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COLLABORATIVE REGISTRY OF PULMONARY HYPERTENSION IN ARGENTINA (*RECOPILAR*). FINAL ANALYSIS

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Abstract The epidemiology of pulmonary hypertension (PH), especially pulmonary arterial hypertension (PAH), has not been evaluated in our country, therefore there is no reference parameter to establishing the representativeness of this information in the national order. This registry represents the first collaborative effort to provide a knowledge base of this disease, including 5 scientific societies that represent different specialties (pediatrics, rheumatology, pulmonology and cardiology) with data from 23 Argentine provinces. These efforts involved five societies of various adult (cardiology, rheumatology, and pulmonology) and pediatric (cardiology) specialties. Subjects were grouped (1-5) in accord with the 2013 Nice classification. A total of 627 patients (mean age, 50.8±18 years; women, 69.2%) were recruited. Incident cases accounted for 53%. Functional class III-IV accounted for 69% at time of diagnosis and 33.4% at time of inclusion. Distributions in groups 1-5 were 63.6%, 15.9%, 8.3%, 9.7%, and 2.4%, respectively. Treatment consisted of diuretics (51.2%), mineralocorticoid receptor antagonists (44.7%), digoxin (16.6%), anticoagulants (39.2%), renin-angiotensin antagonists (15.5%), beta blockers (15.6%), and calcium channel blockers (8%). Rates of specific therapies usage in PAH vs. non-PAH group were 80.5% vs. 40.8% (phosphodiesterase-5 inhibitors: 71% vs. 38.6%; endothelin receptor antagonists: 54.4% vs. 14.5%; prostanoids: 14.3 vs. 3.1%; all $p < 0.001$). Three-year survival in PAH and non-PAH differed significantly (82.8% vs. 73.3%; $p = 0.001$). In the Argentine RECOPILAR registry, the clinic-epidemiologic profile was that of advanced-stage disease. Diagnostic workups and therapeutics interventions, including use of specific therapy for PAH, were consistent with current recommendations. Despite delays in diagnosis, survival was aligned with other contemporary registries.

Key words: pulmonary hypertension, registry, pulmonary arterial hypertension

Resumen ***Registro colaborativo de hipertensión pulmonar en Argentina (RECOPILAR): análisis final.*** La epidemiología de la hipertensión pulmonar (HP), especialmente la arterial (HAP), no ha sido evaluada en nuestro país, por lo cual no existe un parámetro de referencia para establecer la representatividad de esta información en el orden nacional. El presente registro representa el primer esfuerzo colaborativo para una base de conocimiento de esta enfermedad, incluyendo 5 sociedades científicas que representan a distintas especialidades médicas (pediatría, reumatología, neumonología y cardiología) con datos de 23 provincias argentinas. Los sujetos se agruparon (1-5) de acuerdo con la clasificación de Niza de 2013. El seguimiento se completó en 583 pacientes (93%) un año después del final de la inscripción. Se incluyeron 627 pacientes (edad media, 50.8 ± 18 años; mujeres, 69.2%). Los casos incidentes representaron el 53%. La clase funcional III-IV representaba 69% en el momento del diagnóstico y 33.4% en el momento de la inclusión. Las manifestaciones clínicas fueron disnea (81.8%), fatiga (54.1%), síncope (10.8%), dolor torácico (14.7%), palpitaciones (20.9%) e insuficiencia cardíaca (20.4%). Las tasas de uso de terapias específicas en la hipertensión arterial pulmonar (HAP) frente al grupo sin HAP fueron del 80.5% frente al 40.8%. La supervivencia a tres años en los subconjuntos de HAP y no HAP difirió significativamente (82.8% vs. 73.3%; $p = 0.001$). En el registro RECOPILAR argentino, que aborda principalmente la HAP, el perfil clínico-epidemiológico fue el de una enfermedad en estadios avanzados. El diagnóstico y las intervenciones terapéuticas, incluido el uso de terapia específica para la HAP, fueron consistentes con las recomendaciones actuales.

Palabras clave: hipertensión pulmonar, registro, hipertensión arterial pulmonar

KEY POINTS

- The RECOPILAR is the first epidemiologic reference on pulmonary hypertension in Argentina. With pulmonary arterial hypertension (PAH) accounting for two-thirds of our study population, the clinical profile was one of advanced disease. All diagnostic evaluations and treatments rendered, including high PAH-specific therapy, were consistent with current recommendations.

Pulmonary hypertension (PH) is a disorder marked by increased pulmonary vascular resistance and progressive right ventricular failure. In those affected, quality of life and survival are subsequently limited. The spectrum of PH ranges from a rare and rapidly progressive form of pulmonary vasculopathy, namely pulmonary arterial hypertension (PAH), to more common variants in the context of heart and lung diseases or chronic pulmonary thromboembolism[1]. As a result, five subtypes of PH have been recognized for treatment purposes, based on related pathophysiologic mechanisms[2, 3]. The estimated worldwide prevalence of PAH is 15 per million inhabitants, with an incidence of 2.4 per million per year[4, 5].

