelines for reporting observational outcomes [12].

### 2.1. Ethics statement

All participating centres received ethical approval from their local ethic committees. The study conforms to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study enrolment and HIV testing was performed, according to national guidelines, with consent.

### 2.2. Study design and setting

The PAPUCO research group was established in 2011 with the aim of establishing a prospective registry cohort study of *de novo* PH cases representative of the wider African population. Consequently, nine specialist care referral centres in Cameroon, Mozambique, Nigeria and South Africa contributed to the registry. Each site recruited consecutive patients on the following basis: (1) newly diagnosed with PH based on standardised clinical and echocardiography criteria; (2) the capacity to return for 6-month follow-up if alive; (3) aged ≥18-years (except for paediatric centres in Mozambique, Cameroon, and Nigeria) and (4) provide written informed consent to participate. Centre eligibility included: (1) availability of echocardiography and training in assessing right heart function; (2) experience in diagnosing PH according to World Health Organization (WHO) classification; (3) experience in clinical management of patients with RHF and (4) resources to review patients at 6-month follow-up.

### 2.3. Study profiling and outcome data

All study data were collected on electronic case report forms (web-based platform) and stored on a dedicated secure central database. Cases were reviewed by at least two investigators (FT, AD, KS, and AOM) for completeness and data validated. As described previously, once definitive assessment and treatment had been applied, the following data were documented for each participant - a) socio-demographic and ethnic profile; b) antecedent risk profile (including environmental exposures and cardiovascular risk factors); c) medical history; d) relevant clinical findings; e) prescribed treatment and management; f) all major cardiovascular diagnoses according to International Classification of Diseases (ICD) 10 coding; and g) up to five non-cardiovascular diagnoses according to ICD-10 coding [13]. Clinical assessment included symptoms scoring, a full clinical examination, physical and clinical status. Functional tests included WHO Functional Class (FC), 6-minute walk test (6MWT), and Karnofsky Performance Score. Technical procedures included echocardiography, chest X-ray, and 12-lead ECG. Patient outcomes, including hospitalisation and death during planned 6-month follow-up were also prospectively collected. A verbal autopsy was performed to record survival at the end of the study. Survival data were available for 91% of those in the registry (189/209 adults and 11/11 paediatric patients).

### 2.4. Case definition

A diagnostic algorithm to diagnose PH in resource-constraint settings without access to right heart catheterization had been established following the guidelines for the diagnosis of PH of the European Society of Cardiology and European Respiratory Society [1,11]. On this basis, PH was diagnosed by specialist cardiologists and defined as documented elevated right ventricular systolic pressure (RVSP) >35 mm Hg on transthoracic echocardiography in the absence of pulmonary stenosis and acute RHF; usually accompanied by dyspnoea, fatigue, peripheral oedema and other cardiovascular symptoms, ECG and chest X-ray changes in keeping with PH. Additional investigations such as computed tomography, ventilation/perfusion scans or right heart catheterizations were performed at the discretion of the treating physician if available.

### 2.5. Statistical analysis

Data was transferred to GraphPad Prism 5.0d and SPSS Statistics 17.0 for all analyses by FT and AD. Continuous data are presented as median plus interquartile range (IQR); categorical data as number (%). For group comparisons, we used Chi Square ($\chi^2$) analysis with calculation of odds ratios (OR) and 95% confidence interval (CI, where appropriate) for discrete variables, and Students *t*-test and analysis of variance for normally distributed continuous variables. For multiple group comparison we used One-Way ANOVA and Chi-square where appropriate. Mortality data were used to generate Kaplan-Meier survival curves with initial univariate and then step-wise multivariate analysis (including the variables of age, sex, HIV status, RVSP, Tricuspid Annular Plane Systolic Excursion [TAPSE], left ventricular ejection fraction [LVEF], RHF, and 6MWT) used to derive unadjusted and adjusted ORs for mortality during the observational period. Significance was accepted at the two-sided level of 0.05.

## 3. Results

### 3.1. Study cohort

Fig. 1 summarises the total number and distribution (according to country and centre) of consecutive patients initially entered into the registry over a period of 24-months (last baseline entry 29th December 2013 with follow-up completed in June 2014). Subsequently, 34/254 (13%) were subsequently excluded after review by the PAPUCO review committee [11]. Overall, therefore, 220 patients with newly diagnosed PH were retained in the registry; of which, 209 were adult cases of PH (paediatric cases are described separately below).

