Journal of *Respiration*

MDPI

Article

Characterization of a Cohort of Patients with Chronic Thromboembolic Pulmonary Hypertension from Northeastern Colombia (REHINO Study)

Javier Enrique Fajardo-Rivero [1,*], Melissa Mogollón [1], Diego Fernando García-Bohórquez [1], Andrés Villabona-Rueda [1,2], Tania Mendoza-Herrera [1], Alba Ramírez-Sarmiento [3], Fabio Bolívar-Grimaldos [1] and Mauricio Orozco-Levi [3,4]

1 MEDITA Research Group, Department of Internal Medicine, Industrial University of Santander Health Faculty, Bucaramanga 680002, Colombia; melimogollon@hotmail.com (M.M.); difer.ferjo25@gmail.com (D.F.G.-B.); andresvilla.md@gmail.com (A.V.-R.); taniaepi70@gmail.com (T.M.-H.); fbolivar56@gmail.com (F.B.-G.)
2 Division of Pulmonary and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA
3 Cardiovascular Foundation of Colombia—Hospital Internacional de Colombia, Floridablanca 681004, Colombia; albaramirezsarmiento@gmail.com (A.R.-S.); mauricio.orozco.levi@gmail.com (M.O.-L.)
4 EMICON Research Group, MINCIENCIAS, Bogotá 111321, Colombia
* Correspondence: jfajardo.mi@gmail.com; Tel.: +57-317-641-1735

Abstract: Chronic thromboembolic disease (CTEPH) is one of the causes for developing pulmonary hypertension (PH). PH is characterized by an increase in pulmonary vascular pressure and resistance, ultimately leading to chronic overload. This study describes the clinical, functional, and hemodynamic characteristics as well as the established treatment strategy for a cohort of patients diagnosed with CTEPH in Bucaramanga, Colombia. In Colombia, PH is considered as an orphan disease with limited epidemiological data. We aim to provide useful information in order to help guide future clinical decisions for PH treatment and prevention. We conducted a cross-sectional study, obtaining clinical data from patients under follow-up, over 18 years of age, with hemodynamic confirmation of CTEPH in two pulmonary outpatient centers in Bucaramanga, Colombia between 2012 and 2018. 35 patients with diagnosis of CTEPH were included. Mean age was 52.3 ± 17.9 years. The mean time between the onset of symptoms to diagnosis was 14 months. 71% had a previous thrombotic event and 69% had functional class III and IV according to the world health organization (WHO) criteria. Most of the patients were classified as at high risk of mortality according to the European Society of Cardiology (ESC) and the European Respiratory Society (ERS/ESC) criteria and 60% were referred to undergo thromboendarterectomy. Most of the patients were under monotherapy treatment with Bosentan, the most prescribed medication in both monotherapy and dual therapy. This study identified a high number of patients in advanced stages of CETPH due to late diagnosis, related to health care limitations. This resulted in worse prognosis and quality of life. In addition, low adherence to non-pharmacological interventions was evidenced in patients who were not candidates for thromboendarterectomy despite the onset of pharmacological therapy.

Keywords: pulmonary embolism; chronic thromboembolic pulmonary hypertension; mortality; venous thromboembolic disease

Citation: Fajardo-Rivero, J.E.; Mogollón, M.; García-Bohórquez, D.F.; Villabona-Rueda, A.; Mendoza-Herrera, T.; Ramírez-Sarmiento, A.; Bolívar-Grimaldos, F.; Orozco-Levi, M. Characterization of a Cohort of Patients with Chronic Thromboembolic Pulmonary Hypertension from Northeastern Colombia (REHINO Study). *J. Respir.* **2021**, *1*, 105–113. https://doi.org/10.3390/jor1020012

Academic Editor: Cesar A. Moran

Received: 7 February 2021
Accepted: 29 March 2021
Published: 5 April 2021

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a leading cause of Pulmonary hypertension (PH) which is defined as a resting mean pulmonary artery pressure of 25 mmHg or above. CTEPH is the most serious long-term complication of pulmonary embolism and is classified as group 4 according to the World Health Organization (WHO).