PH registries have mainly collected data on patients with PAH[6-10] and few of them have included chronic thromboembolic pulmonary hypertension (CTEPH)[11]. The demographics and evolution of PAH are well characterized by registries in the United States, Europe, and Asia. Such studies also attest to dramatic improvement in both the clinical evolution and the natural history of this condition, owing to diagnostic and strategic therapeutic advances of past decades.

Epidemiologic data on PH in Latin America[12, 13], particularly in Argentina, are scarce and are confined to patients treated at referral centers[14]. Based on the present body of data, the prevalence of PAH in Latin America varies between 4000 and 15 000 cases, with roughly 700-4600 new patients added each year. Hence, the magnitude of this problem is troubling[15]. It is also essential that any planned analysis take into account the differing etiologic profiles of wealthier and developing regions[5]. Chief contributors to

pulmonary vascular disease in more privileged nations are left heart disease (55%), chronic obstructive pulmonary disease (COPD; 42%), and PAH (3%); whereas COPD (27%) and other diverse pathologies (i.e., schistosomiasis,16%; altitude sickness, 22%; human immunodeficiency virus [HIV], 10%; rheumatic diseases, 10%; and congenital heart disease, 2%) are instead implicated in low-resource countries[5, 15, 16].

The Collaborative Registry of Pulmonary Hypertension in Argentina (RECOPILAR) was a national, multicenter project designed to collect data from a broad spectrum of patients with PH (all groups), supported by five national scientific societies. Their goal was to obtain a broader, more accurate epidemiologic profile of PH in our country through a shared inter-institutional national registry. Hence, objectives of this study were to investigate the epidemiologic traits, clinical features, diagnostic/treatment strategies, and 3-year survival outcomes of PH in Argentina.

Materials and methods

This registry was jointly supported by the following national societies, all collaborating to create a multicentric, prospective and observational model: Argentine Federation of Cardiology (FAC), Argentine Society of Cardiology (SAC), Argentine Association of Respiratory Medicine (AAMR), Argentine Society of Rheumatology (SAR), and Argentine Society of Pediatrics (SAP). Design and general aspects of the protocol have been previously published[17]. In brief, patients with PH were included between July 1, 2014 and October 30, 2016. The stated closing date had been extended for an additional year by the Coordinating Scientific Committee (CSC). Based on set time frames, patients were considered either prevalent (diagnosed between July 1, 2009 and June 30, 2014) or incident (diagnosed after July 1, 2014 through end of enrollment) cases.

Eligible subjects qualified for one of the five PH groupings specified by the Nice classification[2] and met all of the following criteria: age > 3 months; mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, as determined by right cardiac catheterization (RHC); and clinical stability (i.e. no hospitalization in the prior month). In children <16 years of age with congenital heart disease and shunting, decisions to perform RHC were made by a pediatric cardiologist, taking into account the chief direction of flow. Any existing pathology other than PH that limited life expectancy to < 1 year was an exclusion criterion.

The CSC included representatives of each collaborating institution tasked with protocol and database designs and conducting/coordinating the registry. Computer support was provided by the Center of Medical Tele-informatics of the Argentine Federation of Cardiology (CETIFAC), under the Engineering School/ Bioengineering/CONICET, National University of Entre Ríos (UNER). Such resources devised systems for electronic data capture via the Internet and maintained a functional online database, ensuring each researcher access. A data control group safeguarded the quality of information gathering through surveillance and analysis of compliance with inclusion/exclusion criteria. This registry received no corporate, industrial, or individual sponsorship, residing under the sole protective domain of the CSC and CETIFAC to guarantee data privacy.

The RECOPILAR project was approved on August 6, 2014 by the Bioethics Committee of the Specialized Maternal and Child Hospital Victorio Tetamanti and the *Hospital General Interzonal de Agudos Dr. Oscar Alende*, from Mar del Plata (Buenos Aires). Approval was also granted by the Teaching Secretary of the Argentine Federation of Cardiology. Each patient signed an informed consent, as required by institutional policies and national and state privacy regulations governing medical information.

Categorical variables were expressed as percentages, using Pearson's chi-square test to compare values. Continuous variables were aptly presented as mean± standard deviation or median and 25-75% interquartile interval (IQ), conducting comparisons via Student's *t*-test or Mann-Whitney U test. Kaplan-Meier survival curves were then plotted and compared by log-rank test. All computations relied on standard software (SPSS Statistics v24; IBM, Armonk, NY, USA), setting significance at $p < 0.05$.

Results

The RECOPILAR enlisted a total of 627 patients with PH. Mean age was 50.8±18.7 years, and 434 (69.2%) were women. Incident cases comprised 53% of the population (first year, 32%; second year, 76.3%; $p < 0.001$). Insurance coverage was provided as follows*: Instituto Nacional de Servicios Sociales para Jubilados y Pensionados* (INSSJyP), 18.3%; private health systems, 14.5%; provincial social security, 17.1%; or *Superintendencia de Seguro de Salud*, 32.5%. Those lacking social security (17.5%) were treated in public hospitals. Only 3.5% of the population was <16 years old, all classified as PH group 1. Histories of prior hospitalization, largely due to heart failure (52%), pneumonia (6.5%), or pulmonary embolism (5%), were elicited in 208 patients (33.2%).