### 3.2. Socio-demographic and risk profile

Table 1 summarises the socio-demographic characteristics and risk factor profile of the adult cohort on a sex-specific basis. Patients were predominantly of African descent (97%) and comprised 124 women (59%) with a median age of 48-years. Almost two-thirds completed only primary education or never went to school and almost one third lived in non-solid housing structures. Significantly more women lived below the poverty threshold compared to men. Of those subject to active screening (64%), 47/134 (35%) were HIV-positive. Known risk factors for PH were prevalent including - hypertension (42%), previous or concurrent tuberculosis (22% and 5% respectively), indoor cooking/heating without chimney (32%) and HIV-infection (22% overall). There were no significant differences in the risk factor profiles of men and women besides exposure to indoor cooking/heating without chimney (more women), history of smoking (more men) and alcohol abuse (more men). Although 167 patients (80%) lived in areas endemic for schistosomiasis there was only one related case.

### 3.3. Clinical findings

Table 2 summarises the clinical profile of the adult cohort on a sex-specific basis. The majority presented with advanced symptomatology. This included dyspnoea, palpitations, and cough in the majority of

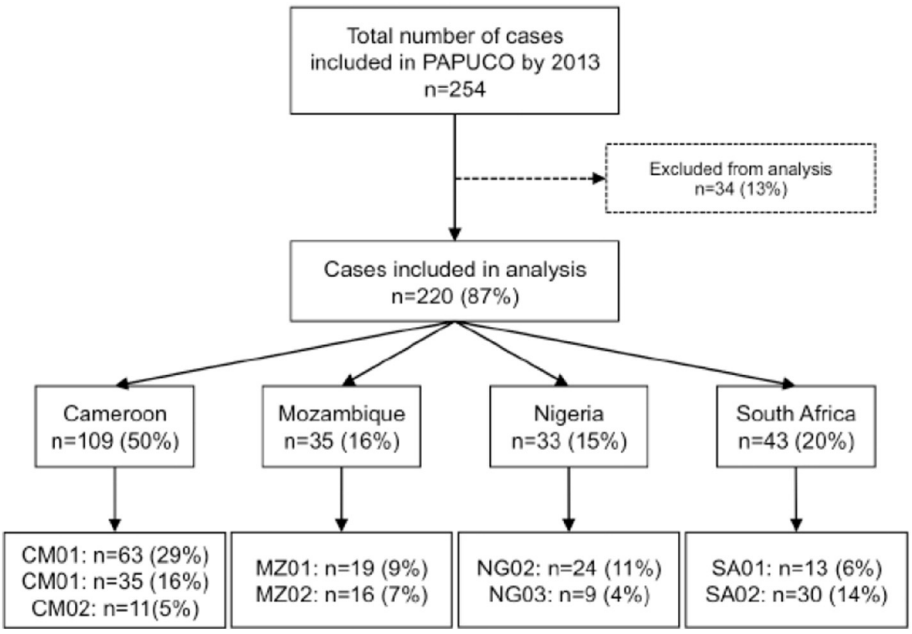


**Fig. 1.** Flow diagram of the PAPUCO Registry. Abbreviations: CM01, Douala General Hospital, Douala, Cameroon; CM02, Cardiac Centre, Shisong Hospital, Kumbo, Cameroon; CM03, Douala Cardiovascular Centre, Douala, Cameroon; MZ01, Instituto Nacional de Saúde, Maputo, Mozambique; MZ02, Division of Cardiology, Maputo Central Hospital, Maputo, Mozambique; NG02, Department of Medicine, Bayero University and Aminu Kano Teaching Hospital, Kano, Nigeria; NG03, Department of Medicine, College of Medicine, Lagos, Nigeria; SA01, Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; SA02, Infectious Diseases Referral Clinic, GF Jooste Hospital, Mannenberg and Rapid Assessment Unit, Khayelitsha District Hospital, Khayelitsha, South Africa.

