doi: http://dx.doi.org/10.11606/issn.1679-9836.v101i6e-184119 Rev Med (São Paulo). 2022 Nov-Dec;101(6):e-184119.

Original Article

# Clinical-hemodynamic profile of patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) from a tertiary hospital in São Paulo

## *Perfil clínico-hemodinâmico de pacientes com hipertensão arterial pulmonar e hipertensão pulmonar tromboembólica crônica de um hospital terciário de São Paulo*

**Pamela Cristina Costa dos Santos[1], César Henrique Morais Alves[2], Patrícia Kittler Vitório[3], Mauri Monteiro Rodrigues[4]**

Santos PCC, Alves CHM, Vitório PK, Rodrigues MM. Clinical and hemodynamic profile of patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) in a tertiary hospital of São Paulo / *Perfil clínico-hemodinâmico de pacientes com hipertensão arterial pulmonar e hipertensão pulmonar tromboembólica crônica de um hospital terciário de São Paulo. São Paulo*. Rev Med (São Paulo). 2022 Nov-Dec;101(6):e-184119.

**ABSTRACT:** *Objective.* To describe the clinical and hemodynamic characteristics of patients with Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) treated at the Hospital do Servidor Público Estadual de São Paulo (HSPE). *Methods.* The medical records of patients being followed up between 2012 and 2019 at the Pulmonary Circulation ambulatory of HSPE were reviewed. Pulmonary hypertension was confirmed by pulmonary artery catheterization and the final diagnosis of PAH or CTEPH was confirmed after specialized evaluation. *Results.* Forty-six cases of pulmonary hypertension were evaluated, of which 31 were PAH and 15 were CTEPH. The overall mean age was 67.5 (± 10.5) years and 73.9% of the participants were over 60 years old. Most participants were female (69.6%). The median time of dyspnea until diagnosis was 2 years. The main etiology of PAH was systemic sclerosis and there were no cases of schistosomiasis in the studied population. There were signs of right ventricle dysfunction at the time of diagnosis in 73.3% of cases. Among patients with CTEPH, 46.7% were unaware of previous thromboembolic events. *Conclusions.* This study addressed a predominantly elderly population with pulmonary hypertension, highlighting the characteristics of two subtypes of the disease. Further studies are necessary to improve the understanding of PH in the Brazilian population, especially of patients with CTEPH.

**Keywords.** Epidemiology; Pulmonary arterial hypertension; Pulmonary hypertension.

**RESUMO:** *Objetivo.* Descrever as características clínicas e hemodinâmicas dos pacientes com Hipertensão Arterial Pulmonar (HAP) e Hipertensão Pulmonar Tromboembólica Crônica (HPTEC) atendidos no Hospital do Servidor Público Estadual de São Paulo (HSPE). *Métodos.* Foram revisados os prontuários dos pacientes em seguimento no ambulatório de Circulação Pulmonar do HSPE em acompanhamento entre 2012 e 2019. Hipertensão pulmonar (HP) foi confirmada por cateterismo cardíaco direito e o diagnóstico final de HAP ou HPTEC foi confirmado após avaliação especializada. *Resultados.* Foram avaliados 46 casos de HP, sendo 31 de HAP e 15 de HPTEC. A média de idade foi de 67,5 (± 10,5) anos, com uma frequência de participantes com idade maior que 60 anos de 73,9%. Houve predomínio do sexo feminino (69,6%). A mediana do tempo de dispneia até o diagnóstico foi de 2 anos. A principal etiologia da HAP foi a esclerose sistêmica e não houve casos de esquistossomose na população estudada. Havia sinais de disfunção do ventrículo direito no momento do diagnóstico em 73,3% dos casos. Entre os pacientes com HPTEC, 46,7% desconheciam evento tromboembólico prévio. *Conclusões.* Este estudo abordou uma população predominantemente idosa com diagnóstico de HP, destacando as características de dois subtipos da doença. Há necessidade de novos estudos para melhorar o entendimento sobre HP na população brasileira, em especial sobre os portadores de HPTEC.