It is characterized by thrombotic emboli and vascular remodeling that occludes the pulmonary arteries, generating an increase in pulmonary vascular pressure and resistance, leading to right heart dysfunction and finally to death due to heart failure [1].

CTEPH is defined by the hemodynamic confirmation of a mean pulmonary artery pressure (PAPm) ≥25 mmHg, pulmonary occlusion pressure <15 mmHg and pulmonary vascular resistance ≥3 Woods units in the right cardiac catheterization at rest [2], associated with chronic infusion defects on pulmonary ventilation/perfusion scintigraphy in computed tomography angiography (with bands or total occlusions), nuclear magnetic resonance imaging and/or pulmonary arteriography performed after at least three months of effective anticoagulation [3].

The incidence of CTEPH after an acute episode of pulmonary embolism has been reported in prospective studies as between 0.4% and 6.2% with a pooled incidence of around 3.4% [4]; however, in up to 30% of patients there was no history of venous thromboembolic disease, suggesting that other risk factors such as thrombosis in situ or recurrent silent pulmonary embolism might be present [5,6]. In Colombia PH is considered as an orphan disease with limited epidemiological data. Up to date the most recent study published in Colombia reported a prevalence and incidence of 52 and 20 cases per million inhabitants, respectively [7].

Prior to new treatment strategies the overall survival of patients with CTEPH was on average 2.8 years after diagnosis. Currently CTEPH is the only group of PH with potential interventional management through pulmonary thromboendarterectomy (PTE), which remains the treatment of choice [8]. This approach shows a clear improvement in survival rates. However, determining the intervention eligibility requires evaluation by an experienced multidisciplinary group. In selected cases balloon pulmonary angioplasty may serve as an alternative in specialized centers. In patients not meeting criteria, or those refusing surgery, Riociguat is the only medication approved for CTPEPH treatment. Riociguat is also approved for patients with persistent or recurrent PH even after thromboendarterectomy. Medications such as Macitentan have been studied but there is limited data supporting its use [9–12].

Multidisciplinary expert assessment is required for evaluation and indication of PTE in each individual case. Moreover, the complexity of CTEPH presentation paired with late diagnosis leads to poor prognosis and low survival rates.

Up to date there is no clinical data that includes the clinical presentation, treatment, and overall outcomes of patients with CTEPH in Colombia. We aimed to describe a cohort of patients from northeastern Colombia diagnosed with CTEPH and hence help guide future clinical decisions.

2. Methods

2.1. Ethical Considerations

This study was considered as a risk-free study due to its descriptive nature. The study was conducted in accordance with the Declaration of Helsinki of 2000 and Colombian legislation according to Resolution 8430 of 1993 of the Ministry of Health, complying with all the requirements stipulated in article 11. This research was approved by the Ethics Committees from Universidad Industrial de Santander (Minutes N° 25 of 3 November 2017) and the participating institutions: Instituto Neumologico del Oriente and Fundacion Cardiovascular—Hospital Internacional de Colombia (Minutes N° 454 of 17 July 2018), who guaranteed the adherence to the ethical commitments in all conducted research and waived patient consent. Informed consent was obtained from all subjects involved in the study.

2.2. Study Design

This was a retrospective cross-sectional study with concurrent non-probability sampling in two pulmonary centers in the city of Bucaramanga, Colombia, between 2012 and 2018.

2.3. Patients

Sociodemographic, clinical, diagnostic and treatment information were collected from patients over 18 years of age with diagnosis of CTEPH. CTEPH was defined by right cardiac catheterization (pulmonary artery pressure ≥25 mmHg and pulmonary vascular resistance ≥3 Woods units), and/or ventilation perfusion images or pulmonary angio-tomography (with evidence of perfusion or filling defects) at the time of inclusion. Patients with other forms of pulmonary hypertension and those lacking more than 20% of clinical data were excluded.

2.4. Statistical Analysis

Descriptive analysis was performed using measures of central tendency (mean and median), measures of dispersion (standard deviations, ranges), percentages and 95% confidence intervals.