**Table 1**
Socio-demographic and risk factor profile of the 209 adults (≥18 years) presenting with pulmonary hypertension.

| | All (n = 209) | Male (n = 85) | Female (n = 124) | *P*-value[#] |
|---|---|---|---|---|
| *Socio-demographic characteristics* | | | | |
| Median age in years (IQR) | 48 (35 to 64) | 54 (37 to 65) | 43 (33 to 64) | 0.0948 |
| African descent | 203 (97%) | 83 (98%) | 120 (97%) | 1.0000 |
| Education | | | | |
| Completed only primary education | 79 (38%) | 35 (41%) | 44 (36%) | 0.4682 |
| Never went to school | 46 (22%) | 13 (15%) | 33 (27%) | 0.0620 |
| Income <30 USD per month | 73 (35%) | 21 (25%) | 52 (42%) | 0.0121[#] |
| Housing conditions | | | | |
| Temporary shelter (e.g. shacks) | 51 (24%) | 18 (21%) | 33 (27%) | 0.4147 |
| Traditional hut | 12 (6%) | 2 (2%) | 10 (8%) | 0.1282 |
| *Risk factor profile* | | | | |
| Cardiovascular risk factors | | | | |
| Family history for CVD | 69 (33%) | 30 (35%) | 39 (32%) | 0.6535 |
| Hypercholesterolemia[a] | 12 (6%) | 8 (9%) | 4 (3%) | 0.0728 |
| Hypertension[a] | 87 (42%) | 42 (49%) | 45 (36%) | 0.0646 |
| Diabetes[a] | 17 (8%) | 9 (11%) | 8 (7%) | 0.3109 |
| Co-morbidities | | | | |
| Haemolytic anaemia[a] | 2 (1%) | 2 (2%) | 0 | 0.1642 |
| Rheumatic disease[a] | 6 (3%) | 1 (1%) | 5 (4%) | 0.4045 |
| Chronic liver disease[a] | 6 (3%) | 3 (4%) | 3 (2%) | 0.6889 |
| Chronic lung disease[a] | 24 (12%) | 11 (13%) | 13 (11%) | 0.6605 |
| Previous DVT/PE[a] | 8 (4%) | 4 (5%) | 4 (3%) | 0.7179 |
| Chronic infectious diseases | | | | |
| Previous[a] or concurrent tuberculosis | 47 (23%) | 16 (19%) | 31 (25%) | 0.3164 |
| Concurrent tuberculosis | 10 (5%) | 3 (4%) | 7 (6%) | 0.7433 |
| HIV-infected (n = 134 tested) | 47 (35%) | 14 (11%) | 33 (25%) | 0.0938 |
| Exposure to smoke and recreational drugs | | | | |
| Indoor cooking/heating without chimney | 66 (32%) | 14 (17%) | 52 (42%) | 0.0001[#] |
| History of smoking | 26 (12%) | 22 (26%) | 4 (3%) | <0.0001[#] |
| Alcohol abuse | 29 (14%) | 21 (25%) | 8 (7%) | 0.0004[#] |
| Recreational drug use | 3 (1%) | 3 (4%) | 0 | 0.0659 |

Supplement Table 1: Data are number (%) or median (IQR) except age (range); *p*-values based on *t*-test, chi-square or Fisher's exact test were appropriate. Abbreviations: USD, US dollar; CVD, cardiovascular disease; DVT, deep vein thrombosis; PE, pulmonary embolism; HIV, human immunodeficiency syndrome.

[a] Diagnosed condition prior to presentation.

[#] Statistically significant ($p < 0.05$).