**Palavras-chave***:* Epidemiologia; Hipertensão arterial pulmonar; Hipertensão pulmonar.

1. Hospital do Servidor Estadual de São Paulo. Pulmonology Service. https://orcid.org/0000-0003-3086-7978. Email: pamela.sts@hotmail.com
2. Hospital do Servidor Estadual de São Paulo. Medical Clinic Service. https://orcid.org/0000-0001-8191-8240. Email: henrique.morais72@gmail.com
3. Hospital do Servidor Estadual de São Paulo. https://orcid.org/0000-0003-2755-6183. Email: kittler@uol.com.br
4. Hospital do Servidor Estadual de São Paulo. Pulmonology Service. https://orcid.org/0000-0001-9073-9076. Email: rodrigues.mauri@yahoo.com.br

## INTRODUCTION

Ever since the first World Symposium on Pulmonary Hypertension in 1973, pulmonary hypertension (PH) has been defined as an elevation in Mean Pulmonary Artery Pressure (PmAP) ≥ 25 mmHg, measured by pulmonary artery catheterization. However, with new studies on the early diagnosis of pulmonary hypertension, in 2018, the threshold of the definition of PH was modified to 20 mm Hg[1].

Due to the complexity of the disease, PH is divided into groups according to hemodynamic measurements and pathophysiological characteristics, allowing the definition of aetiology and specific therapeutic management. Group 1 is called Pulmonary Arterial Hypertension and includes diseases classified as pre-capillary PH (mPAP ≥ 20 mmHg associated with Pulmonary Arterial Wedge Pressure ≤ 15 mmHg and Pulmonary Vascular Resistance ≥ 3 Wood Units), such as hereditary and idiopathic PAH, connective tissue disease, drug induced disease, portal hypertension, congenital heart disease, among others. Group 2 comprises PH due to left heart disease and Group 3 corresponds to PH due to chronic lung diseases with or without hypoxemia. Group 4 comprises CTEPH and Group 5 corresponds to PH with unclear or multifactorial pathophysiological mechanisms[2].

PAH (Group 1) and CTEPH (Group 4) are both rare and often underdiagnosed. According to European data, the estimated incidence and prevalence are, respectively, from 0.9 to 3.7 and from 7 to 52 cases per million inhabitants for PAH and from 0.3 to 5.7 and from 3 to 19 cases per million inhabitants for CTEPH[3].

In Brazil, there are still few specialized centers for diagnostic confirmation and specific treatment. Therefore, PH is still a disease with few epidemiological data available in the literature, especially on the particularities of the Brazilian population. Thus, it is relevant to describe the clinical and hemodynamic profile of patients with PAH and CTEPH at a hospital for older adults in the city of São Paulo.

## OBJECTIVE

To describe the clinical and hemodynamic characteristics of patients with Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) treated at the *Hospital do Servidor Público Estadual de São Paulo* (HSPE).

## METHODS

The study was conducted through a retrospective survey of the medical records of patients with a confirmed diagnosis of PH by pulmonary artery cathererization (defined by PmAP > 20 mmHg), treated at the Pulmonary Circulation outpatient clinic of the Hospital do Servidor Público do Estado de São Paulo (HSPE) from 2012 to 2019. Among a total of 64 patients, those with an etiological diagnosis of PAH (Group 1) or CTEPH (Group 4) were included. Patients without a pulmonary artery catheterization or those who met the criteria for PH of other etiologies (groups 2, 3 and 5) were excluded, resulting in a sample of 46 patients.

The following data were evaluated:

1. Clinical variables: age, gender, time of dyspnea until diagnosis, history of syncope, lower limb edema, coughing, hemoptysis and paroxysmal nocturnal dyspnea. Clinical classification of the patients according to the New York Heart Association (NYHA) Functional Classification and need for oxygen supplementation;
2. Hemodynamic variables: mean pulmonary artery pressure (mPAP), mean right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR), cardiac output (CO) and cardiac index (CI);
3. Echocardiographic variables: left ventricular ejection fraction, estimated pulmonary artery systolic pressure (PASP), signs of right ventricular dysfunction (defined as right heart enlargement and paradoxical septal motion), and presence of pericardial effusion;
4. Pulmonary function parameters: obtained by spirometry, plethysmography, cardiopulmonary exercise testing and six-minute walk test (6MWT), according to the clinical assessment of the physician. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), diffusing capacity for carbon monoxide (DLCO), distance walked in the six-minute walk test, maximal oxygen consumption during exercise (VO2 max) and VE/VCO2 ratio (minute ventilation/CO2 production) at lactate threshold were evaluated;
5. Other data: serum BNP (Brain Natriuretic Peptide) levels and alteration in the ventilation-perfusion scan compatible with the diagnosis of CTEPH;
6. Therapeutic data: targeted therapies initially used and use of anticoagulation, if indicated.

