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Impact of BMPR2 mutation on the severity of pulmonary arterial hypertension: a systematic review and meta-analysis

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Abstract

Objective To evaluate the association between PAH severity in patients with and without BMPR2 mutation. Additionally, subgroup analyses were also performed to investigate whether differences existed among different ethnicities.

Methods A literature search of the PubMed-MEDLINE, EMBASE, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases was conducted from inception through June, 2024, to identify eligible studies. Analyses were performed using Stata.

Results Seventeen nonrandomized studies comprising a total of 2,190 patients were included in the analysis. Among the hemodynamic variables, the mPAP (WMD = 6.41, 95% CI: 5.07 ~ 7.76, $P = 0.000$), PVR (WMD = 3.66, 95% CI: 2.79 ~ 4.53, $P = 0.000$), CI (WMD=-0.38, 95% CI: -0.45 ~ -0.32, $P = 0.000$), and CO (WMD=-0.60, 95% CI: -0.99 ~ -0.21, $P = 0.003$) were significantly different at diagnosis between patients with and without BMPR2 mutations. No significant differences were found in RAP and PAWP. Furthermore, subgroup analysis was conducted on data showing significant differences, revealing no significant differences in mPAP and PVR between Asian and Caucasian patients with BMPR2 mutations. However, significant differences in CI and CO were observed between these two ethnic groups, with CI and CO in Caucasians being more affected by BMPR2 mutations and decreasing more than in Asians.

Conclusion There is a statistically significant difference in the hemodynamic variables of PAH between BMPR2 mutation carriers and non-carriers, highlighting the mutation's impact on PAH severity. This influence is not associated with ethnicity in mPAP and PVR; however, it is associated with ethnicity in CI and CO, with Caucasians being more affected by BMPR2 mutations than Asians. This suggests that Caucasians may be more sensitive to BMPR2 mutations. These findings underscore the necessity of genetic testing for PAH patients, particularly among the Caucasian population. Given the poorer clinical phenotype and prognosis of BMPR2 mutation carriers, closer follow-up may be required.

Keywords Pulmonary arterial hypertension, BMPR2, Ethnicity, Review, Meta-analysis

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Introduction

Pulmonary hypertension (PH) is a potentially fatal disease caused by progressive remodeling of peripheral pulmonary arteries, resulting in elevated mean pulmonary arterial pressure (mPAP) [1]. These pathophysiological changes lead to right heart failure, premature death, and affect all age groups [2]. Despite treatment advances, PH remains a global issue with poor survival, high mortality, and economic burden [3, 4]. The WHO classifies PH into five subtypes, with pulmonary arterial hypertension (PAH) as the first [2]. PAH is rare, with an estimated incidence of 15 to 50 cases per million annually in Europe and the United States [5]. However, reliable data on its incidence in China is lacking [6]. Moreover, ethnicity may influence PAH occurrence and characteristics [7].

The pathogenesis of PAH is complex and not fully understood. The link between bone morphogenetic protein receptor 2 (BMPR2) mutations and PAH has significantly advanced our understanding [5, 8]. BMPR2 deficiencies have been linked to inflammation and pulmonary vascular remodeling [9], although the exact mechanisms remain unknown. BMPR2 mutations account for 20-30% of all PAH patients, their prevalence is approximately 70-80% in heritable PAH (HPAH) and 10-40% in idiopathic PAH (IPAH) patients [5, 10, 11]. Studies have reported that PAH patients with BMPR2 mutations often present at a younger age and exhibit poorer clinical conditions [12, 13].

The clinical condition of PAH can be assessed using hemodynamic variables such as mPAP, pulmonary vascular resistance (PVR), cardiac index (CI), cardiac output (CO), right atrial pressure (RAP), and pulmonary artery wedge pressure (PAWP) [14–16]. These variables are critical for prognosis assessment, survival prediction, and evaluating the efficacy of therapeutic regimens [17, 18]. However, the associations and differences in these variables between patients with and without BMPR2 mutations remain inconsistent. Changes in hemodynamic parameters are closely related to the progression and duration of PAH. Moreover, these individual studies usually have small cohorts as PAH is rare, and BMPR2 mutations do not occur in every patient, leading to limited statistical power.

