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Systematic Review

Clinical and hemodynamic phenotype of BMPR2 variation carriers with pulmonary arterial hypertension: a systematic review and a call to action

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ABSTRACT:

Background: Carriers of variations in the gene encoding bone morphogenetic protein receptor type 2 (BMPR2△) are at high risk for severe pulmonary arterial hypertension (PAH+).

Aim: To define the clinical and hemodynamic phenotype of BMPR2△/PAH+ patients.

Methods: We performed a systematic review encompassing observational data from January 2000 to July 2019 about BMPR2△ and confirmed PAH diagnosis. According to international clinical guidelines, we aimed to determine the clinical and hemodynamic phenotype of BMPR2△/PAH+. We also explored functional assessment and risk stratification. PROSPERO ID CRD42019124324.

Results: We included 54 reports with 6,668 PAH+ patients, 1,220 were BMPR2△/PAH+ with an allele frequency within studies ranging from 8.8% to 24.9%. Female sex was predominant, and age at diagnosis ranged from 32.2 to 46.2 years. We observed the occurrence of BMPR2△ across all PAH clinical classifications, except for schistosomiasis. BMPR2△ correlated with severity signs and symptoms in PAH, poor functional class, severe pulmonary hypertension with elevated pulmonary vascular resistance, and low cardiac index and output. The clinical and hemodynamic missing data ranged between 28%-49% and 50%-65%, respectively.

Conclusion: BMPR2△/PAH+ present a phenotype with high mortality risk. The clinical triad of dyspnea, syncope, and hemoptysis could suggest BMPR2△/PAH+. However, poor clinical and hemodynamic characterization hinders translating the benefits of genomic analyses to the clinical setting.

Keywords: Pulmonary arterial hypertension; BMPR2; Clinical phenotype; Hemodynamic phenotype; Systematic review.

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Introduction

Pulmonary arterial hypertension (PAH) comprises rare vascular disorders characterized by endothelial cell dysfunction and proliferative and obstructive remodeling of small pulmonary arterioles. These events lead to a progressive increase of pulmonary vascular resistance (PVR) and pulmonary artery (PA) pressure followed by secondary vascular and right ventricular (RV) remodeling, which in turn induce RV dysfunction, heart failure syndrome, and premature death (Garcia-Rivas, Jerjes-Sánchez, Rodriguez, Garcia-Pelaez, & Trevino, 2017). While patient survival and quality of life have improved significantly over the past two decades, mortality rates remain high. (Jing et al., 2013; Sandoval et al., 2012; White et al., 2013).

The bone morphogenetic protein receptor type 2 (encoded by the *BMPR2* gene) is a member of the transforming growth factor-ß (TGF-ß) superfamily of receptors and regulates cell growth and differentiation. Variations in this gene have been identified in ~70% of cases of heritable PAH (HPAH) and ~10–40% of cases of idiopathic PAH (IPAH) (Thomson, 2000; Morrell et al., 2019). Furthermore, over 400 different *BMPR2* mutations are implicated in PAH pathobiology (White et al., 2013; Amano et al., 2004; Ghigna et al., 2016; Southgate, Machado, Gräf, & Morrell, 2020). Moreover, *BMPR2* variations in PAH patients (*BMPR2*Δ/PAH+) are a determinant factor for the development and progression of the disease (Cogan et al., 2012; Ma & Chung, 2017; Southgate et al., 2020). However, the molecular mechanisms by which *BMPR2* mutations and polymorphisms influence the disease onset and progression are still not fully understood (Zhu et al., 2019).

Despite the progress in genetic testing and counseling that could improve survival and quality of life by early identification, the diagnosis still occurs at advanced stages (≥2 years after disease onset) (J. S. R. Gibbs, 2007) and at different ages (Sandoval Zarate et al., 2017). Therefore, considering the significance of *BMPR2* variants in PAH development, we designed a systematic review to define the clinical and hemodynamic phenotype of *BMPR2*Δ/PAH+, since the identification of early clinical presentation, improvement of risk stratification, and therapeutic approach are crucial in ensuring optimal PAH patient care.