3. Results

519 electronic medical records corresponding to ICD-10 code for primary pulmonary hypertension were filtered from the two participating institutions. 484 participants were excluded due to misdiagnosis (177), non-CTEPH (177), pediatric population (27) and lack of clinical data (35). A total of 35 patients diagnosed with CTEPH were included in the study (Figure 1). Patient baseline characteristics are shown in Table 1.

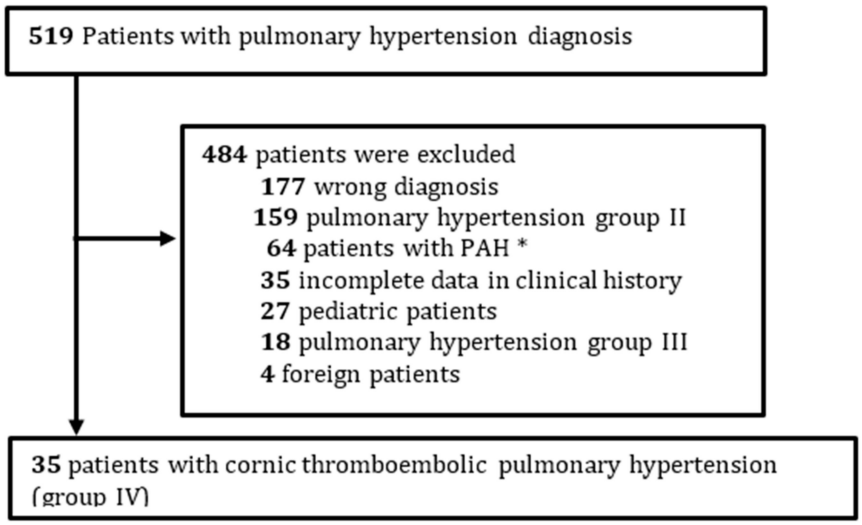

Figure 1. Screening, inclusion and exclusion criteria of the medical records from patients diagnosed with Pulmonary Hypertension (PH). * PAH: Pulmonary arterial hypertension (group I).

Table 1. Patient baseline characteristics.

Variable	N	Mean ± SD or (%)
Age at diagnosis [years]	35	52.3 ± 17.9
Time from onset of symptoms to diagnosis (months)	35	13.8 ± 15
Gender (Male n (%))	35	17 (48.6%)
BMI (kg/m^2)	29	25.3 ± 4.2
Alive at enrolment time	35	27 (77.1%)
Location		
Urban area	35	23 (65.7%)
Rural area	35	12 (34.3%)
Past medical history		
Pulmonary embolism		25 (71.4%)
Deep venous thrombosis		13 (37.1%)

Table 1. *Cont.*

Variable	N	Mean ± SD or (%)
Thrombophilia		12 (34.3%)
Antiphospholipid syndrome		8 (66%)
Protein C deficiency		1 (8.3%)
Protein S deficiency		1 (8.3%)
Antithrombin III deficiency		1 (8.3%)
No past medical history		1 (8.3%)
Cancer		0
Comorbidities		
Arterial hypertension		12 (34.3%)
COPD		9 (25.7%)
Chronic kidney disease		4 (11.8%)
Diabetes Mellitus		3 (8.6%)
Coronary heart disease		1 (2.8%)
Interstitial lung disease		1 (2.8%)
Dyslipidemia		1 (2.8%)
Cerebrovascular disease		1 (2.8%)
Atrial fibrillation		1 (2.8%)
Functional class according to WHO		
II		11 (31.4%)
III		16 (45.7%)
IV		8 (22.9%)
Symptoms		
Dyspnea		35 (100%)
Chest pain		20 (57%)
Syncope		8 (22.8%)
Clinical parameters		
BNP [pg/mL]	14	338 ± 342
Computed tomography Angiogram (CT-Angiogram)	35	30 (85.7%)
Pulmonary ventilation/perfusion scan	35	15 (42.8%)
6 min walking test (6MWT) (meters)	7	365.3 ± 127
VO2 Max (ml/kg/min)	6	12.9 ± 3.8
VE/VCO2	6	43.4 ± 9.1

Median and interquartile range values are described. Acronyms: COPD: Chronic Obstructive Pulmonary Disease, NT ProBNP: N-terminal brain natriuretic peptide.