To confirm this further on a larger scale, we conducted a meta-analysis to assess the association between BMPR2 mutations and PAH severity using hemodynamic variables. Subgroup analyses were performed to examine differences across ethnicities.

Methods

Search strategy

For this analysis, the PubMed-MEDLINE, EMBASE, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases were searched from inception through June, 2024 for peer-reviewed publications in English. The following search strategy and Medical Subject Heading terms were used: "pulmonary hypertension" AND ""bone morphogenetic protein receptor type 2" OR "BMPR2"". Reference lists of meta-analyses, systematic reviews, and original studies detected by the database search were also reviewed to find other studies of interest. This study was conducted following the PRISMA guidelines [19, 20].

Literature inclusion and exclusion criteria

Studies conforming to the following inclusion criteria were selected: language limited to English; patients sequenced for BMPR2 mutations; recorded data on demographics and hemodynamics at initial diagnosis; and studies that reported the difference in PAH with and without BMPR2 mutation carriers. The following exclusion criteria were applied: duplicate publications; research not available in full text; unable to conduct data extraction or incomplete information; research based on animal experiments; specific publication types, including reviews, systematic reviews, case reports, letters; and studies in languages other than English.

Literature screening and data extraction

The extracted data included the following baseline characteristics: author(s), publication year, research type, study area, number of cases, age, and gender, along with outcome indicators, including mPAP, PVR, CI, CO, RAP, and PAWP.

Quality assessment

The overall quality of the included cohort studies was assessed with the Newcastle-Ottawa Scale (NOS) in an independent manner [19, 20]. The NOS consists of 4 items (maximum of 4 points) for "Research Subject Selection", 1 item (maximum of 2 points) for "Comparability between Groups", and 3 items (maximum of 3 points) for "Result Measurement". A maximum score of 9 and ≥ 7 points is considered as high-quality literature, while < 7 points is considered as literature of lower-quality.

Statistical analysis

Statistical analysis was conducted with the software STATA (version 16; StataCorp, College Station, TX, USA). Continuous variables, included weighted mean difference (WMD) with a 95% confidence interval (CI) and combined effect sizes. Odds ratio (OR, 95% CI) was used as the binary variable. The Cochran's Q statistic and I^2 statistic were applied to determine whether heterogeneity existed among included studies. If the heterogeneity test results were $p \geq 0.1$ and $I^2 \leq 50\%$, no evidence of heterogeneity between the studies was indicated, in which case the fixed effects model was used in combined

analysis. If the results showed $p < 0.1$ and $I^2 > 50\%$, it indicated that the study was heterogeneous. If the results show other situations, specific analysis is required. The random effects model or descriptive analysis was applied in case the heterogeneity remained large. We conducted subgroup analysis according to ethnicity (Asians vs. Caucasians). Furthermore, sensitivity analysis was conducted by each time eliminating one study to evaluate the stability of the results. The potential publication bias was analyzed by funnel plot and Egger's bias test. Statistically significant differences in the article are indicated by a $P < 0.05$.

Results

Literature search

According to the search strategy, 1,363 studies in total were identified in the various databases. After removing duplicates, 679 studies were left. After reading the full titles and abstracts, 40 potentially eligible studies were found. Of these studies, 23 were excluded after evaluation as they did not include the data of interest. Finally, following full-text reading, a total of 17 relevant studies were included in the meta-analysis (Fig. 1).