Methods

We performed a systematic review, encompassing all published data from January 2000 to July 2019, through PubMed, Ovid/Willey, the Cochrane Library, BiorXiv.org, and OpenGrey.eu searching for observational studies (cohorts, case-control, case-series, and case reports), systematic reviews, letters to the editor, and abstracts about adult BMPR2△ and confirmed PAH diagnosis according to European Society of Cardiology and the European Respiratory Society guidelines (Galiè et al., 2016). We used the snowballing method and manual search to expand our search without language restriction (Greenhalgh, 2005). Our primary objective was to define the clinical and hemodynamic phenotype of BMPR2△/PAH+. As a secondary aim, to describe the echocardiographic findings and B-type natriuretic peptide (BNP), N-terminal-proBNP (NT-proBNP), and cardiac troponins plasma levels. We defined ten clinical and eight hemodynamic variables for phenotype characterization according to clinical guidelines (Galiè et al., 2016). We excluded papers on experimental models, pediatric populations, and studies without clinical or hemodynamic data. The search strategy, inclusion, exclusion criteria, and definition of clinical and hemodynamic variables are fully detailed in the supplementary material. To assess eligibility criteria, we obtained full articles based on titles and abstracts before the critical appraisal. We categorized reports by evidence levels (case reports, case-control, cohorts, and familial studies). Two authors (DR and MAFB) performed data extraction and verification in duplicate through an online collaborative database and solved discrepancies by consensus. To optimize the quality of the results, we monitored data extraction four different times by duplicate. We implemented the study quality assessment tools provided by the National Heart, Lung, and Blood Institute (National Heart, Lung, and Blood Insitute, National Institutes of Health, n.d.). Our systematic review protocol is available at the International Prospective Register of Systematic Reviews (ID CRD42019124324), and the results are reported according to the PRISMA statement (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

Statistical analysis

We used summary statistics for continuous (median and interquartile range) and categorical (frequency and percentage) variables according to their type and distribution. Some of the retrieved studies reported qualitative data. Due to the extensive clinical and hemodynamic data heterogeneity, risk estimation or null hypothesis significance testing are inappropriate (Deeks, Higgins, & Altman, 2020). All data were analyzed using Stata 14.2 (College Station, Tx, USA). We performed the final data analysis in January 2020.

Results

We performed a systematic review up to July 31, 2019. During the identification phase, we obtained 1,037 records (Figure 1). We collected 161 full-text documents with supplementary material for critical assessment. In the eligibility phase, we discarded 107 articles due to missing data or to avoid overreporting (some studies included previously described populations). Finally, we incorporated 54 papers, including 19 cohorts, 17 case reports, 11 cross-sectional and familial studies, five retrospective familial studies, and two case-control studies. The first report was published in 2000. In 2016, 11 reports were published, followed by 2013 and 2017 with five publications, respectively (median 2.5, 95% CI 1-4).

The demographic and clinical phenotype of BMPR2Δ/PAH+

Table 1 shows demographic and clinical findings according to study classification. Collected reports were from Europe (29), North America (11), Asia (13), and the Middle East (1) (Figure 2). Race and ethnicities were not fully disclosed. Of 6,668 PAH patients, 1,220 were BMPR2Δ/PAH+ with an allele frequency within study groups ranging from 8.8 to 24.9%. All case reports were BMPR2Δ/PAH+. The list of all BMPR2 variations is in the supplementary material (Tables S12-S16). The female gender was predominant (60-70%) with a ratio from 1.5:1 to 3:1. We identified BMPR2Δ/PAH+ across all the group 1 of the clinical classification; except for schistosomiasis, IPAH (9), HPAH (7), PAH associated with connective tissue disease (2), drugs and toxins induced (1), congenital heart disease (3), human immunodeficiency virus infection (HIV) (1), hereditary hemorrhagic telangiectasia (2), and pulmonary vascular obstructive disease (1) (Simonneau et al., 2019). The age at diagnosis ranged around the fourth and fifth decade of life (32.2-46.2 years). We identified two octogenarian PAH patients (Johri, Dunnington, & Vnencak-Jones, 2010; Raamsteeboers, Jan Bogaard, & Vonk Noordegraaf, 2014), one of them developed idiopathic pulmonary fibrosis three years after PAH diagnosis (Raamsteeboers et al., 2014).