At the time of data collection, 25% of the patients had died and information was obtained by consulting the Unique Affiliate Database (BDUA) from the General System of the Department of Health and Social Care, which is updated according to the reports generated by the major medical insurance companies (EPS). 33 of these deaths were attributed to CTEPH.

Dyspnea was present in all the patients in the cohort, followed by chest pain and syncope (57% and 23%, respectively). At the time of diagnosis, the echocardiographic variables in the cohort showed preserved systolic ventricular function by ejection fraction of the left ventricle measurements (mean: 58.2% (± 5.2)). 20% had pericardial effusion, which is a determinant of poor prognosis. Regarding the invasive hemodynamic variables, means were calculated for the systolic pressure of the pulmonary artery (PASP), diastolic pressure for the pulmonary artery (PADP), mean pressures of the pulmonary artery (MPAP), wedge pressure of the pulmonary artery, cardiac index, and pulmonary vascular resistance (See Table 2).

In this cohort, 38% underwent PTE and no patient was referred to balloon angioplasty. 89% received pulmonary vasodilator treatment. Monotherapy was administered in 64.5% of cases, Bosentan being the most prescribed medication (60%) followed by sildenafil (25%), Riociguat (10%) and nifedipine (5%). Only 32.2% received combined therapy (Table 3). All patients were under anticoagulant treatment with warfarin (60%), Rivaroxaban (29%), and low molecular weight heparin (11%). 63% had home oxygen therapy.

Table 2. Baseline Invasive Echocardiographic and Hemodynamic Variables.

Variable	N	Mean ± SD or (%)
Basal echocardiography		
LVEF (%)	35	58.2 ± 5.2
TAPSE (centimeters)	16	13.5 ± 3.8
Pulmonary systolic pressure (mmHg)	35	86.2 ± 20.9
Pericardial effusion	35	7 (20.6%)
Hemodynamics measured by right cardiac catheterization.		
Mean PAP (mmHg)	35	48.9 ± 10.7
MPAP 25–30 (mmHg)		2 (5.7%)
MPAP 30–35 (mmHg)		2 (5.7%)
MPAP > 35 (mmHg)		31 (88.5%)
Wedge pressure of the pulmonary artery (mmHg)	26	15.3 ± 7.2
Cardiac output (L/min)	25	3.9 ± 1.4
Cardiac index (L/min/m^2 median –RIQ)	25	1.89 (RIQ 1.38)
Pulmonary vascular resistance (U Wood)	30	13.5 ± 8.4
Pulmonary vascular resistance (U Wood) > 12		15 (50%)

LVEF: Left ventricular ejection fraction. TAPSE: Tricuspid Ring Systolic Excursion. TAPSE: Tricuspid annular plane systolic excursion. Mean PAP: Mean pulmonary arterial pressure.

Table 3. Description of vasodilator treatment.

Vasodilator Drug	N	n (%)
Patients under pharmacological therapy	35	31 (89%)
Monotherapy	20	20 (64.5%)
Bosentan		12 (60%)
Sildenafil		5 (25%)
Riociguat		2 (10%)
Nifedipine		1 (5%)
Therapy Dual	10	10 (32.2%)
Sildenafil + Bosentan		5 (50%)
Riociguat + Bosentan		1 (10%)
Sildenafil + Nifedipine		1 (10%)
Sildenafil + Iloprost		1 (10%)
Bosentan + Iloprost		1 (10%)
Nifedipine + Bosentan		1 (10%)
Therapy Triple	1	1 (100%)
Sildenafil + Nifedipine + Bosentan		1 (100%)

Follow-up visits were performed in 51% of the patients. Control echocardiogram was performed in 11 patients, where a decrease in the PASP was evidenced (from 78.9 ± 18.0 mmHg to 59.0 ± 24.4 mmHg). Regarding the invasive echocardiographic findings and hemodynamics, the cohort saw remarkable changes from the first cardiac catheterization to the follow-up, especially in the mean pulmonary artery pressure (51.6 ± 7.2 mmHg to 43.3 ± 16.48 mmHg) and pulmonary vascular resistances (14.3 ± 9.2 Wood Units to 7.0 ± 5.8 Wood Units), but did not display differences in cardiac output (Table 4).