**Table 2**
Clinical findings of 209 adults (≥18 years) presenting with pulmonary hypertension.

| | All (n = 209) | Male (n = 85) | Female (n = 124) | *P*-value[#] |
|---|---|---|---|---|
| Symptoms at presentation | | | | |
| Dyspnoea | 194 (93%) | 81 (95%) | 113 (91%) | 0.2890 |
| Cyanosis | 26 (12%) | 12 (14%) | 14 (11%) | 0.6702 |
| Cough | 126 (60%) | 57 (67%) | 69 (56%) | 0.1141 |
| Fatigue | 184 (88%) | 75 (88%) | 109 (88%) | 1.0000 |
| Dizziness | 65 (31%) | 19 (22%) | 46 (37%) | 0.0382[#] |
| Syncope | 15 (7%) | 5 (6%) | 10 (8%) | 0.5985 |
| Palpitations | 153 (73%) | 62 (73%) | 91 (73%) | 1.0000 |
| Chest pain | 35 (17%) | 15 (18%) | 20 (16%) | 0.8510 |
| WHO functional class (FC) (n = 207) | | | | |
| WHO FC I/II | 69 (33%) | 20 (24%) | 49 (40%) | 0.0171[#] |
| WHO FC III | 92 (44%) | 46 (54%) | 46 (37%) | 0.0164[#] |
| WHO FC IV | 46 (22%) | 17 (20%) | 29 (23%) | 0.6128 |
| Karnofsky performance score | 70 (50–80) | 70 (60–80) | 65 (50–80) | 0.4030 |
| 6MWT distance | 252 (120–350) | 275 (110–351) | 234 (120–345) | 0.8036 |
| 6MWT <300 m | 71 (34%) | 25 (29%) | 51 (41%) | 0.1072 |
| BMI | 23.4 (20.5–27.7) | 23.5 (20.6–27.7) | 23.3 (20.6–27.5) | 0.6150 |
| Heart rate at rest (beats per min) | 91 (76–100) | 90 (72–98) | 93 (80–102) | 0.1706 |
| Systolic BP (mmHg) | 120 (108–133) | 121 (110–137) | 117 (107–130) | 0.0464[#] |
| Diastolic BP (mmHg) | 77 (68–86) | 78 (70–89) | 76 (67–86) | 0.1303 |
| Respiration rate at rest (breaths per min) | 24 (20–29) | 24 (20–28) | 25 (20–30) | 0.5553 |
| Pulse oximetry at rest (%) | 96 (92–98) | 96 (91–98) | 96 (92–98) | 0.2020 |
| Cardiac auscultation | | | | |
| Systolic murmur | 119 (57%) | 45 (53%) | 74 (60%) | 0.3938 |
| Loud P2 | 86 (41%) | 31(37%) | 55 (44%) | 0.3166 |
| Electrocardiogram | | | | |
| Sinus rhythm | 92 (44%) | 43 (51%) | 49 (40%) | 0.1210 |
| Sinus tachycardia | 49 (23%) | 15 (18%) | 34 (27%) | 0.1343 |
| Atrial fibrillation | 30 (14%) | 12 (14%) | 18 (15%) | 1.0000 |
| P-pulmonale | 30 (14%) | 10 (12%) | 20 (16%) | 0.4267 |
| Right ventricular strain pattern | 39 (19%) | 20 (24%) | 19 (15%) | 0.1506 |
| Left ventricular strain pattern | 48 (23%) | 24 (28%) | 24 (19%) | 0.1801 |
| Chest X-ray | | | | |
| Cardiomegaly | 124 (59%) | 41 (48%) | 73 (59%) | 0.1575 |
| Prominent pulmonary arteries | 46 (22%) | 14 (17%) | 32 (26%) | 0.8539 |
| Echocardiography | | | | |
| Median LVEF (%) | 46 (35–65) | 45 (33–63) | 48 (36–66) | 0.2994 |
| Median RVSP (mmHg) | 58 (49–74) | 56 (50–70) | 60 (48–74) | 0.7751 |
| Median TAPSE (mm) | 13 (11–17) | 13 (10–17) | 13 (11–16) | 0.8041 |
| Right atrial hypertrophy | 121 (58%) | 44 (52%) | 77 (62%) | 0.137 |
| Right ventricular hypertrophy | 115 (55%) | 44 (52%) | 71 (57%) | 0.433 |
| Combined right atrial and ventricular hypertrophy | 96 (46%) | 36 (42%) | 60 (48%) | 0.0390 |
| TAPSE <15 mm** | 92 (44%) | 35 (41%) | 57 (46%) | 0.5708 |
| Signs of RHF at baseline | | | | |
| Raised JVP | 150 (72%) | 63 (74%) | 87 (70%) | 0.6391 |
| Peripheral oedema | 134 (64%) | 61 (72%) | 73 (59%) | 0.0586 |
| Raised JVP or peripheral oedema | 174 (83%) | 75 (88%) | 99 (80%) | 0.1327 |
| Diagnosis of RHF at baseline (n = 153) | 78 (37%) | 33 (39%) | 45 (36%) | 0.7714 |

Data are number (%) or median (IQR); *p*-values based on t test, chi-square or Fisher's exact test were appropriate; *diagnosed condition prior to presentation. ECG, chest X-ray and TAPSE was captured in 188 (90%), 143 (68%), and 160 (77%) patients, respectively. Abbreviations: WHO, World Health Organization; 6MWT, 6-minute walk test; BMI, body mass index; BP, blood pressure; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion. **TAPSE was assessed in 160/209 (77%) of patients. ***Right heart failure was diagnosed in patients meeting the following criteria: TAPSE <15 mm and at least one clinical sign of heart failure (raised JVP or peripheral oedema).