Baseline characteristics and quality assessment of the included studies

Overall, 17 studies were included in this meta-analysis. The cohort sizes varied from 44 to 382 between studies, and totaled a number of 2,190 patients who were included in the analysis. The included patients of 8 studies were of Asian descent, while the patients of the remaining studies were Caucasians. Table 1 shows that the studies included IPAH, FPAH and HPAH patients in general with varying severities of disease, usually selected in an unbiased manner. Moreover, the NOS scores of all the studies were above 7, which indicates that they are of high quality.

Publication bias

The funnel plot was symmetrical upon visual inspection. The quantitative evaluation by Egger's test ($P = 0.809$) according to the funnel plot indicated that no significant

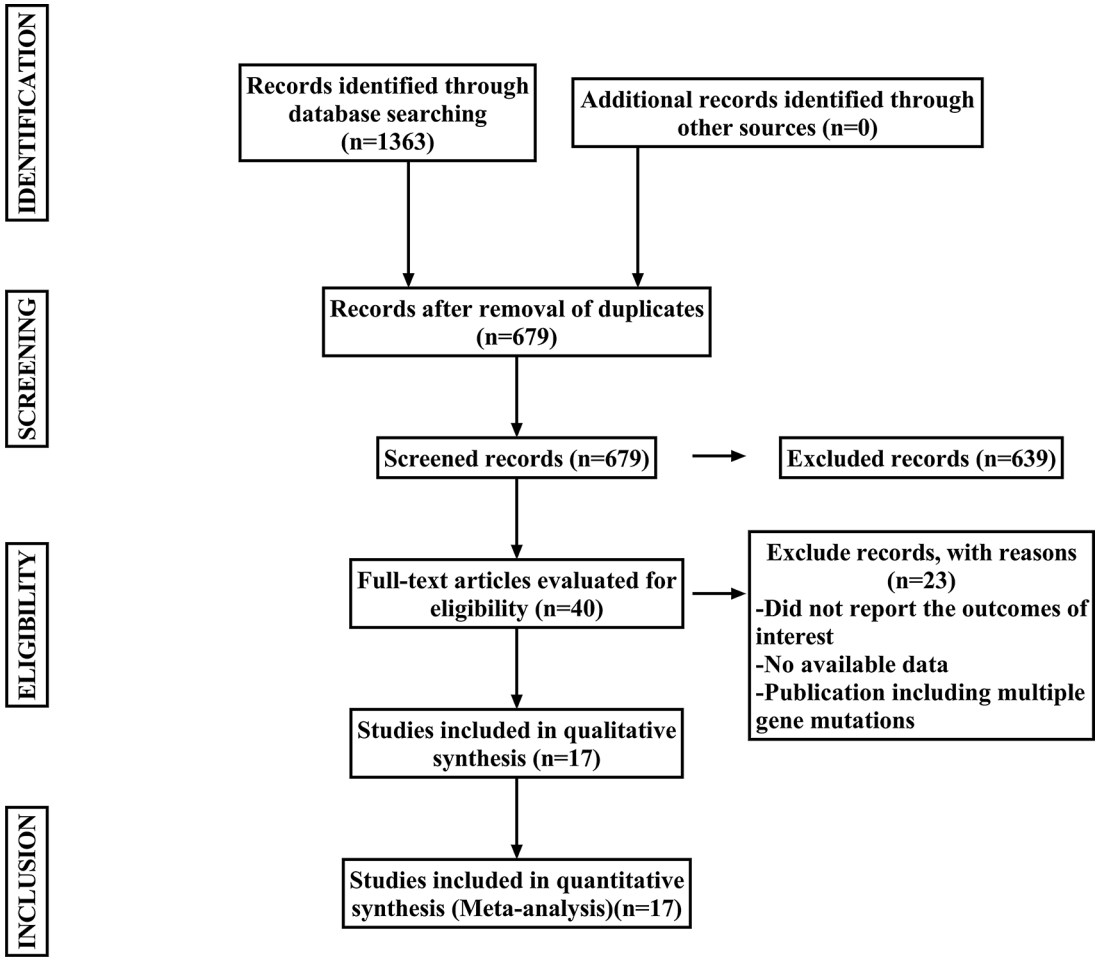

Fig. 1 Flow chart of literature selection

Table 1 Main characteristics of included studies and quality evaluation

Study	Study area	Number of patients		Gender (Female/Male)		Age Mean ± SD		Diagnosis	Study period	NOS score
		BMPR2 mutation	BMPR2 non-mutation	BMPR2 mutation	BMPR2 non-mutation	BMPR2 mutation	BMPR2 non-mutation			
Theobald [21]	Germany	23	56	17/6	41/15	50.9 ± 14.7	51.7 ± 16.6	IPAH HPAH	2019–2020	7
Theobald [22]	Germany	23	56	17/6	41/15	50.9 ± 14.7	51.7 ± 16.6	IPAH HPAH	2019–2020	7
[23]	China	8	37	5/3	31/6	30.0 ± 11.0	49.0 ± 13.0	IPAH HPAH	2021–2022	7
Zhang [24]	China	28	105	15/13	79/26	28 (22–34)	39(29–53)	IPAH	2010–2013	7
[25]	Korea	16	57	12/4	42/15	27.2 ± 11.1	46.6 ± 19.6	IPAH	2010–2015	8