Table 4. Invasive Echocardiographic and Hemodynamic Variables at Follow-up.

Variable	N	CTEPH	
		Basal Average ± SD o n y (%)	Follow-up Average ± SD on y (%)
LVEF (%)	11	61.5 ± 5.6	58.4 ± 5.7
Pulmonary systolic pressure (mmHg)	9	78.9 ± 18.0	59.0 ± 24.4 **
Hemodynamics measured by right cardiac catheterization			
Pulmonary artery systolic pressure (mmHg)	11	89.5 ± 16.1	69.5 ± 28.0
Diastolic pressure of the pulmonary artery (mmHg)	11	29.9 ± 8.2	23.3 ± 11.0
Mean pulmonary arterial pressure (mmHg)	10	51.6 ± 7.2	43.3 ± 16.48
Wedge pressure of the pulmonary artery (mmHg)	7	15.3 ± 5.3	14.3 ± 8.2
Cardiac output (L / min)	8	4.1 ± 1.9	4.6 ± 1.7
Pulmonary vascular resistance (U Wood)	9	14.3 ± 9.2	7.0 ± 5.8

*LVEF: Left ventricular ejection fraction. ** Wilcoxon test (sum of ranges) to evaluate differences between baseline and follow-up ($p < 0.05$).*

4. Discussion

CTEPH is a progressive disease of the pulmonary vasculature that leads to high morbidity and mortality. The pathophysiological mechanisms and patient characteristics differ from other forms of PH, therefore, characterizing the population and establishing the most accurate treatment is highly relevant. In Colombia, CTEPH is considered an orphan disease due to difficulties in establishing the right diagnosis and treatment. This results in a burden on the health system due to the high demand on limited resources in order to cover the cost of the health providers, diagnostic testing and medications [13].

The apparent low prevalence of CTEPH in the Colombian northwest may be due to underreporting, due to the fact that the patient registry comes from highly specialized centers and, in addition, most CTEPH cases are referred to one single reference center, which may not reflect the real incidence. Importantly, apart from Villaquirán et al. who reported data (n = 5 (2010) and n = 52 (2015)) from patients with CTEPH in Bogotá [14], no other similar study has been published in Colombia on CTEPH. The Spanish registry of pulmonary arterial hypertension REHAP for the year 2012 reported an incidence of 0.9 cases per year and a prevalence of 3.2 cases per million adults [14]. Taken together this highlights the need to publish more data on the prevalence and characteristics of CTEPH in order to improve patient outcomes.

REHINO is a study of patients with PH in northeastern Colombia. It aimed to include patients diagnosed with PH focusing on group 4; there was no sex and age difference in patients diagnosed with CTPEH (mean age over the sixth decade of life). However, age may have been a non-modifiable variable associated with onset of thrombotic events prior to the development of CTEPH in some patients. In our cohort, there was no previous history of Pulmonary Embolism (PE), even in up to 60% of cases, which contrasts with other registries where 71% of the patients a had history of PE, and 37% had deep vein thrombosis [15].

The time from onset of symptoms to CTEPH diagnosis appears to have decreased globally due to improvement in the diagnosis of venous thromboembolic diseases including better interpretation of radiological chest studies. In our cohort the time to diagnosis was similar to the one reported in more recent studies (mean: 14 months) [10]. Exertional dyspnea, chest pain, tachypnea and syncope were the most frequent symptoms and signs in our cohort, which did not differ from other registries [1]. In the registry published by Villaquirán et al., a higher number of patients were in functional class III and IV at the time of diagnosis (87%), in contrast to our study (68.6%). This might be explained by the later detection and progression of the disease [15].