The symptoms cited most frequently were dyspnea, fatigue, and palpitations (Fig. 1), whereas chief physical findings were ankle edema, Dressler's sign, and hepatomegaly (Fig. 2). One of five patients had a past diagnosis of heart failure (20.4%).

The mean time between symptom onset and RHC was 24 ± 40 months (median, 11 months [IQ, 4-26 months]), and the mean interval from RHC to registry inclusion was 17 ± 22 months (median, 8 months [IQ, 0-27 months]).

Baseline characteristics of the patient population are shown in Figure 3. Chest x-rays, electrocardiograms, and echocardiography were performed in a majority (> 80%). Chest computed tomography (CT) and lung perfusion scintigraphy were also frequently obtained. The 6-min walking test (6MWT) was the preferred method of evaluating exercise capacity. Pulmonary function testing and rheumatology screening were both underutilized.

The distribution of patients with PH was as follows: group 1, 63.6%; group 2, 15.9%; group 3, 8.3%; group 4, 9.7%; and group 5, 2.4% (Fig. 2, Fig. 4, Table 1). Although age across the five groups were generally diverse,

Fig. 1.– Symptoms present in the patients included in the RECOPILAR registry at the time of diagnosis

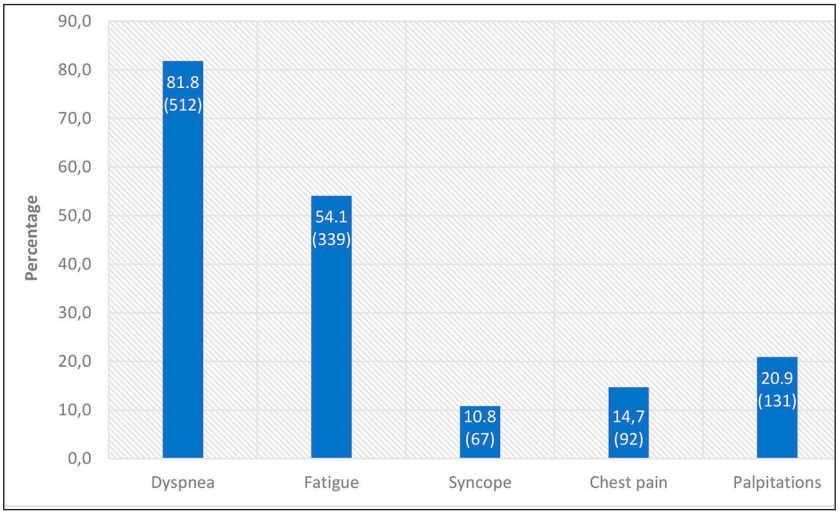
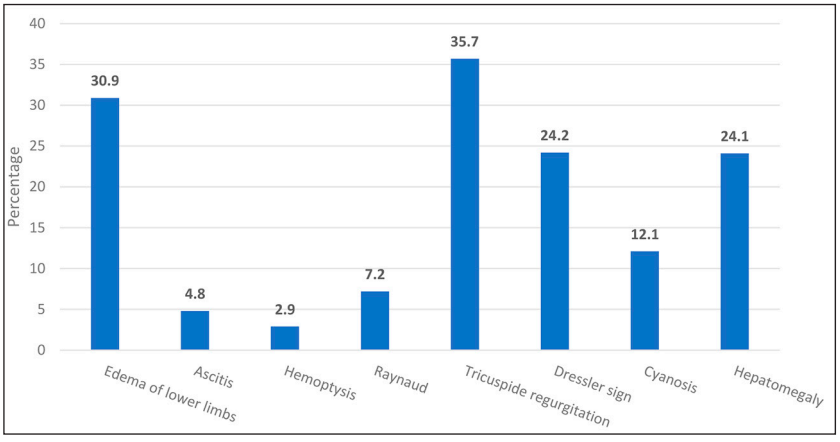


Fig. 2.– Findings in physical examination in the patients included in the RECOPILAR registry at the time of diagnosis



group 1 harbored the youngest patients, and the oldest were found in group 2. Women represented more than two-thirds of groups 1, 4, and 5 but were limited to 40% of group 2. Cardiovascular comorbidities, such as arterial hypertension, diabetes mellitus, dyslipidemia, obesity, or atrial fibrillation, were identified most frequently in group 2.