Yang [26]	China	56	129	38/18	99/30	27.2 ± 9.9	31.6 ± 10.5	IPAH HPAH	2016–2017	8
Zhang [27]	China	19	85	11/8	65/20	27 (21–35)	41 (29–51)	IPAH	2009–2010	7
Bruggen [28]	Netherlands	28	67	22/6	50/17	42.0 ± 14.0	49.0 ± 16.0	IPAH HPAH	1995–2014	8
Isobe [29]	Japan	23	36	19/4	23/13	35.0 ± 13.0	34.0 ± 11.0	IPAH HPAH	2000-2015	7
Ghigna [30]	France	23	21	14/9	14/7	28.6 ± 12.7	28.5 ± 10.4	IPAH HPAH	2005–2014	7
Tio [31]	Netherlands	18	31	/	/	50.6 ± 15.3	50.8 ± 14.6	IPAH HPAH	1989–2011	7
[32]	Japan	19	30	13/6	19/11	37.4 ± 12.7	25.9 ± 11.3	IPAH FPAH	1999–2007	7
[33]	China	50	255	28/22	190/65	28 (25–31)	32 (24–47)	IPAH HPAH	2006–2010	7
[13]	Germany	49	179	32/17	134/45	38.5 ± 12.4	45.8 ± 11.3	IPAH HPAH	2006–2009	7
[34]	Britain	12	46	7/5	34/12	32.6 ± 10.5	52.4 ± 13.7	IPAH HPAH	2001–2007	7
[35]	France	115	267	81/34	188/79	/	/	IPAH FPAH	2004–2010	7
[36]	France	68	155	45/23	112/43	36.5 ± 14.5	46.0 ± 16.1	IPAH FPAH	2004–2007	7

Note: IPAH: idiopathic pulmonary arterial hypertension; FPAH: familial pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; PAH: pulmonary arterial hypertension

publication bias was present in the included studies (Fig. 2).

Results of the meta-analysis

mPAP (Mean Pulmonary arterial pressure)

Seventeen studies, including 2,190 patients, reported the mPAP in patients with and without BMPR2 mutations. Since no significant heterogeneity was present, a fixed effects model was applied ($I^2 = 15.3\%$, $p = 0.274 > 0.1$). The pooled results indicated that mPAP was significantly higher in BMPR2 mutation carriers compared to PAH patients without the mutation (WMD = 6.41, 95% CI: 5.07 ~ 7.76, $P = 0.000 < 0.05$) (Fig. 3).