Interestingly, many patients did not have reports of natriuretic peptides, 6-min walk test or integrated cardiopulmonary test, due to administrative, geographical and socioeconomic barriers. Presence of cardiovascular limitation for exercise and ventilatory inefficiency was evident in the limited number of patients who underwent the stress test

(n = 6). Those barriers represent challenging targets for improving the comprehensive clinical evaluation of patients with CTEPH in the area.

Most of the patients in our cohort had findings in the right cardiac catheterization, correlated with greater severity of their symptoms, which also led to higher mortality at the time of diagnosis. The sub-analysis performed in our cohort showed a weak correlation between clinical and hemodynamic variables, similar to that described in other cohorts. Therefore, it is important to develop a comprehensive approach including biomarkers, functional exercise tests, imaging and hemodynamic evaluation, rather than assessing the clinical profile alone.

Surgical PTE is currently the treatment of choice, which is only performed in 63% of patients eligible for surgery in high income countries [16]. In contrast, only 40% of the patients in our cohort underwent this procedure. No patient was referred to undergo balloon angioplasty due to the lack of experience in the participating institutions at the time of data collection [17].

Riociguat is a guanylate cyclase stimulant, indicated for the treatment of patients with CTEPH who are not candidates for surgery according to the current evidence, which has been approved by the Colombian local authorities (INVIMA) since 2014. Those recommendations are supported by the CHEST-1 study, which included 261 patients (189 with inoperable CTEPH and 72 with persistent PHT after the surgical procedure); compared to placebo, Riociguat-treated patients improved in the 6-MWT (39-m) and PVR, (246.4 dyn·s·cm-5; $p < 0.0001$; CI 95% (303,3 a 189,5)) with no major side effects reported [11]. These improvements were also evident in the long-term extension study CHEST-2 [11]. In this study, Riociguat was prescribed in less than 10% of the cohort. A total of 64.5% of patients were under monotherapy treatment with Bosentan (60%) and sildenafil (25%) which are generally known for the management of patients with PAH. Prior to the publication of the CHEST-1 study, the use of Bosentan was supported by studies such as BENEFIT [9,12,18,19].

All patients were under chronic anticoagulation. Warfarin was the most prescribed anticoagulant (60%); 30% were prescribed with Rivaroxaban, and 10% with low molecular weight heparin. Currently, the use of vitamin K antagonists (VKA) is considered as the standard anticoagulation therapy empirically. Nonetheless, studies that support VKA's superiority over other oral anticoagulants are still limited. Therefore, the indication of the best pharmacological agent for anticoagulation should rely on individual risk-benefit assessment for each patient [20].

Improvement was evidenced in both objective parameters (echocardiogram and cardiac catheterization) and clinical variables in the cohort. 77% of the patients had changes in their functional class, from whom improvement was seen in 71%. The lack of follow-up visits may be due to the constant conflicts between the health care insurance companies and caregivers, which limit clinical attention given to patients diagnosed with "orphan" diseases. Despite those difficulties, patients who underwent treatment showed improvement after starting medication, even though the treatment of choice and appropriate health care programs were lacking.

We recognize several limitations in the present study inherent to the design such as the lack of information in the medical records (some variables are not systematically described) and limited clinical follow-up (less than 50%). However, from an epidemiological standpoint, this study provides valuable data on the health status of the population diagnosed with CTEPH.

5. Conclusions

This is the first study describing the clinical, hemodynamic and treatment characteristics of patients diagnosed with CTEPH in northeastern Colombia. The present study highlights the lack of epidemiological reports on CTEPH and limited health policies to support this population. Here, we also describe relevant clinical, functional and hemodynamic data, including the diagnostic and treatment approach of the REHINO cohort. The symptoms of CTEPH are nonspecific and very subtle during the early stages of the

disease. Therefore, early diagnosis may be challenging and requires a high degree of clinical suspicion.