Exploratory data analysis included mean, median and standard deviation, as well as range for continuous variables and number and proportion for categorical variables. The distribution of continuous variables was verified by asymmetry, kurtosis and the Kolmogorov-Smirnov test. The Student's t-test or Wilcoxon Rank Sum Test were used to compare continuous variables between the two groups. Statistical analysis was performed using the IBM-SPSS Statistics software version 24 (IBM Corporation, NY, USA). All tests were two-tailed and p-values <0.05 were considered significant. This project was approved by the Research Ethics Committee of the *Instituto de Assistência ao Servidor Público Estadual de São Paulo* (Opinion number 3,773,609).

## RESULTS

The mean age of the sample studied was 67.5 ± 10.5 years, 74% of the participants were over 60 years of age and 70% were female. The subgroup of patients with a final diagnosis of PAH represented 67.4% of the sample, while patients with a confirmed diagnosis of CTEPH represented 32.6%. The general characteristics of the sample are described in Table 1.

**Table 1.** General characteristics of the studied sample

| Characteristics | N = 46 |
|---|---|
| Age, years | 67.5 ± 10.5 |
| Female, n (%) | 32 (69.6) |
| Functional class (NYHA), n (%) | |
| Class I | 9 (19.6) |
| Class II | 12 (26.1) |
| Class III | 18 (39.1) |
| Class IV | 7 (15.2) |
| Time of dyspnea until diagnosis, years | 2.0 (0 - 9) |
| Oxygen saturation, % | 94 (82 - 99) |
| Need for supplemental $O_2$, n (%) | 16 (34.8) |
| Symptoms, n (%) | |
| Lower limb edema | 15 (32.6) |
| Coughing | 7 (15.2) |
| Syncope | 4 (8.7) |
| Chest pain | 2 (4.3) |
| Paroxysmal nocturnal dyspnea | 1 (2.2) |
| Hemoptysis | 0 (0) |
| Diagnosis, n (%) | |
| PAH | 31 (67.4) |
| CTEPH | 15 (32.6) |

Continuous variables are described as mean ± standard deviation or median (variation), and categorical variables are described as number (percentage). NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

Among the individuals diagnosed with PAH, the most common etiologies were connective tissue disease (45.2%), especially Systemic Sclerosis, and idiopathic PAH (25.8%). No cases of schistosomiasis infection were recorded. Among the patients with CTEPH, 53% had a known history of thromboembolism. Pericardial effusion was found in 20% of patients with PAH and 13.3% of patients with CTEPH (Table 2). The hemodynamic measurements, BNP level and functional data of the patients described in Tables 3 and 4 did not differ between the two groups.

The cases analyzed were divided by severity, according to the New York Heart Association Functional Classification. Patients in classes 1 and 2 have mild symptoms and minor limitations on activities of daily living, while patients in Functional Classes 3 and 4 are more symptomatic. The comparative analysis showed that the most severely ill patients had higher Right Atrial Pressure (RAP) and Pulmonary Vascular Resistance (PVR) and worse performance on the six-minute walk test (6MWT), as shown in Table 5.

**Table 2.** Demographic and clinical data of the patients included, according to the pulmonary hypertension diagnostic group

| Variable | PAH N = 31 | CTEPH N = 15 |
|---|---|---|
| Age, years | 65.8 ± 10.9 | 70.9 ± 8.9 |
| Female, n (%) | 24 (77.4) | 8 (53.3) |
| Functional class, n (%) | | |
| Class I | 7 (22.6) | 2 (13.3) |
| Class II | 4 (12.9) | 8 (53.3) |
| Class III | 15 (48.4) | 3 (20.0) |
| Class IV | 5 (16.1) | 2 (13.3) |
| Time of dyspnea until diagnosis, years | 2.0 (0-9) | 2.0 (0-7) |
| Oxygen saturation, % | 94 (82-99) | 94 (85-98) |
| Need for supplemental $O_2$, n (%) | 12 (38.7) | 4 (26.7) |
| Echocardiographic sign of RV dysfunction, n (%) | 22/30 (73.3) | 11 (73.3) |
| Pericardial effusion, n (%) | 6/30 (20.0) | 2 (13.3) |
| Etiology of pulmonary hypertension, n (%) | | |
| Connective tissue disease | 14 (45.2) | - |
| Idiopathic PAH | 8 (25.8) | - |
| Congenital heart disease | 3 (9.7) | - |
| Portal Hypertension | 3 (9.7) | - |
| Anorectic Agent | 2 (6.5) | - |
| Other | 1 (3.2) | - |
| Venous thromboembolism, n (%) | 3 (9.7) | 8 (53.3) |

Continuous variables are described as mean ± standard deviation or median (variation), and categorical variables are described as number (percentage). PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; RV: right ventricle.