PVR (pulmonary vascular resistance)

Fourteen studies reported the PVR of 1,536 patients in total with and without BMPR2 mutation. Due to the lack of significant heterogeneity, a fixed effects model was used ($I^2 = 5.7\%$, $p = 0.389 > 0.1$). The results indicated that the PVR of BMPR2 mutation carriers was significantly higher compared to that of PAH patients with no BMPR2 mutation (WMD = 3.66, 95% CI: 2.79 ~ 4.53, $P = 0.000 < 0.05$) (Fig. 4).

CI (cardiac index)

A total of thirteen studies, encompassing a total of 1,944 patients, reported the CI for both BMPR2 mutation

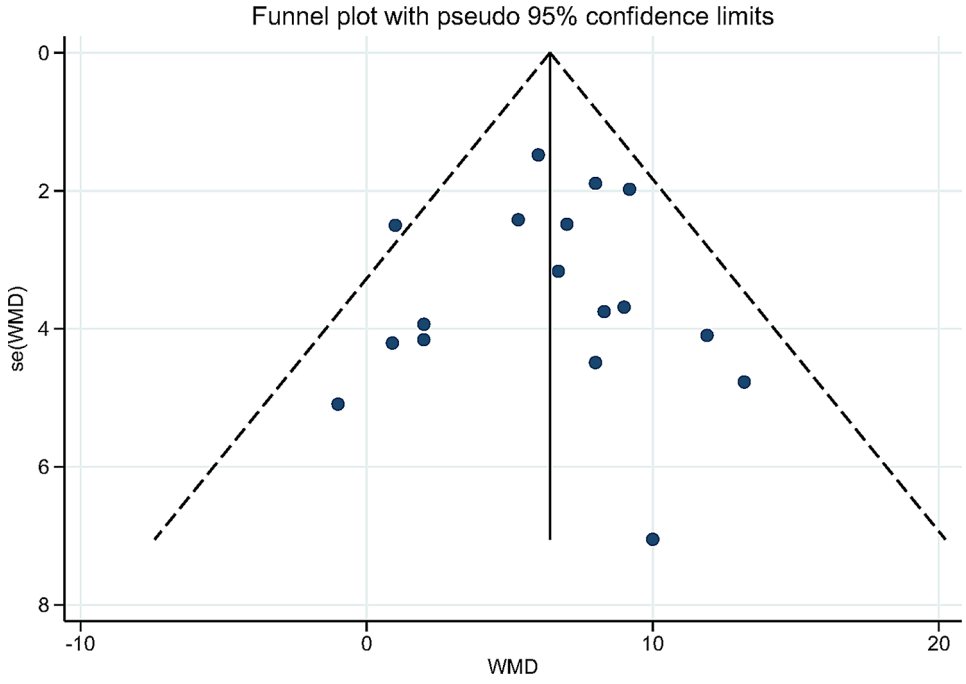

Fig. 2 Funnel plot for assessing publication bias. Se: standard error; WMD: weighted mean difference