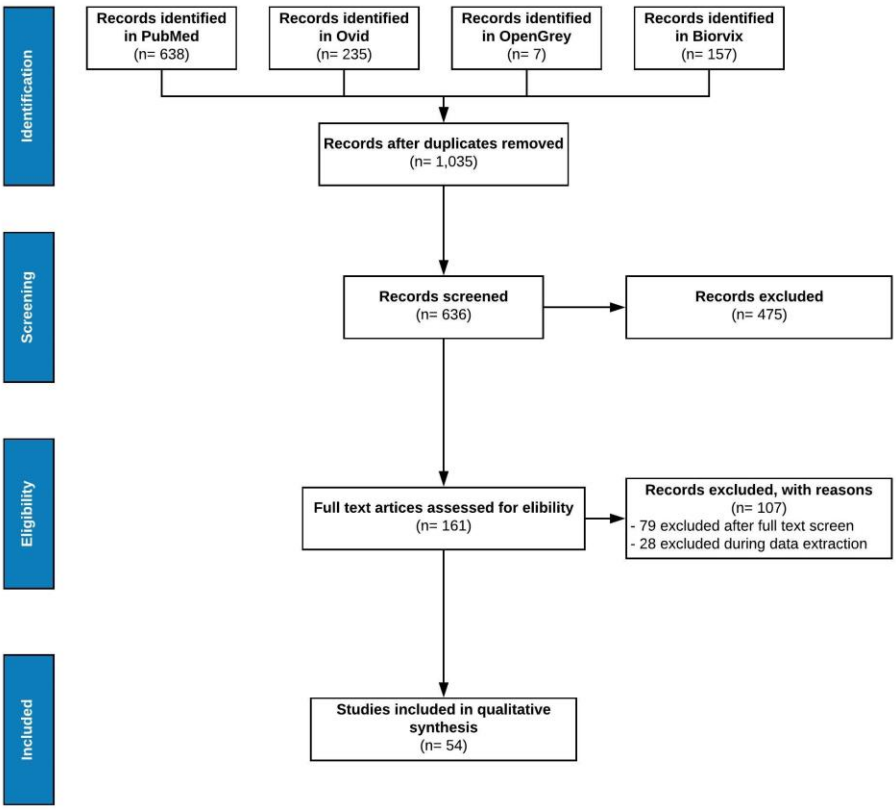

Figure 1. PRISMA flowchart.

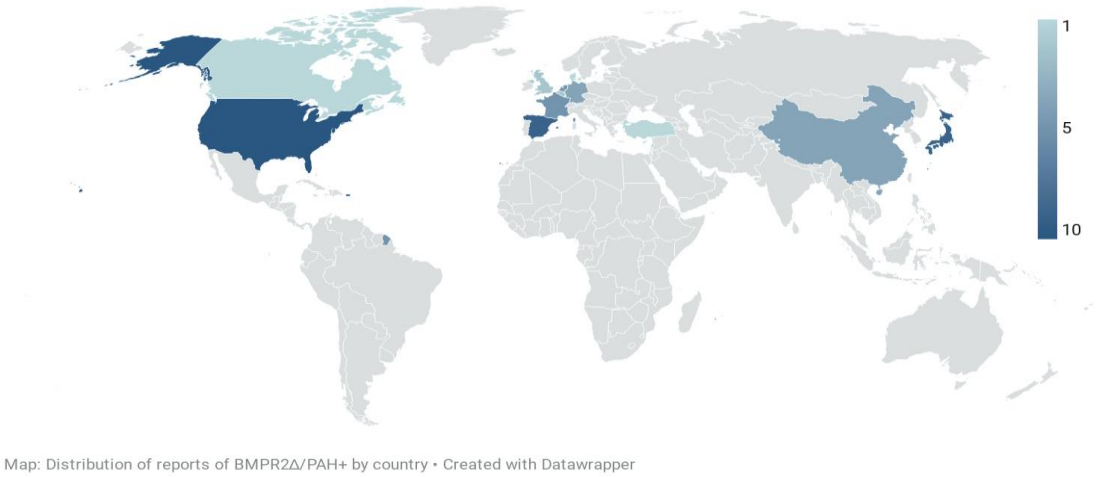

Figure 2. Distribution of all reports included in the analysis. United States of America (10), Spain (9), Japan (9), France (5), The Netherlands (5), Germany (4), China (4), United Kingdom (2), Belgium (2), Turkey (1), Denmark (1), Canada (1), and Lebanon (1).