[#] Statistically significant ($p < 0.05$).

cases. Two-thirds presented at WHO FC III or IV and one third could not walk further than 300 m on 6MWT when assessed. Clinical observations were largely similar for men and women; exceptions being more women with preserved functional status, experiencing more dizziness and with lower systolic blood pressure compared to men. Most commonly observed pathological ECG findings were sinus tachycardia and left ventricular strain pattern in around one fifth of cases. PH-specific abnormalities such as p-pulmonale (14%) and evidence of right ventricular hypertrophy (19%) were documented in less than one quarter of cases. On echocardiography, left ventricular function was moderately impaired (median LVEF 46%, IQR 35 to 65%) overall. As expected, RVSP was markedly elevated (58 mm Hg, IQR 49 to 74 mm Hg) with concurrent moderate to severe right atrial 58% and right ventricular (55%) hypertrophy a common feature; with only one-third of cases (n = 69; 33%) showing no evidence of right atrial or ventricular enlargement. Overall, 78 patients (37%) presented with a diagnosis of RHF based on available echocardiography for 153 patients (TAPSE <15 mm plus one or more clinical signs of HF).

### 3.4. Clinical sub-groups

As shown in Supplementary Table 1, subgroup classification of adult cases according to contemporary criteria [1] revealed that 16% of patients as Group 1 (pulmonary arterial hypertension, PAH), 69% as Group 2 (PH due to left heart disease, PHLHD), 11% as Group 3 (PH due to lung disease and/or hypoxia), 2% as Group 4 (chronic thromboembolic pulmonary hypertension, CTEPH), and 2% as Group 5 (PH with unclear multifactorial mechanism). Comparison of clinical findings between the three major sub-groups (PAH, PH-LHD, PH-LD) as shown in Table 3 revealed differentials in respect to age, WHO FC, Karnofsky

Performance Score, LVEF and RVSP. No difference was found in the diagnosis of RHF at presentation between men and women.

### 3.5. Therapeutic management

Fig. 2 summarises the pharmacological management of the three major sub-groups (PAH, PH-LHD, PH-LD) of cases with some expected differences on this basis; but with no differences according to functional status (data not shown). Overall, loop diuretics were most commonly prescribed (89% of all cases). Alternatively, none of the cohort patients received home oxygen. Only a small proportion received advanced therapy such as a Phosphodiesterase-type-5 inhibitor (3%).

### 3.6. Outcomes

Of those adults with 6-month follow-up data (n = 189), 150 were known to be alive and 39 (21%) had died.

Fig. 3 compares 6-month the survival profile of these cases according the three major PH groups, WHO FC, sex and haemodynamic profile. Univariate analyses showed few correlates of mortality at this time-point. On multivariate analysis, increasing functional impairment, according to WHO criteria ($p = 0.021$), was associated with increased risk of mortality; the adjusted ORs for WHO Class III and IV being 1.68 (95% CI 0.13, 4.36) and 2.88 (95% CI 0.28, 9.97) relative to those assessed as Class I at baseline. In addition, those with combined right atrial and ventricular hypertrophy on echocardiography were almost three-fold more likely to die (adjusted OR 2.88, 95% CI 1.45, 5.72).

### 3.7. Paediatric cohort

Supplementary Table 2 individually profiles the 11 paediatric cases with an age range of 1 to 17 years (8 females) captured by the registry. The most common symptoms at presentation were dyspnoea, fatigue, cough, and palpitations. Six and three children were classified as PAH-CHD and PH-LHD respectively. The remaining two cases comprised PH of multiple mechanisms (pulmonary thromboembolism and PH-LHD related to endomyocardial fibrosis) and idiopathic PAH. At 6-months (with no loss to follow-up) 2/11 (18%) children had died.