Follow-up of patients with risk factors (especially those with a history of PE) is essential. The organization of multidisciplinary groups in pulmonary centers that offer PTE are essential, due to the potential that this intervention has for treating CTEPH in the long-term, which would improve the survival and quality of life of these patients.

For patients who are not candidates for surgical intervention, the best pharmacological therapy is guanylate cyclase stimulants, according to the current literature. However, despite the availability of Riociguat in Colombia since 2014 (being the only drug approved for CTEPH), low adherence to current recommendations by the caregivers was observed, opting for the traditional prescription of Bosentan and sindenafil instead.

Author Contributions: J.E.F.-R. and M.M. contributed equally. Aceptado. Conceptualization, M.M., A.V.-R. and J.E.F.-R. Methodology, T.M.-H. Software, T.M.-H. Validation, T.M.-H., M.O.-L., F.B.-G. and J.E.F.-R. Formal analysis T.M.-H., D.F.G.-B., J.E.F.-R. and M.O.-L. Investigation J.E.F.-R., M.M., D.F.G.-B., A.V.-R. and A.R.-S. Data curation, T.M.-H., A.V.-R. and M.O.-L. Writing—original draft preparation, M.M. and D.F.G.-B. Writing—review and editing, J.E.F.-R., A.R.-S., M.O.-L. and F.B.-G. Visualization M.M. and J.E.F.-R. Supervision, J.E.F.-R., M.O.-L. and F.B.-G. Project administration. A.V.-R. and D.F.G.-B. Funding acquisition, J.E.F.-R. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Bayer. The funder (Bayer S.A. Colombia) had no role in the study design, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the article for publication.

Institutional Review Board Statement: The author(s) declare(s) that this article adhered to the existing national and international regulations regarding biomedical research, to the guidelines of good clinical practices of the international harmonization committee and to the ethical principles of the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Elwing, J.M.; Vaidya, A.; Auger, W.R. Chronic Thromboembolic Pulmonary Hypertension. *Clin. Chest Med.* **2018**, *39*, 605–620. [CrossRef] [PubMed]
2. Simonneau, G.; Montani, D.; Celermajer, D.S.; Denton, C.P.; Gatzoulis, M.A.; Krowka, M.; Williams, P.G.; Souza, R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* **2019**, *53*, 1801913. [CrossRef] [PubMed]
3. Kim, N.H.; Delcroix, M.; Jais, X.; Madani, M.M.; Matsubara, H.; Mayer, E.; Ogo, T.; Tapson, V.F.; Ghofrani, H.-A.; Jenkins, D.P. Chronic thromboembolic pulmonary hypertension. *Eur. Respir. J.* **2019**, *53*, 1801915. [CrossRef] [PubMed]
4. Pengo, V.; Lensing, A.W.; Prins, M.H.; Marchiori, A.; Davidson, B.L.; Tiozzo, F.; Albanese, P.; Biasiolo, A.; Pegoraro, C.; Iliceto, S.; et al. Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism. *N. Engl. J. Med.* **2004**, *350*, 2257–2264. [CrossRef] [PubMed]
5. Klok, F.A.; Couturaud, F.; Delcroix, M.; Humbert, M. Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Eur. Respir. J.* **2020**, *55*, 2000189. [CrossRef] [PubMed]
6. Verano, R.J.; Rojas, M.X.; Molina, Á.; Roa, J.; Granados, M.; Londoño, A.; Tobón, L.I.; Dueñas, C.; Rodríguez, M.N.; González, M.; et al. Curso clínico y supervivencia en embolia pulmonar. *Acta Médica Colomb.* **2008**, *33*, 111–116.
7. Pablo, M.; Guzman, R.; Baños, I.; Alvarez, A. Epidemiologia de la hipertension pulmonar en colombia Epidemiology of pulmonary hypertension in colombia. *Salud Uninorte* **2018**, *34*, 607–624.
8. Auger, W.R. Surgical and Percutaneous Interventions for Chronic Thromboembolic Pulmonary Hypertension. *Cardiol. Clin.* **2020**, *38*, 257–268. [CrossRef] [PubMed]
9. Ghofrani, H.-A.; D'Armini, A.M.; Grimminger, F.; Hoeper, M.M.; Jansa, P.; Kim, N.H.; Mayer, E.; Simonneau, G.; Wilkins, M.R.; Fritsch, A.; et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *N. Engl. J. Med.* **2013**, *369*, 319–329. [CrossRef] [PubMed]
10. Ghofrani, H.-A.; Simonneau, G.; D'Armini, A.M.; Fedullo, P.; Howard, L.S.; Jaïs, X.; Jenkins, D.P.; Jing, Z.-C.; Madani, M.M.; Martin, N.; et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): Results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir. Med.* **2017**, *5*, 785–794. [CrossRef]