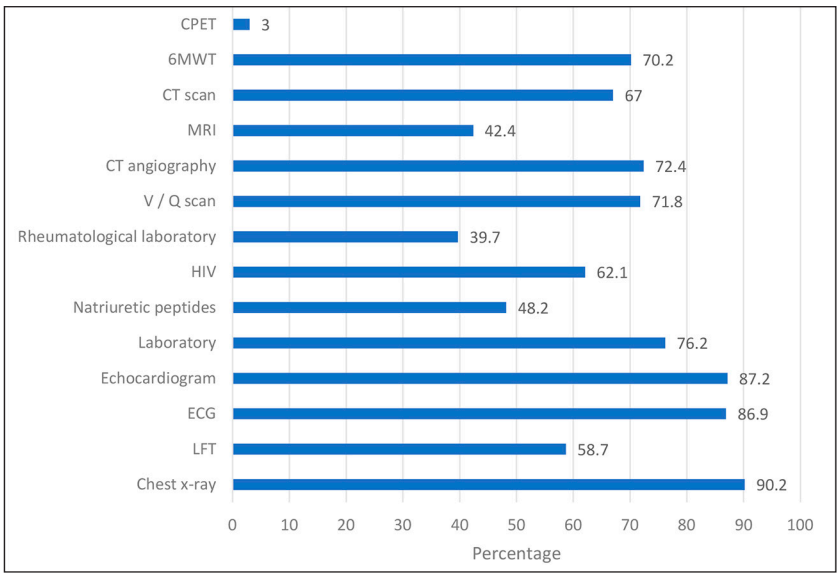
At time of diagnosis, World Health Organization (WHO) functional class III-IV predominated; and in this regard, all groups were proportionately similar. Although functional improvement was noted upon registry inclusion, particularly in groups 1, 2, and 4; total distances logged during 6MWT were low in all groups, especially group 3.

Hemodynamic profiles showed group-wise differences. Those patients with PAH displayed the highest levels of pulmonary arterial pressure and vascular resistance; and PH secondary to left heart disease produced the lowest cardiac output, typically elevating left filling pressures, with mid-range values shown by groups 3, 4, and 5 (Table 1).

Among all groups, loop diuretics were regularly used (> 50% of patients); there was broad mineralocorticoid receptor antagonist use, albeit proportionately lower; and digoxin was administered, especially in group 2. Use of angiotensin receptor antagonist/angiotensin converting enzyme inhibitors and beta blockers was generally limited to group 2 (Table 2). Anticoagulants were likewise prescribed across all groups, particularly to patients with CTEPH (> 70%); and in large part, oxygen therapy was reserved for patients of group 3 (Table 2).

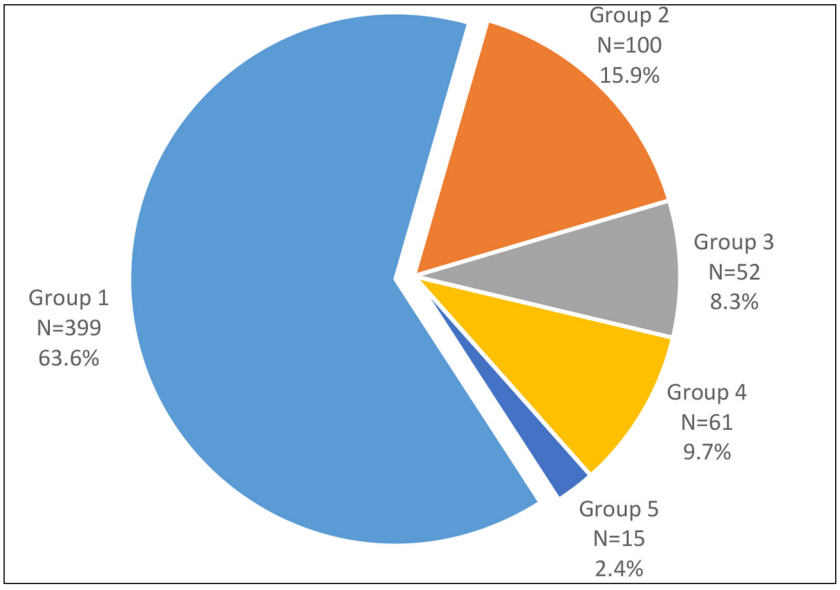
Specific treatments, usually 5-phosphodiesterase inhibitors and endothelin receptor antagonists were administered primarily for PAH or CTEPH. Combined strategy was implemented in more than 50%, but in contrast, one

Fig. 3.– Complementary methods used in the diagnosis of HP in the RECOPILAR registry at the time of diagnosis



LFT: lung function test; ECG: electrocardiogram; HIV: human immunodeficiency virus; V/Q scan: ventilation/perfusion lung scan; CT angiography: computed tomography angiography; MRI: magnetic resonance imaging; 6MWT: 6 minutes walking test; CPET: cardiopulmonary exercise test

Fig. 4.– Population distribution in pulmonary hypertension groups (Nice Classification[3]) at the time of diagnosis



of every five patients in group 1 received no specific therapies. However, it is important to note that the prescription of this kind of drugs was high in groups 2, 3 and 5.