## 4. Discussion

PAPUCO represents the largest registry-type cohort study on patients diagnosed with PH in sub-Saharan Africa. It provides important insights into the clinical profile and treatment of PH from a uniquely African context. Our data indicate that in sub-Saharan Africa, PH is predominantly derived from a high burden and interaction between non-communicable and infectious diseases. Those affected are mostly young, female and present late in an advanced state of HF. Not unexpectedly, survival is poor and linked to advanced symptomatic and clinical deterioration. To improve outcomes our findings highlight the need for pragmatic management guidelines for the cost-effective diagnosis and treatment of PH in sub-Saharan Africa; particularly when considering that access to right heart catheterization is limited and PH-specific therapies remain largely unaffordable.

We suspected that many pathways to PH that are hyper-endemic in Africa including HIV/AIDS, tuberculosis, RHD, hereditary haemoglobinopathies, schistosomiasis, other parasitic infections, and chronic hepatitis B and C infection were the primary cause of PH. This could be confirmed only partially. HIV/AIDS contributed to <10% of cases in our cohort, but almost three times more were HIV-positive. Consequently, HIV should be considered as a co-morbidity and not necessarily causative of PH; especially in the presence of concurrent immunosuppression/tuberculosis [14]. Significantly, most patients with PH-LD were found to have tuberculosis-associated PH (it can cause a distinct clinical phenotype of chronic obstructive pulmonary disease) [14]; a finding consistent for a region where tuberculosis remains endemic [15]. In our study, PH-LHD was the most common type of PH (around two-thirds of cases). Although PH-LHD is generally found to be the most common cause of PH, most registries are dedicated to a single group of PH [16–18], except a European registry (COMPERA) [19]. The prevalence of PH-LHD in our study is similar to the 67.9% reported in the Armadale echocardiography cohort [20]. In a large Italian echocardiography cohort, 52.6% had left heart disease, 7.5% lung disease, 1.3% CTEPH, while 10.5% had unknown PH aetiology [21]. That HF with reduced ejection fraction was the most common cause of PH-LHD in our cohort is consistent with its predominance in sub-Sahara Africa (as reported in the THESUS cohort study) [22]. Unlike previous reports from high-income countries, our results showed that RHD is still a frequent cause of PH in sub-Sahara Africa; reflecting both its high prevalence and late diagnoses. Indeed, in the Rheumatic Heart

**Table 3**
Clinical findings in adults between the three major pulmonary hypertension groups (n = 201).

| | Group 1 PAH (n = 34) | Group 2 PH-LHD (n = 144) | Group 3 PH-LD (n = 23) | *P*-value |
|---|---|---|---|---|
| Age (years) | 36 (20–69) | 53 (19–98) | 43 (21–91) | 0.0003[#] |
| Female | 22 (65%) | 85 (59%) | 10 (44%) | 0.2617 |
| WHO functional class III/IV | 17 (50%) | 107 (74%) | 20 (87%) | 0.0041[#] |
| Karnofsky performance score | 80 (63–90) | 70 (60–80) | 70 (50–80) | 0.0331[#] |
| 6MWT distance | 150 (120–401) | 240 (120–345) | 298 (132–320) | 0.7778 |
| 6MWT <300 m (n = 99) | 8 (41%) | 37 (71%) | 6 (55%) | 0.3693 |
| Echocardiography | | | | |
| Median LVEF (%) | 64 (50–78) | 40 (29–59) | 65 (54–76) | 0.0000[#] |
| Median RVSP (mmHg) | 71 (56–95) | 58 (48–69) | 60 (50–68) | 0.0000[#] |
| Median TAPSE (mm) | 15 (9–20) | 13 (10–16) | 13 (11–19) | 0.9961 |
| TAPSE <15 mm (n = 155) | 14 (50%) | 65 (61%) | 12 (60%) | 0.6011 |
| Signs of RHF at baseline | | | | |
| Raised JVP | 21 (64%) | 105 (75%) | 18 (82%) | 0.2679 |
| Peripheral oedema | 17 (50%) | 97 (67%) | 15 (65%) | 0.6996 |
| Raised JVP/peripheral oedema | 27 (79%) | 121 (84%) | 20 (87%) | 0.1327 |
| Diagnosis of RHF at baseline (n = 153) | 12 (45%) | 54 (51%) | 10 (50%) | 0.4853 |

Data are number (%) or median (IQR), except age (range); *p*-values based on One-Way ANOVA (Nonparametric Kruskal-Wallis test) and chi-square were appropriate. Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; LHD, left heard disease; LD, lung disease; WHO, World Health Organization; 6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; JVP, jugular venous pressure.