Clinical variables	**Case reports and case series** (n= 20)	**Case-control** (n= 147)	**Cohorts** (n= 4,611)	**Cross-sectional and familial studies** (n= 510)	**Retrospective cohorts and familial studies** (n= 1,380)
Country, (n)	JP (4), US (3), ES (3), NL (2), BE (1), FR (1), DK (1), CA (1), CN (1)	JP (1), ES (1)	US (5), FR (4), ES (4), JP (2), UK (1), BE (1), NL (1), CN (1)	DE (4), JP (2), TU (1), US (1), ES (1), CN (1), LB (1)	NL (2), US (1), CN (1), NL (1), UK (1)
*BMPR2*Δ/PAH+, n (%)	20 (100)	13 (8.8)	807 (17.5)	127 (24.9)	253 (18.3)
Female, n, %, sex ratio	15, 75, 3:1	9, 69.2, 2.5:1	575, 70, 2.3:1	86, 67.7, 2:1	154, 60.8, 1.5:1
PAH Classification, (n*)	IPAH (9), HPAH (7), DTI (1), CHD (3), HIV (1), HHT (2), PVOD (1)	IPAH, HPAH, CTD (2)	IPAH, HPAH, DTI, CHD	IPAH, HPAH	IPAH, HPAH
Age, median (IQR)	35.5 (27-47)	46.2 (38-54)	37.2 (35.5-41)	32.2 (27-36.2)	39 (37.1-42)
Signs and symptoms, (%),#	Dyspnea (70), syncope or near syncope (15), hemoptysis (10), chest pain (10), dizziness (9.5), and fatigue (5)	Not reported	Pregnancy, dyspnea, and syncope	Dyspnea, hemoptysis, and digital clubbing	Hemoptysis and digital clubbing
NYHA/WHO functional class, (%)	III (70), II (20), I (10)	III (1§), II (2§)	III (18.2), IV (3.8), II (3.6), I (3.1)	III (22.8), IV (4.7), II (5.5)	III (10), IV (0.3)
6MWT meters, median (IQR)	275 (235-396)	450	375.6 (351-396.8)	369.5 (285-463.5)	421 (399-423)
Follow-up years, median (IQR)	3 (0.2-2.45)	3	4-15	5 (4-8)	3.4 (1.2-4)
Time to worsening, median (IQR)	Not defined	Not defined	Not defined	Not defined	Not defined
Survival, (n)	Alive (4)	Alive (1)	Alive (2)	Alive (2)	Dead (22)
Missing data, (%)†	28	40	49	40	44

PAH: pulmonary arterial hypertension; **BMPR2△/PAH+:** bone morphogenetic protein receptor 2 mutation carrier with confirmed diagnosis of PAH; **IPAH:** idiopathic pulmonary arterial hypertension; **HPAH:** heritable pulmonary arterial hypertension; **DTI:** drug and toxins-induced; **CHD:** congenital heart disease; **HIV:** human immunodeficiency virus; **HH:**. Hereditary hemorrhagic telangiectasia; **PVOD:** pulmonary veno-occlusive disease; **IQR:** interquartile range; **NYHA/WHO:** New York Heart Association/World Health Organization; **6MWT:** 6-minute walk test; **JP:** Japan; **US:** United States; **ES:** Spain; **NL:** The Netherlands; **BE:** Belgium; **FR:** France; **DK:** Denmark; **CA:** Canada; **CN:** China; **UK:** United Kingdom; **DE:** Deutschland; **TU:** Turkey; **LB:** Lebanon; *: *not all the reports specified the frequencies of different etiologies*; #: absolute frequencies defined only in case reports; §: absolute number of patients; †: 10 clinical variables.

Table 1. Clinical features of BMPR2△/PAH+ patients.