A pre-established follow-up was completed by 583 (93%) of the 627 patients enlisted. Survival rates at 36 months in patient groups 1-5 were 82.8%, 74.4%, 67.3%, 73.7%, and 85.7%, respectively (p = 0.008) (Fig. 5A). Survival was significantly better in the presence (vs. absence) of PAH (82.8% vs. 73.3%, p = 0.001) (Fig. 5B). The observed difference was entirely attributable to prevalent

TABLE 1.– *Comparison of clinical features and hemodynamics measurements among different groups of pulmonary hypertension*

Variable	Group 1 n = 399	Group 2 n = 100	Group 3 n = 52	Group 4 n = 61	Group 5 n = 15	p
Age, years	47 ± 18	61 ± 14	57 ± 17	53 ± 19	52 ± 20	< 0.001
Female, %	78.7	40	51.9	68.9	73.3	< 0.001
Arterial hypertension, %	8.5	35	19.2	18	26.7	< 0.001
Diabetes, %	3.5	14	11.5	3.3	0	< 0.001
Obesity, %	18.6	38.2	36.8	25	25	0.003
Dyslipidemia, %	4.8	27	17.3	11.5	6.7	< 0.001
Atrial fibrillation, %	6.6	24.2	4.7	2.0	0	< 0.001
FC III-IV baseline, %	64.9	74.4	75.6	80.4	72.7	ns
FC III-IV at inclusion, %	28.3	38.2	50	47.8	18.2	0.005
LVEF, %	62 ± 9	40 ± 19	51 ± 5	62 ± 7	63 ± 7	< 0.001
CO (l/min/m^2)	2.8 ± 1	2.3 ± 0.6	2.8 ± 0.7	2.5 ± 0.6	3.1 ± 0.9	< 0.001
PVR (dynas)	794 ± 488	384 ± 266	540 ± 85	696 ± 423	602 ± 231	< 0.001
RAD (mmHg)	9.6 ± 5.4	11.4 ± 5.7	8.2 ± 4.4	9.1 ± 4.7	9 ± 3.7	0.013
PAOP (mmHg)	11 ± 4.6	20.5 ± 6.3	10.4 ± 4.2	10.4 ± 4.1	10.5 ± 4.1	< 0.001
PAPm (mmHg)	52 ± 17	39 ± 12	41 ± 12	46 ± 16	49 ± 14	< 0.001
6MWT (m)	367 ± 118	362 ± 124	291 ± 108	348 ± 134	383 ± 104	0.012

FC: functional class (World Health Organization); LVFE: left ventricular ejection fraction; CO: cardiac output; PVR: pulmonary vascular resistance; RAP: right atrial pressure; PAOP: pulmonary arterial occlusion pressure; PAPm: mean pulmonary arterial pressure; 6MWT: 6 minutes walking test

TABLE 2.– *General and specific treatment in pulmonary hypertension (PH) groups*

Drugs	PAH (Group 1) n = 399	Non-PAH (Groups 2 to 5) n = 228	Comparison PAH vs Non-PAH p	Group 2 n = 100	Group 3 n = 52	Group 4 n = 61	Group 5 n = 15	Comparison among Groups 1 to 5 p
Diuretics %	47.1	58.3	0.007	77	50	41	33.3	< 0.001
Aldosterone antagonist, %	42.6	48.2	0.17	62	42.3	34.4	33.3	0.003
Digoxin, %	17.5	14.9	0.39	20	13.5	9.8	6.7	0.34
Anticoagulant, %	37.1	43	0.15	37	28.8	68.9	26.7	< 0.001
Betablocker, %	7	30.7	< 0.001	58	11.5	8.2	6.7	< 0.001
ACE-i/ARB, %	8.5	27.6	< 0.001	51	7.7	9.8	13.3	< 0.001
Calcium antagonist, %	10.8	3.1	0.001	3	1.9	1.6	13.3	0.007
Oxygen supplemetation, %	11.3	19.7	0.004	2	48.1	26.2	13.3	< 0.001
Phosphodiesterase-5 inhibitor, %	71.2	38.6	< 0.001	20	48.1	55.7	60	< 0.001
Entohelin receptor antagonist, %	54.4	14.5	< 0.001	5	9.6	27.9	40	< 0.001
Prostanoid %	14.3	3.1	< 0.001	0	1.9	9.8	0	< 0.001
Specific therapy								
• None %	19.5	59.2	< 0.001	80	51.9	36.1	40	< 0.001
• Monotherapy %	29.6	27.2		15	38.5	39.3	20	
• Combined %	50.9	13.6		5	9.6	24.6	40	

PAH: pulmonary arterial hypertension; ACE-i/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker

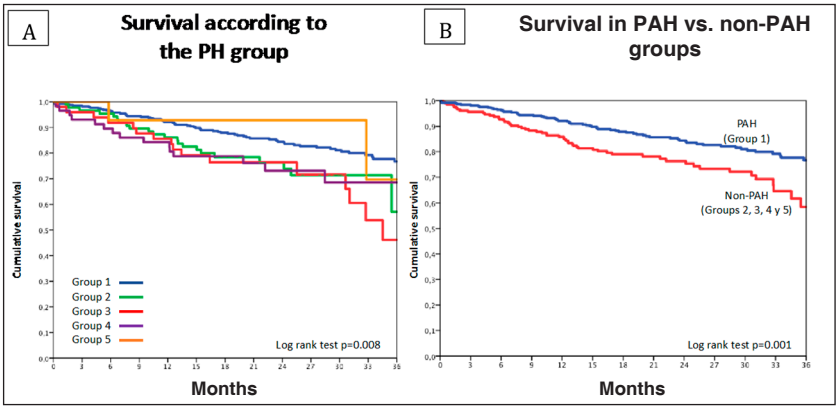
cases (group 1, 81.3%; no PAH, 67.1%; p = 0.002), proving similar in incident cases (PAH, 84.3%; no PAH, 77.4%; p = 0.15) (Fig. 6A and B).

Discussion

The RECOPILAR project was the first of its kind in Argentina to comprehensively evaluate the full spectrum of RHC-verified PH, owing to collaborative efforts of five scientific societies. This multidisciplinary consortium enabled access to data from 627 patients seen by a variety of specialists across all provinces, giving rise to the only epidemiologic reference for PH in Argentina. In our country, it is subsequently apparent that such patients are largely middle-aged and mostly female, qualifying primarily as group 1 disease. By the time diagnosis was established, most patients exhibited functionally advanced disease; and, even if evaluations were properly done, suboptimal adherence was evident in terms of the algorithm set forth. The utilization of specific therapies was high, yielding acceptable 3-year survival rates, in particular for patients with PAH and prevalent cases. These findings are comparable to what other contemporary registries have reported.

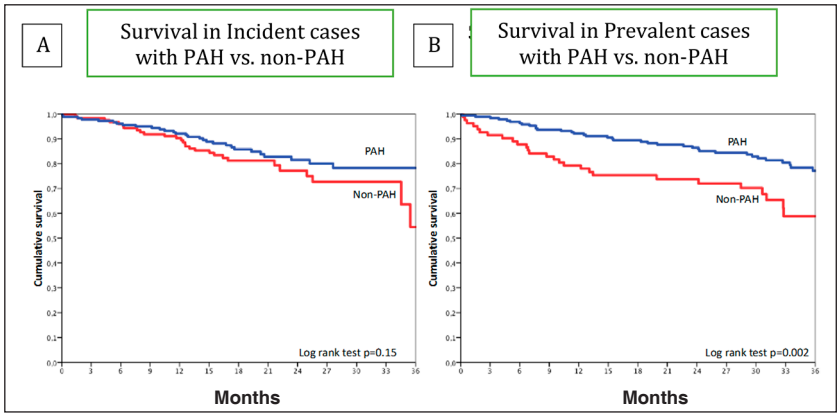
Most of the patients studied were middle-aged, similar to those in French and North American registries[18]. However, both a Chinese[10] survey and an early US registry (National Heart, Lung, and Blood Institute) included comparatively younger subjects[6]. The percentage of women studied was also distinctly less than figures recorded in other Latin and North American registries[12, 14] but was aligned with registries undertaken in France and China.

Fig. 5.– Three-year survival curves: A-According with pulmonary hypertension (PH) groups and B-Pulmonary artery hypertension (PAH) vs. non-PAH group



Non-HAP group: it is constituted between groups 2 to 5 of the Nice Classification

Fig. 6.– Three-year survival curves in patients with PAH (pulmonary artery hypertension) and non-PAH groups in incident (A) and prevalent cases (B)



Non-HAP group: it is constituted between groups 2 to 5 of the Nice Classification

When comparing and contrasting our findings with other published studies, one must consider specific features of the RECOPILAR, particularly the stratification of patients in five etiologic groups as well as the inclusion of incident and prevalent cases. In addition, the phenotypic characteristics of our country must be kept in mind, especially the many races and ethnicities of inhabitants who have entered through various migratory channels[19].

The time to diagnosis of PH averaged 2 years, with two-thirds of patients at functional class III-IV and a high proportion of adults showing signs of right ventricular failure, suggesting that diagnosis was made late in the course of disease with an advanced clinical condition. With some differences, this reality is echoed in studies of PAH only[20] or of less selective nature[21]. One Australian study has shown that multiple visits involving general practitioners and even specialists took place prior to accurately diagnosing PH via RHC[22].