[#] Statistically significant ($p < 0.05$).

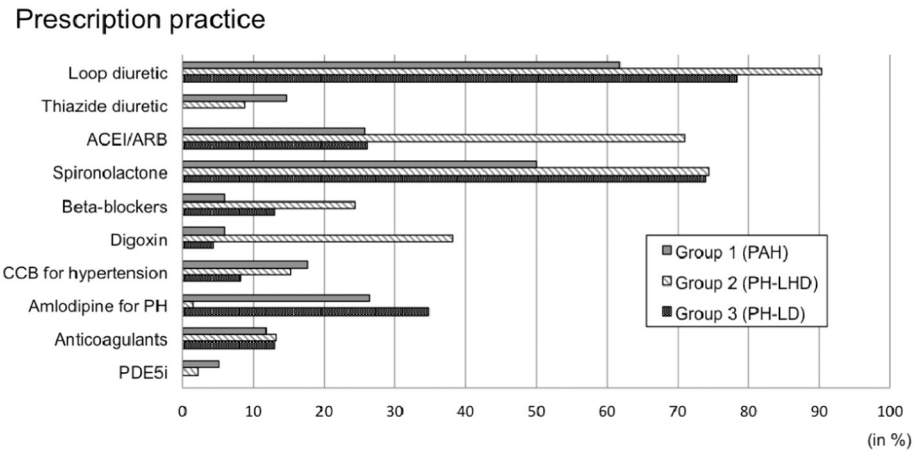


**Fig. 2.** Pharmacological treatment per pulmonary hypertension group. Group 1 pulmonary arterial hypertension (PAH), Group 2 pulmonary hypertension due to left heard disease (PH-LHD), and Group 3 pulmonary hypertension due to lung disease and/or hypoxia (PH-LD). Angiotensin-converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), calcium channel blockers (CCB), pulmonary hypertension (PH), Phosphodiesterase type 5 inhibitors (PDE5i).

Disease Global Registry up to 28% of cases present with PH-LHD [23]. Since all of our centres are peri-urban referral clinics, we expected a strong selection bias due to well-described reasons that delay or even inhibit access to care. This may explain why schistosomiasis – a rural infectious disease and one of the most common causes of PAH worldwide – was relatively scarce [24]. Furthermore, schistosomiasis-associated PAH has been described to be less severe, potentially, limiting the number of affected cases seeking medical attention. One of the most striking features of the adult cohort is their age profile (15–20 years younger) when compared to equivalent registries conducted in Europe [17]. This is even more surprising when considering that two-thirds of PH cases in our cohort were due to left heart disease, the heart disease of elderly men. Nonetheless, women were predominately affected by PH in our cohort, as described elsewhere. PH affects patients in the prime of their lives in Africa, especially young women who are often the breadwinners and caregivers of families in Africa. The women in our cohort were also less educated and more likely to live below the poverty threshold. More than one-third presented in HF. This reflects a combination of factors (not all African-specific) including generally poor access to health care in Africa, cultural barriers contributing to seeking health care only at advanced stage, PH is often missed during the early stages due to the subtle nature of its presentation, a lack of awareness by primary care doctors and low index of suspicion and limited access to echocardiography services and tertiary care. In the absence of routine right heart catheterisation, we have developed a unique diagnostic algorithm to diagnose PH in resource-constraint settings [11].

Medication use in our cohort showed a high prescription rate for loop diuretics and spironolactone, a lower prescription rate for calcium channel blockers and beta-blockers, while very few patients were on