**Table 3**. Hemodynamic characteristics and BNP

| Feature | N = 46 |
|---|---|
| CO, L/min | 4.47 ± 1.3 |
| CI, L/min/m $^2$ | 2.62 ± 0.77 |
| RAP, mmHg | 10.3 ± 4.7 |
| PmAP, mmHg | 43.5 (22 - 103) |
| POAP, mmHg | 12.0 (5 - 27) |
| RVP, Wood | 7.16 (2.9 - 22.0) |
| BNP, pg/mL | 150.3 (5.3 - 2941.0) |

Continuous variables are described as mean ± standard deviation or median (variation). CO: cardiac output; CI: cardiac index; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; BNP: brain natriuretic peptide.

**Table 4.** Variables related to lung function

| Feature | Result | evaluated |
|---|---|---|
| 6MWT, meters | 321.3 ± 100.2 | 35 |
| FVC, L | 2.51 ± 0.67 | 30 |
| FVC, % | 82.48 ± 19.1 | 29 |
| FEV1, L | 1.92 ± 0.53 | 31 |
| FEV1, % | 78.63 ± 17.3 | 30 |
| DLCO, L | 10.9 (3.9-41.5) | 17 |
| VO2 max< 15, n (%) | 4/8 (50.0) | 8 |
| VE/VCO2 > 35, n (%) | 7/9 (77.8) | 9 |

Continuous variables are described as mean ± standard deviation or median (variation) and categorical variables in number (percentage). 6MWT, Six Minute Walk Test; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide; VO2max, maximal oxygen uptake; VE/VCO2, ratio between minute ventilation and carbon dioxide production at lactate threshold.

The drug treatment for patients with PAH was predominantly with sildenafil (74.2%) alone or in combination with bosentan (12.9%) or ambrisentan (35.5%). Anticoagulation therapy was indicated for 29% of patients and only one patient used calcium channel blocker in monotherapy, since vasoreactivity testing with inhaled nitric oxide was recently implemented in the hemodynamic service of the HSPE (Table 6). The treatment of patients with CTEPH is described in Table 7.

**Table 5**. Comparative analysis of hemodynamic characteristics and BNP between functional classes 1-2 and 3-4

| | Functional Class | | |
|---|---|---|---|
| **Variable** | **I - II** | **III - IV** | **p-value** |
| 6MWT | 377.5 ± 99.5 | 273.9 ± 74.3 | **0.001** |
| CO | 4.69 ± 1.2 | 4.27 ± 1.4 | 0.291 |
| CI | 2.67 ± 0.67 | 2.57 ± 0.85 | 0.678 |
| RAP | 8.00 ± 3.3 | 12.3 ± 4.9 | **0.002** |
| PVR | 5.59 (2.9-12.0) | 8.45 (3.3-22.0) | **0.013** |
| BNP | 79.1 (5.3-1953.0) | 236.0 (31.9-2941.0) | 0.234 |

Continuous variables are described as mean ± standard deviation or median (variation). 6MWT, 6 Minute Walk Test; CO, cardiac output; CI, cardiac index; RAP, right atrial pressure; PVR, pulmonary vascular resistance; BNP, brain natriuretic peptide.

**Table 6.** Drug therapy used by patients with PAH

| **Approach** | **N = 31** |
|---|---|
| Initial targeted therapy, n (%) | 24 (77.4) |
| Sildenafil, n (%) | 23 (74.2) |
| Ambrisentan, n (%) | 11 (35.5) |
| Bosentan, n (%) | 4 (12.9) |
| Amlodipine, n (%) | 1 (3.2) |
| Anticoagulant, n (%) | 9 (29.0) |
| Warfarin | 8/31 (25.8) |
| Rivaroxaban | 1/31 (3.2) |

Categorical variables are described in number (percentage). PAH, pulmonary arterial hypertension.