Dyspnea (70%), syncope or near syncope (15%), hemoptysis and chest pain (10%), dizziness (9.5%), and fatigue (5%) were the most common clinical findings in *BMPR2*Δ/PAH+, followed by digital clubbing (qualitative data) (Table 1). We identified four *BMPR2*Δ/PAH+ during the gravid-puerperal state at the PAH diagnosis (Handa et al., 2014; Limoges et al., 2016; Rigelsky et al., 2008). Additionally, a cohort study reported 16.7% of pregnant *BMPR2*Δ/PAH+ (Austin et al., 2009). Most patients were in New York Heart Association/World Health Organization (NYHA/WHO) functional class III (18.2-70%), and a minority of papers (37%) reported the 6-minutes walk distance test (6MWD) varied between 275 to 450 meters. Patient follow-up ranged from 0.2 to 15 years. The most reported clinical variables were the number of carriers and non-carriers, age at diagnosis, and clinical etiology. In contrast, the less reported variables were clinical signs and symptoms, the 6MWD, NYHA/WHO functional class, time to worsening, follow-up, and survival. The missing clinical data ranged from 28% in case reports to 49% in cohort studies (Table 1). The case-control studies excluded the report of signs or symptoms (Supplementary Material, Table S1-S5).

The hemodynamic phenotype of BMPR2Δ/PAH+

Table 2 shows the hemodynamic parameters of BMPR2Δ/PAH+ across the different studies. BMPR2Δ/PAH+ showed elevated right atrial pressure (8-15 mmHg), PA systolic pressure (PASP) (50-91 mmHg), PVR (10.5-17.7 Wood units), and low cardiac index (CI) (1.7-2.6 L/min/m2), cardiac output (CO) (2.71-4.5 L/min), and PA wedge pressure (8-9 mmHg). The mean pulmonary artery pressure (mPAP) ranged between 42-59 mmHg. Vasoreactivity testing was not systematically disclosed.

Clinical variables	**Case reports and case series** (n=20)	**Case-control** (n=147)	**Cohorts** (n=4,611)	**Cross-sectional and familial studies** (n=510)	**Retrospective cohorts and familial studies** (n=1,380)
*BMPR2*Δ/PAH+, n (%)	20, (100)	13, (8.8)	821, (17.7)	127, (24.9)	253, (18.3)
RAP mmHg, median (IQR)	15 (12-19)	Not reported	8 (6.9-10.3)	10 (5.8-11)	8.5 (7-10.1)
PASP mmHg, median (IQR)	91 (66-101)	50 (45-70)	65 (60-70)	Not reported	Not reported
mPAP mmHg, median (IQR)	55 (47-65)	48.5 (42-55)	58.8 (55-62)	59 (50-67)	57 (56.4-60.7)
PAWP mmHg, median (IQR)	9 (7-11)	Not reported	8 (7-10)	9 (7.1-9)	8.9 (8.8-9)
PVR Wood units, median (IQR)	12.5 (9.2-19.85)	10.5 (7.5-13.6)	17.75 (14.45-19.65)	17 (15.7-18.9)	14.6 (13.8-15)
Cardiac index L/min/m², median (IQR)	1.75 (1.48-2.11)	2.6 (2.3-2.8)	2.27 (2.12-2.4)	2.1 (1.9-2.8)	2.14 (2.0-2.19)
Cardiac output L/min, median (IQR)	4.3 (3.2-5.3)	2.71¶	3.4 (3.1-3.4)	4.5 (3.5-5.6)	3.42 (3-3.8)
Vasoreactivity responders, (n)	Negative (7)	Not reported	Negative (3), Positive (7)	Positive (2)	Negative (1), Positive (3)
NT-proBNP/[BNP] pg./mL, median (IQR)	267 (14.7-758) / [548 (220-876)]	Not reported	1,432.1¶	163 (73.5-305)	Not reported
Cardiac troponin ng/mL, median (IQR)	0.22¶	Not reported	Not reported	Not reported	Not reported
Missing data (%)†	55	65	57	59	50

PAH: pulmonary arterial hypertension; **BMPR2Δ/PAH+:** bone morphogenetic protein receptor 2 mutation carrier with confirmed diagnosis of PAH; **RAP:** right atrium pressure; **PASP:** pulmonary artery systolic pressure; **mPAP:** mean pulmonary artery pressure; **PAWP:** pulmonary artery wedge pressure; **PVR:** pulmonary vascular resistance; **NT-proBNP/BNP:** N-terminal proB-type natriuretic peptide/B-type natriuretic peptide; **IQR:** interquartile range; **¶**: one paper reported this parameter. † 10 hemodynamic variables.