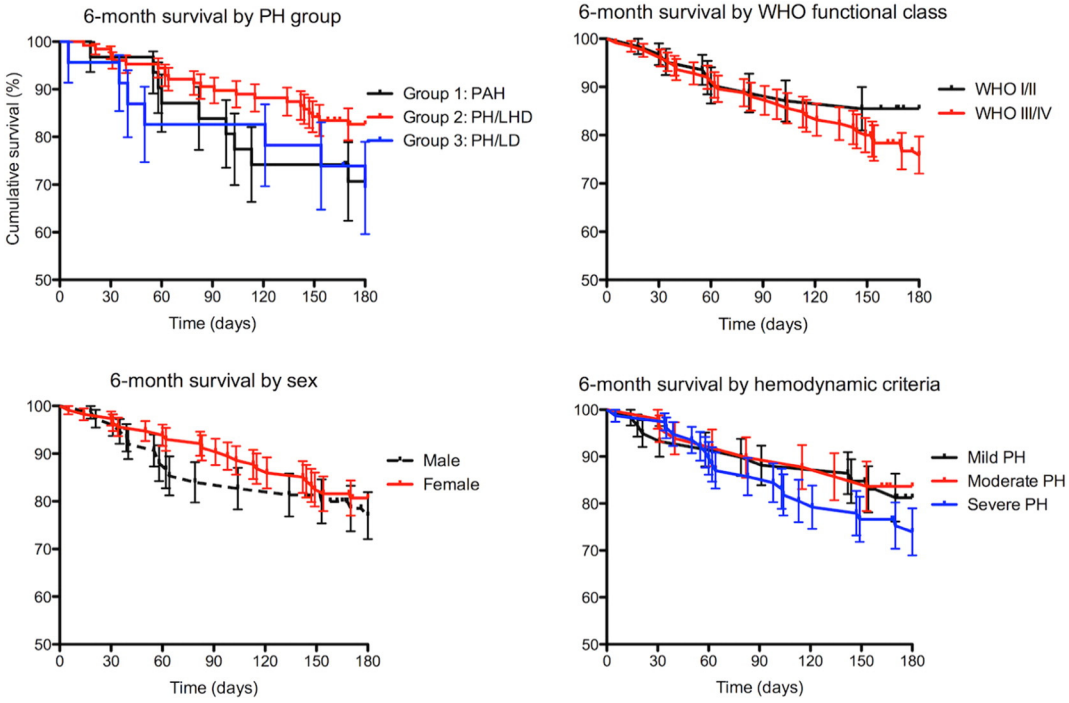


**Fig. 3.** Kaplan-Meier cumulative survival estimates. Pulmonary hypertension (PH), Group 1 pulmonary arterial hypertension (PAH), Group 2 pulmonary hypertension due to left heard disease (PH/LHD), Group 3 pulmonary hypertension due to lung disease and/or hypoxia (PH-LD), World Health Organization (WHO) functional class.

disease modifying agents and anticoagulation. This undoubtedly reflects the predominance of PH-LHD in our cohort and the application of gold-standard treatments [25]. The low prescription of anticoagulants is probably due to the bleeding risk in the absence of regular prothrombin time testing in sub-Sahara Africa. It is important to note that except for sildenafil and high dose calcium channel blockers which were essentially prescribed in Group 1 and 3 of our cohort, other drugs approved for PAH are not yet available. Our data shows that there is a profound lack of research on suitable and affordable management options for African patients with PH; especially in the context of different aetiologies of PH. Accordingly, we report poor health outcomes with 39 deaths (19%) at 6-month follow-up with a high mortality rate overall and across all clinical sub-groups. The high mortality rate reflects the natural course of PH in Africa; clinical signs of RHF at presentation were common (83%) and possibly contributing to a worse prognosis in those with non-left ventricular dysfunction, if not to all groups of PH.

### 4.1. Strengths and limitations

The limitations pertaining to these data largely reflect the challenges of conducting a registry within a low-resource setting. Diagnosis of PH necessitated the use of echocardiography rather than right heart catheterisation and many investigations were applied on a discretionary basis according to availability. However, according to the 2015 ESC/ERS guidelines for the diagnosis of PH [1,13], right heart catheterisation is recommended as a Class IC indication in patients with PAH. Right heart catheterisation for patients with PH due to left heart disease has an IIB indication and is indicated only to support treatment decisions. Right heart catheterisation would therefore not have been indicated in the majority of this cohort. The generalisability of these data to the wider African context is difficult to determine, but there is a clear need to establish larger, more purposeful registries beyond specialist centres. The small number of paediatric cases limited any substantive analyses of the same.

### 4.2. Conclusion

This unique registry documents the intersection of communicable and non-communicable diseases in sub-Saharan Africa with, generally, late presenting patients of these two entities contributing to a broad range of PH in the region. Pathways leading to PH need to be identified early and managed accordingly. PAPUCO provides the basis to develop a comprehensive and appropriate management algorithm for Africa. This includes a sound medical history, identifying signs and symptoms of PH, as well as echocardiography in conjunction with supportive diagnostic procedures [11] to address typically poor health outcomes.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.06.242.

## Competing interest

We declare no competing interest.

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