11. Galiè, N.; Humbert, M.; Vachiéry, J.-L.; Gibbs, S.; Lang, I.M.; Kaminski, K.A.; Simonneau, G.; Peacock, A.; Noordegraaf, A.V.; Beghetti, M.; et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur. Heart J.* **2015**, *37*, 67–119. [CrossRef] [PubMed]
12. Jaïs, X.; D'Armini, A.M.; Jansa, P.; Torbicki, A.; Delcroix, M.; Ghofrani, H.A.; Hoeper, M.M.; Lang, I.M.; Mayer, E.; Pepke-Zaba, J.; et al. Bosentan for Treatment of Inoperable Chronic Thromboembolic Pulmonary Hypertension. *J. Am. Coll. Cardiol.* **2008**, *52*, 2127–2134. [CrossRef] [PubMed]
13. Villaquirán-Torres, C. Evaluación diagnóstica en hipertensión arterial pulmonar. *Rev. Colomb. Cardiol.* **2017**, *24*, 20–27. [CrossRef]
14. Escribano-Subias, P.; Blanco, I.; López-Meseguer, M.; Lopez-Guarch, C.J.; Roman, A.; Morales, P.; Castillo-Palma, M.J.; Segovia, J.; Gómez-Sanchez, M.A.; Barberà, J.A. Survival in pulmonary hypertension in Spain: Insights from the Spanish registry. *Eur. Respir. J.* **2012**, *40*, 596–603. [CrossRef]
15. Villaquirán-torres, C. Hipertensión arterial pulmonar en Bogotá: Descripción de un grupo de pacientes pertenecientes al Programa Institucional de la Fundación Neumológica Colombiana. *Rev. Colomb. Neumol.* **2010**, *22*, 3–10.
16. Mahmud, E.; Madani, M.M.; Kim, N.H.; Poch, D.; Ang, L.; Behnamfar, O.; Patel, M.P.; Auger, W.R. Chronic Thromboembolic Pulmonary Hypertension. *J. Am. Coll. Cardiol.* **2018**, *71*, 2468–2486. [CrossRef] [PubMed]
17. Jenkins, D.; Madani, M.; Fadel, E.; D'Armini, A.M.; Mayer, E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. *Eur. Respir. Rev.* **2017**, *26*, 160111. [CrossRef] [PubMed]
18. Van Thor, M.C.J.; Klooster, L.T.; Snijder, R.J.; Kelder, J.C.; Mager, J.J.; Post, M.C. Bosentan or Macitentan Therapy in Chronic Thromboembolic Pulmonary Hypertension? *Lung* **2019**, *197*, 753–760. [CrossRef]
19. Consulta de datos de producto. Instituto Nacional de Vigilancia de Medicamentos y Alimentos. 2020. Available online: http://consultaregistro.invima.gov.co:8082/Consultas/consultas/consreg_encabcum.jsp (accessed on 1 November 2020).
20. Wilkens, H.; Konstantinides, S.; Lang, I.M.; Bunck, A.C.; Gerges, M.; Gerhardt, F.; Grgic, A.; Grohé, C.; Guth, S.; Held, M.; et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018. *Int. J. Cardiol.* **2018**, *272*, 69–78. [CrossRef]