According with the proportion of use of complementary methods during evaluation work-up, three levels might be identified. The first level, with a utilization in over 80% of cases, included ECGs, chest x-ray, general laboratory, and echocardiography. Both, the large accessibility to these resources at various centers nationwide, and their high sensitivities might explain the broad acceptance, despite low specificities to establish the initial suspicion of pulmonary hypertension, matching with current recommendations[1, 3, 8]. The second level (60-70% utilization) involved ventilation/ perfusion (V/Q) lung scans, computed tomography pulmonary angiography (CTPA), and 6MWTs. With less than 25% of the study population qualified as PH groups 2 and 3 and according with guidelines recommendations, there was underutilization of the V/Q lung scan as a tool to accurately identify group 4 disease. In addition, excessive use of CTPA diverged from guidelines. Because cardiopulmonary exercise testing is unavailable at most centers, the 6MWT has become a simple and valid option for functional class determinations. At the third level (<60%), essential tools to differentiate frequent causes of PH were relegated, such as pulmonary function tests, diffusing lung capacity for carbon monoxide (DLCO), rheumatology screening, and HIV serology. Also, natriuretic peptides that reflecting risk of PH, were in this level. The possible explanations for these findings could be related to the specialty of the physicians responsible for patient diagnosis and follow-up or other impediments, such as low availability, high costs, or reluctance of doctors to order these tests.

A distinguishing feature of this registry was the fact that patients belonging to all five groups of PH were included. Most registries have been confined to PAH, whereas others have focused on PAH and CTEPH. However, the disproportion of patients in the RECOPILAR, where two-thirds were classified as PAH and less than a quarter as groups 2 and 3, does not reflect a real epidemiological situation[4,5]. The ASPIRE Registry (Assessing the Spectrum of Pulmonary hypertension Identified at a Referral center) is the only other contemporary registry (N = 1344) assigning incident cases to the five groups, all evaluated during a 9-year period at a reference center[21]. In this study, patient percentages among PH groups 1-5 were 44.5%, 11.7%, 13.2%, 18%, and 2.4%, respectively. The clear data similarity suggests that the RECOPILAR has accurately documented activities at referral centers in Argentina. Causes of PH in industrialized and developing countries differ. In industrial nations, chronic obstructive pulmonary disease and left heart disease are the leading etiologies (PAH 3% only). In countries with limited resources, infectious origins (ie, schistosomiasis, HIV, rheumatic valvular pathology), uncorrected congenital heart disease, and hemoglobinopathies are common. and in many regions of Latin America, PH is also a consequence of high altitude[4, 5].

Patients of PH group 1 were comparatively younger, and women predominated; whereas patients in group 2 were older, showing the highest prevalence of cardiovascular comorbidities (i.e. atrial fibrillation and lower left ventricular ejection fractions). Patients in group 3 showed the greatest functional impairment, as indicated by 6MWT walking distances, while 4 of 5 patients in group 4 were functional class III-IV at time of diagnosis. Corresponding with clinical characteristics, hemodynamics among groups also differed. PAH imposed higher pulmonary arterial pressures and vascular resistance, whereas PH due to left heart disease exhibited lower cardiac output and higher left ventricular/right atrial filling pressures. These findings resemble those of the ASPIRE registry and indicate that differing clinical and hemodynamic profiles among groups may influence long term evolution. Three-year survival was better in PH groups 2 (73%) and 4 (71%), intermediate in PAH (68%), and worse in groups 3 (44%) and 5 (59%)[21].

Unlike other registries, the RECOPILAR confirmed the use of supportive therapy in PH. Loop diuretics and mineralocorticoids receptor antagonists were used more frequently in group 2 and in half of patients in groups 1 and 3, all showing high prevalence of heart failure in this population. Digoxin was indicated in only 20% of group 2 and to a lesser extent in the rest, failing to correlate with presence of atrial fibrillation; so presumably, it served to treat right ventricular or left heart failure. For patients with PAH, digoxin brought acute improvement in cardiac output[23], but its long-term efficacy is unknown. According to current guidelines, it is recommended as a means of lowering heart rate during supraventricular arrhythmias[1,3]. Despite concerns of potential toxicity outside its narrow therapeutic range, particularly in hypoxemic states, empiric digoxin usage persists. Inhibitors of conversion enzyme and beta-blockers were prescribed more frequently in group 2, reflecting recommended dosing for heart failure, as well as frequently observed comorbidities[24].

Another group of drugs currently questioned is anticoagulants. These were prescribed in 37% of patients with PAH and in 69% of those in group 4, conflicting with usage (81.6%) reported by an Argentine reference center registry of patients with PAH[14]. The rationale for anticoagulation in patients with idiopathic PAH is supported by a high prevalence of *in situ* vascular thrombotic lesions, coexisting coagulation and fibrinolytic abnormalities, and the potential for venous thromboembolism due to heart failure and immobility[25-28] Evidence favoring anticoagulation comes from rather inconclusive retrospective and small-sized studies, so current recommendations should not be construed as definitive[3, 9, 29]. In addition, reported benefits seem limited to idiopathic, hereditary forms of PAH and those associated to anorexigenic drugs, with otherwise neutral effects or increased risk in the another subgroups of PAH[30]. A recent meta-analysis has shown a 27% reduction in mortality from idiopathic PAH and a 58% increase in PAH associated with scleroderma[31]. In instances of CTEPH, anticoagulation is considered essential and has been implemented in nearly all pertinent studies published[32-35], The reported incidence of clinically relevant bleeding is as high as 29.2%, with bleeding rates > 5.0% per person-year[36]. Beyond the potential for bias, there was striking underutilization of anticoagulants throughout our country.