Table 2. Hemodynamic features of BMPR2Δ/PAH+ patients

Twenty-three papers (n=581 BMPR2△/PAH+) reported 12 positive and 11 negative vasoreactivity tests. The most reported hemodynamic variables were mPAP, PVR, and CI, while CO, vasoreactivity test, and PASP were less commonly reported (Supplementary Material, Table S6-S10). The missing hemodynamic data ranged between 50% in retrospective and familial cohorts to 65% in case-control studies.

Echocardiographic features and circulating cardiac biomarkers

The echocardiographic features of nine reports of BMPR2△/PAH+ (16.3%), showed high PASP (48-111 mmHg) and tricuspid annular plane systolic excursion (TAPSE), that ranged between 1.1 to 3.0 cm. Only one paper reported pericardial effusion (Baloira, Bastos, Pousada, & Valverde, 2016) (Supplementary Material Table S11). Eleven reports (20%) described variable BNP/NT-proBNP plasma levels from163 to 1,432.1 pg./mL (Aimi et al., 2013; Baloira et al., 2016; Digne et al., 2012; Eichstaedt et al., 2016; Handa et al., 2014; Isobe et al., 2016; Johri et al., 2010; Limoges et al., 2016; Pousada, Baloira, & Valverde, 2015; Yang et al., 2018; Zhang et al., 2016). Only one case reported both BNP and standard cardiac troponin (0.22 ng/mL) (Digne et al., 2012) (Table 2).

Discussion

To our knowledge, this is the first systematic review investigating the clinical and hemodynamic phenotype of BMPR2△/PAH+. Our findings are as follows: first, whereas demographic, clinical, and hemodynamic characteristics are consistent across studies, the clinical characterization is far from optimum, hindering the applicability of genetic data to the clinical setting (Tables 1 and 2). Second, with the available evidence, we propose that the clinical triad, including dyspnea, syncope, and hemoptysis, could suggest BMPR2△/PAH+. Also, we identified high-risk mortality patients based on pulmonary hemodynamics indicated by elevated mPAP and PVR, low CI and CO, and poor vasoreactivity (Evans et al., 2016; Girerd et al., 2015; Ma & Chung, 2014). Finally, we evidenced a deficit in right ventricular echocardiographic assessment and circulating biomarker usage for risk stratification and follow-up (Galiè et al., 2016). (Table 2 and Supplementary Material, Table S11).

Demographics

The available demographic features of *BMPR2*Δ/PAH+ are from developed countries (Figure 2) and were consistent across all reviewed studies (Table 1). Although poorly explored, subtle racial and ethnic differences have been observed related to PAH etiologies, clinical presentation, and treatment response (Al-Naamani et al., 2017; Sandoval Zarate et al., 2017; Valverde et al., 2018). Female sex patients (1.5:1 to 3:1) during the fourth and fifth decades of life are the most affected population (Batton et al., 2018; Evans et al., 2016). Previous evidence showed limited penetrance of *BMPR2* mutations (~20%) with variable risk development during follow-up (14% males and 42% females), suggesting additional hormonal, environmental, and other genetic variations contributing to the development and progression of the disease (Amano et al., 2004; Frost et al., 2019; Ghigna et al., 2016; Southgate et al., 2020; White et al., 2013). For example, 17β-estradiol and its metabolite, 16α-hydroxy estrone, were identified as penetrance mediators in female *BMPR2*Δ/PAH+ (Lahm & Kawut, 2017). In a Chinese cohort, male *BMPR2*Δ/PAH+ were significantly associated with an increased risk of death after adjustment for age at diagnosis (hazard ratio, 3.7; 95% CI, 1.4–9.7; p=0.008 vs. hazard ratio, 1.3; 95% CI, 0.6–2.9; p=0.446) (Liu et al., 2012). In a meta-analysis; however, younger male and female *BMPR2*Δ/PAH+ shared a similar risk of death, lung transplantation, and all-cause mortality (Evans et al., 2016). In experimental models, testosterone was associated with pro-hypertrophy and pro-fibrotic effects. Also, in the clinical setting, testosterone increases inflammation inducing myocardial and vascular remodeling, heart failure, and, death in males, as seen in myocarditis, dilated cardiomyopathy, and atherosclerosis (Batton et al., 2018).

Fertility years correspond with the highest risk of developing PAH in women, especially during the pregnant-puerperal state. We observed four *BMPR2*Δ/PAH+ diagnosed during pregnancy and a cohort study reported 16% pregnant *BMPR2*Δ/PAH+ (Austin et al., 2009; Braam et al., 2016; Handa et al., 2014; Limoges et al., 2016; Rigelsky et al., 2008). These findings may be related to the extensive physiological changes occurring during pregnancy that contribute to RV heart failure (Limoges et al., 2016).