**Table 7.** Therapeutic approach of patients with CTEPH

| **Approach** | **N = 15** |
|---|---|
| Thromboendarterectomy, n (%) | 2 (13.3) |
| Balloon angioplasty, n (%) | 1 (6.7) |
| Initial targeted therapy, n (%) | 4 (26.7) |
| Sildenafil, n (%) | 4 (26.7) |
| Anticoagulant, n (%) | 15 (100.0) |
| Warfarin | 9/15 (60.0) |
| Rivaroxaban | 6/15 (40.0) |

Categorical variables are described in number (percentage). CTEPH, chronic thromboembolic pulmonary hypertension

## DISCUSSION

This study described the characteristics of patients with PH treated at the Hospital do Servidor Público Estadual de São Paulo (HSPE). This institution is regionally recognized for its actions related to comprehensive care for older adults, who are the major users of this service. Due to the profile of the population, the epidemiological characteristics found in this study are similar to those of developed countries. The mean age at diagnosis was similar to that found in Latvia, where the mean age at diagnosis of PAH and CTEPH was 63.7 ± 18.0 and 71.4 ± 8.2 years, respectively[3]. A European registry that analyzed the prevalence of PAH in the population also found that 63% of the sample was composed of older adults, with a mean age of 65 years[4].

In this study, even patients with PAH were of an advanced age, which differs from other two Brazilian studies, which found that the mean age of these patients was 42[5] and 46 years[6]. A Korean study with 1,307 patients in PH Group 1 found a mean age of 44±13 years, corroborating the information from Brazilian registries[7].

Most of our sample was female, similarly to other records in the literature. A Brazilian study with PAH[5] found a 2.3:1 ratio between women and men, which is similar to international data, which shows that women represent 69.3% of patients with PAH[7]. A study that evaluated both etiologies of PH (PAH and CTEPH) also showed a prevalence of females in both groups: 83% in PAH and 74% in CTEPH[3].

The predominance of functional classes III and IV indicates an advanced disease phase at the time of diagnosis, which may be correlated with delayed diagnosis

secondary to the insidious and progressive course of the disease. Brazilian studies that addressed PH Group 1 also found functional classes III and IV at diagnosis in 62%[5] and 45.5%[6] of patients. This rate can vary according to the profile and comorbidities of the population studied, reaching up to 95% of patients with PAH and 65% of patients with CTEPH[3]. The time from dyspnea to diagnosis found in this study was around 2 years. In this context, considering that the study population is mostly elderly, the association with other comorbidities such as coronary artery disease can be a confounding factor for the symptoms and reflect the difficulties in accessing specialized health services in Brazil.

It must be highlighted that, among our patients with PAH, there were no cases of schistosomiasis, even among those who did not meet the inclusion criteria for the study. Brazilian registries highlight this etiology among the main causes of PAH. A Brazilian study[5] assessed the main etiologies and found that 50% of patients were diagnosed with idiopathic PAH, 30% with PAH associated with schistosomiasis, and 10% with PAH associated with connective tissue diseases. Another study[6] found that idiopathic PAH represented 28.7% of cases, followed by PAH associated with connective tissue diseases (25.8%), with systemic sclerosis as the most common, and PAH associated with schistosomiasis (19.7%). International data point to idiopathic PAH as the most common, with 46.2% of cases in the American registry[8], 36.2% in Spain[9] and 51.6% in Korea[7]. The absence of schistosomiasis in our study is probably related to the socioeconomic profile of the patients.

Studies describing the characteristics of the population with CTEPH are rare in the literature[3]. In Brazil, this is the first study with this objective, which demonstrates the need for complementary work with large population samples. In most cases of CTEPH, there is a previous thromboembolic event. A prospective study[10] analyzed cases of CTEPH and found that 74.8% of patients had a history of pulmonary embolism and 56.1% had a history of deep vein thrombosis. It is worth noting that only 53.3% of our sample had a history of thromboembolic disease.

A Brazilian study[5] also analyzed the clinical data of patients at the time of diagnosis, and found that about 20% of the patients had wheezing, paroxysmal nocturnal dyspnea and cyanosis; more than 40% had cough and lower limb edema; and 35% had syncope and chest pain. The hemodynamic data of this study are similar to those found in the literature.

A study that evaluated 587 individuals with PAH[4] compared clinical and hemodynamic data of younger (18 to 65 years old) and elderly patients (over 65 years old) and found statistically significant evidence that older patients had lower mPAP compared to younger ones (mean of 41 *versus* 50 mmHg, respectively), as well as higher PAWP (mean of 10 *versus* 9 mmHg, respectively), lower PVR (8.3 *versus* 12 Woods units among young people) and shorter distance walked (266 *versus* 340 meters in the 6mWT). The cardiac index was similar between the two groups, around 2.2 L/min/m³. The hemodynamic data of this study are similar to the results obtained in our sample of patients with PAH.