The specific therapy was administered predominantly to patients in group 1, half of them received combination therapy and one third monotherapy. The possible explanations for that intervention were the high proportion of patients with functional class III-IV, and because during the inclusion period, usage of more than one drug was mainly sequentially recommended[37]. On the other hand, 20% of this group did not receive specific therapy. Despite subjects with positive pulmonary vasoreactivity (10%) and those underwent to correction of congenital defects may contribute to that percentage, the limited use of drugs is dictated by the socioeconomic reality of Latin American countries, signaling difficulties in health system access and administrative obstacles to high-cost therapy[15, 16]. The specific agents most commonly used were phosphodiesterase 5 inhibitors, followed by endothelin receptor antagonists and finally prostacyclin analogs in only 20%, as permitted by availability and health coverage, which is variable among Latin American countries[12-15]. Knowing the advanced functional class of these patients, prostanoid use was suboptimal. Similar disproportion between patient subsets of advanced functional class and prostanoids use was also observed in French (70% and 23%), North American (54% and 41%) and Argentine registries (58% and 32%)[7, 15, 38]. All current treatment guidelines recommend that patients with PAH who do not demonstrate an acute pulmonary vasodilator response should be treated with PAH-specific therapy based on severity of symptoms or risk of clinical deterioration. The general approach to therapy entails determining severity of disease and initiating oral therapy in less severe PAH and continuous intravenous infusion of prostacyclin in patients with severe PAH[24].

It is remarkable that specific therapy was prescribed for a high proportion of patients in groups 2-5. Despite assorted potential explanations, such as persistence of PH post-thromboendarterectomy and inoperability in group 4, combined forms of PH and diagnostic uncertainty in group 5, or unique cases managed by specialists in group 3, such practices may be viewed as incorrect applications of current recommendations. In any event, this situation was mirrored during a UK study, wherein specific therapy was used in groups 2-5 to treat 12%, 47%, 85%, and 72% of patients, respectively[21].

Our survival analysis showed a significant advantage for patients of group 1 (average annual mortality, 6%), compared with the other four groups, underscoring the impact of specific treatments used. In terms of PAH, other contemporary registries have reported 3-year survival rates of 58.2-72.3% in Europe[7, 9, 11], 67% in North America[20, 39] and 75% in China[10], whereas in Latin America, the rate is 73.9-84%[12,14].

This registry provided additional data on all PH subsets as well. As previously mentioned, only the ASPIRE registry gathered similar information. Coincidentally, the lowest survival was ascribed to PH associated with pulmonary diseases and/or hypoxia[21].

Limitations of this study are those of registries inherently, including its basic design and intrinsic attributes of both centers and patients involved. Ultimately, the participating centers successfully demonstrated how vital they are in managing this condition. Their sophisticated organizational constructs provide access to specialists in this disease and foster multidisciplinary input, clearly demonstrated by the diagnostic and therapeutic measures taken. Extrapolating present results to centers of lesser complexity is thus deserving of caution, deferring to acknowledged experts the decision-making required of this challenging disease.

Another issue is that RECOPILAR provided a static picture of PH in our country, based on a non-continuous registry, as a main objective. So, this registry was not designed to evaluate changes in interventions and its impact on the follow-up. In addition, the follow-up obtained in 93% of the cases can be considered robust enough to accurately demonstrate the medium-term evolution of this disease.

The inclusion of prevalent and incident cases is another recognized source of bias, owing to patients who survived initially severe disease. However, the clear and predefined identification of each one allowed us to observe survival differences between PAH and non-PAH in prevalent cases only, the incident cases being similar. Through our analysis, it was also possible to estimate that the lower limits

for the incidence of PAH in Argentina was 3.6-5.1 per million inhabitants.

As a final note, only 3.5% of study population was infants (all with PAH). This served as a potential source of bias due to participation from pediatric cardiologists exclusively.

Generating an accurate characterization of PH in Argentina allowed us to identify areas of perhaps needed intervention. The first of these is the imperative for early diagnosis. There is a clear call to institute screening strategies in high-risk population, establishing reference networks that allow rapid identification of patients with high probabilities of PH, particularly PAH.

Although diagnostic tools were generously used, a gap remains that may be minimized by incorporating recommended algorithms into national and international guidelines. Observed survival rates, similar to contemporary registries, should not merely taken as therapeutic success, but rather indicate that an appropriated disease classification and risk stratification would eliminate high-cost treatments with no proven gains. Resources are thus made available for patients who may truly benefit. Such actions would undoubtedly help improve the course of this devastating condition.

In conclusion, the RECOPILAR is the first epidemiologic reference on PH in Argentina. With PAH accounting for two-thirds of our study population, the clinical profile was one of advanced disease. All diagnostic evaluations and treatments rendered, including high use of PAH-specific therapy, were consistent with current recommendations. Despite the severity of the disease, evolution was comparable to other contemporary records.

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