Functional analysis and risk stratification

The transthoracic echocardiogram, an essential non-invasive tool for the assessment of PAH (Galiè et al., 2016), was underused and unreported (Supplementary Material, Table S11). Also, BNP and NT-proBNP were unreported despite its key role to identifying the early stages of heart failure, treatment response, and outcomes (Burnett, Ma, & McKie, 2019; Klinger, 2009). Likewise, cardiac troponins, a useful biomarker for assessing cardiomyocyte damage and its

prognostic value for poor outcomes or transplant was underused (G.A. Heresi et al., 2012). Comprehensive risk clinical assessment of BMPR2△/PAH+ could optimize clinical decision-making by integrating echocardiographic and cardiac biomarkers data, as suggested by current clinical guidelines (Galiè et al., 2016).

Study Limitations

We acknowledge the following limitations; first, the high percentage of missing data for both clinical and hemodynamic parameters evidenced reporting bias. These findings restricted association analysis between BMPR2 variations and disease features such as clinical signs and symptoms, progression, and survival, as well as quality assessment. These methodological and reporting challenges in genetic association studies have been widely recognized (Friedman, Jones, & Carey, 2020; The Human Genome Epidemiology Network and the Network of Investigator Networks et al., 2006). Then, the STrengthening the REporting of Genetic Association Studies (STREGA) initiative—An Extension of the STROBE Statement— was developed to maximize the transparency, quality, and completeness of reporting for efficient and reliable human genome epidemiology (Little et al., 2009). Second, potential eligible reports may be missed, despite we searched in five different databases, including grey literature, representing a publication bias. Third, we excluded pediatric populations since genetic expression differences (TBX4 and ACVRL1), frequently associated with chromosomopaties, and outcomes require a specialized approach (Rosenzweig et al., 2019). Finally, we evidenced potential selection (diagnostic access and centripetal) bias since most of the studies were from centers of excellence in developed regions (Delgado-Rodriguez, 2004). We encourage international collaboration to expand the multidimensional phenotyping of PAH patients from different regions, races, and ethnic groups.

This review frames the last 20 years of observational evidence since the identification of altered BMPR2-mediated TGF-ß signaling as the critical risk factor for the development of HPAH and IPAH including the description of more than 400 involved mutations across multiple populations (Deng, Haghighi, et al., 2000; Deng, Morse, et al., 2000; Lane et al., 2000; Southgate et al., 2020; Thomson, 2000). Despite these remarkable achievements and the increased output of PAH patient genetic data, the multidimensional (clinical, hemodynamic, and functional) phenotyping of BMPR2△/PAH+ remains challenging due incomplete and non-systematic reporting of essential clinical and hemodynamic data. Our findings highlight the necessity of collaborations between genetic epidemiologists, geneticists, data scientists, and clinicians to improve the quality of evidence-based clinical practice for BMPR2△/PAH+. The future development of genomic and precision medicine will strongly depend on the thorough application of clinical and standardized reporting guidelines (Feero, 2017; Little et al., 2009; McCarthy, McLeod, & Ginsburg, 2013; Teschendorff, 2019).

Conclusion

BMPR2△/PAH+ had clinical and hemodynamic characteristics indicating severe illness with high mortality risk. On clinical presentation, the clinical triad of dyspnea, syncope, and hemoptysis could suggest BMPR2△/PAH+. However, poor reporting of essential information hinders translating the benefits of genomics to the clinical setting. We advocate for adherence to standardized reporting guidelines to enhance the quality and transparency of data. Vital information that precisely characterizes and estimates prognosis improves the evidence-based clinical practice in the raising of genomics and precision medicine to enhance the care of PAH patients.

Author Contributions: D.R. designed and implemented the systematic review, collected, and analyzed the data, prepared the figures and tables, and wrote the manuscript. MAFB implemented the systematic review and collected the data. BMWI and TLC were involved in the design of the systematic review and supervised the project. ARR analyzed the results and wrote the manuscript. CJS designed the systematic review, analyzed the results, and wrote the manuscript. All authors approved the manuscript

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