In this study, most patients with PAH were initially treated with sildenafil monotherapy, a result similar to those found in the literature. A Brazilian study found that sildenafil was chosen as the first-line treatment in 66% of cases, followed by bosentan in 27% and initial dual therapy in 5%[6]. Another study with patients with PAH and CTEPH found that 95% of them received targeted therapy and most started with monotherapy (80%), with the phosphodiesterase-5 inhibitor as the first choice in 76% of cases. Oral anticoagulation was used in all patients with CTEPH, mostly with warfarin (65%)[3]. Our study also found that warfarin was chosen in 60% of cases, followed by sildenafil in 26.7%. The use of targeted therapy in this context is still considered an off-label treatment, used in selected cases at the discretion of the attending physician. Although the treatment of choice for CTEPH is surgical, only a small number of patients had a thromboendarterectomy in this study, which is related to the advanced age, comorbidities and high surgical risk of the patients, as well as their refusal.

One of the positive points of this study is that it described the characteristics of a predominantly elderly population, contributing to the knowledge of PH in old age. In addition, despite the small sample, the description of patients with CTEPH is a topic still to be explored in further research. The limitations of this study include the small number of patients analyzed stands out, the fact that the diseases analyzed are infrequent, and the analysis performed in a single setting. The particular characteristics of the studied population make it difficult to extrapolate information to the general population and, like any retrospective study, this one was also subject to data loss.

## CONCLUSIONS

The clinical and hemodynamic profile of patients with Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension at the Hospital do Servidor Público Estadual de São Paulo differs from that described in other Brazilian epidemiological studies and is similar to that of developed countries. More extensive epidemiological studies are needed to better characterize pulmonary hypertension in Brazil.

***Ethical Aspects:*** There are no possible conflicts of interest (professional, financial and direct or indirect benefits) that may have influenced the research results or the content. This project was approved by the Research Ethics Committee of the Instituto de Assistência ao Servidor Público de São Paulo; opinion number: 3,773,609 (CAAE 22295819.5.0000.5463).

**Participation of the authors:** *Pamela Cristina Costa dos Santos* - participated in the planning of the study; collection, analysis and interpretation of data; writing and reviewing the manuscript; and final approval of the version to be published. *Cesar Henrique Morais Alves* - participated in the planning of the study, analysis and interpretation of data; writing and reviewing the manuscript; and final approval of the version to be published. Patrícia Kittler Vitório participated in the design and planning of the work, interpretation of data; guidance in writing and reviewing the manuscript; and final approval of the version to be published. *Mauri Monteiro Rodrigues* - participated in the design and planning of the work, interpretation of data; guidance in writing and reviewing the manuscript; and final approval of the version to be published.

## REFERENCES


1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019; 53(1):1801913. https://doi.org/10.1183/13993003.01913-2018
2. 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. Rev Esp Cardiol (Engl Ed). 2016;69(2):177. https://doi.org/10.1016/j.rec.2016.01.002
3. Sablinskis K, Sablinskis M, Lejnieks A, Skride A. Growing number of incident pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in Latvia: a shifting epidemiological landscape? Data from a national pulmonary hypertension registry. Eur J Intern Med. 2019;59:e16-e17. https://doi.org/10.1016/j.ejim.2018.09.017
4. Hoeper M, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: Results from the COMPERA registry. Int J Cardiol. 2013;168:871-880. https://doi.org/10.1016/j.ijcard.2012.10.026
5. Lapa MS, Ferreira EV, Jardim C, Martins Bdo C, Arakaki JS, Souza R. Características clínicas dos pacientes com hipertensão pulmonar em dois centros de referência em São Paulo. Rev Assoc Med Bras 2006;52:139-143. https://doi.org/10.1590/S0104-42302006000300012
6. Alves JL Jr, Gavilanes F, Jardim C, Fernandes CJCDS, Morinaga LTK, Dias B, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. Chest. 2015;147(2):495-501. https://doi.org/10.1378/chest.14-1036
7. Song S, Lee SE, Oh SK, Jeon SA, Sung JM, Park JH, et al. Demographics, treatment trends, and survival rate in incident pulmonary artery hypertension in Korea: A nationwide study based on the health insurance review and assessment service database. PLoS One. 2018;13(12):e0209148. https://doi.org/10.1371/journal.pone.0209148
8. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010;137(2):376-387. https://doi.org/10.1378/chest.09-1140
9. Escribano-Subias P, Blanco I, López-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. Eur Respir J. 2012;40(3):596-603. https://doi.org/10.1183/09031936.00101211
10. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973-1981. https://doi.org/10.1161/CIRCULATIONAHA.110.015008


Received: April 10, 2021
Accepted: September 27, 2022