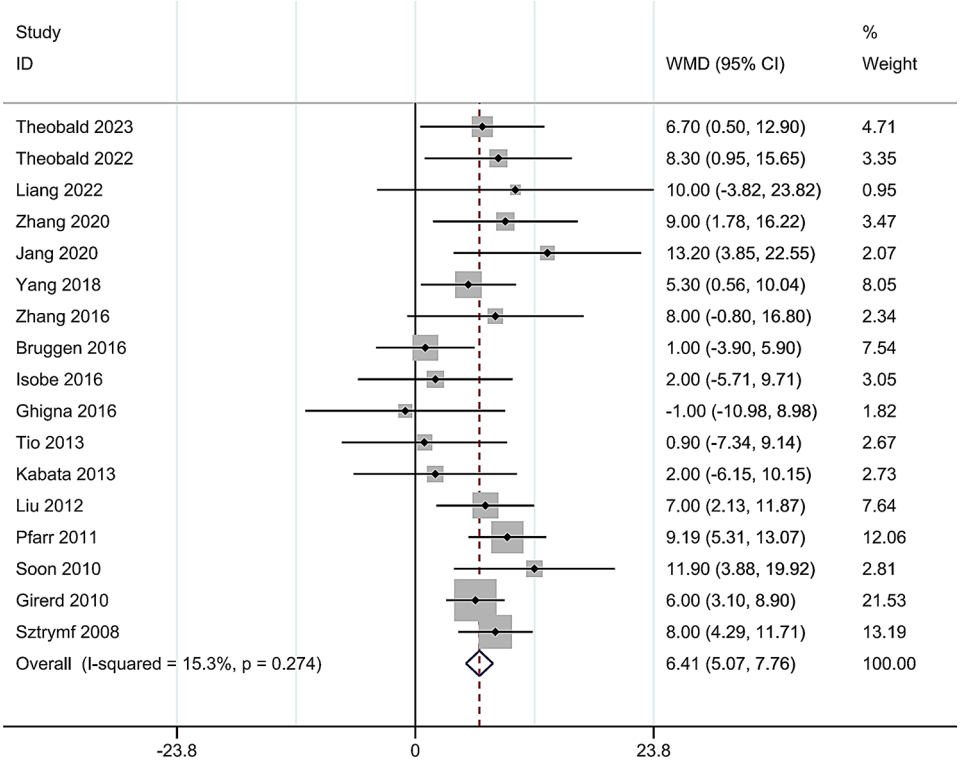

Fig. 3 mPAP in PAH patients with and without BMPR2 mutation

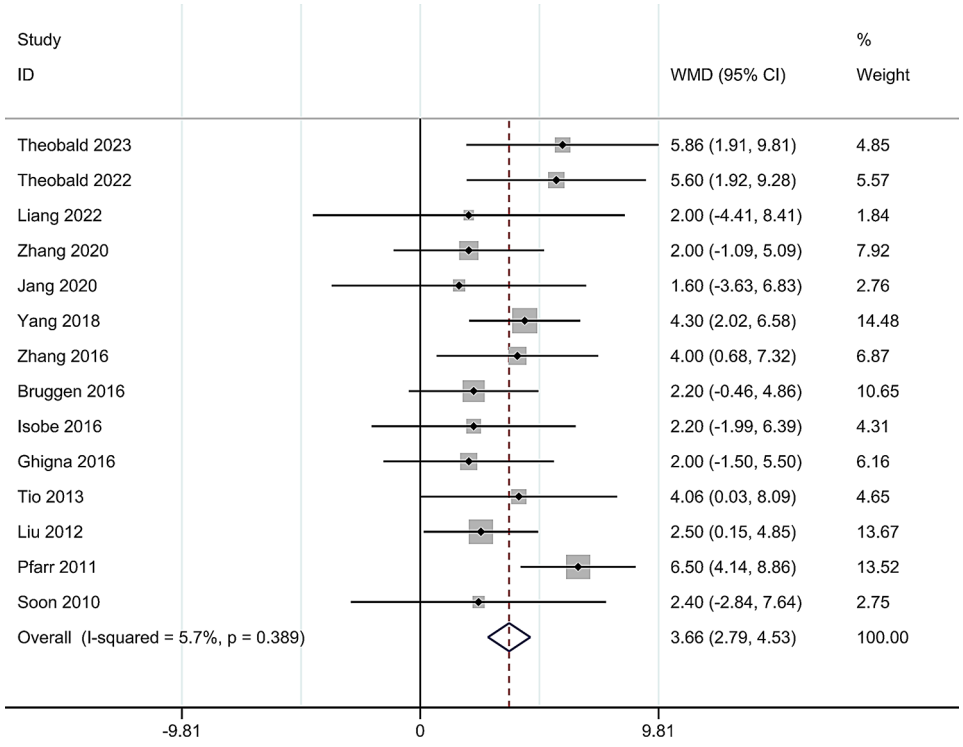

Fig. 4 PVR in PAH patients with and without BMPR2 mutation

carriers and non-carriers. A fixed-effects model was used for the analysis due to the absence of significant heterogeneity ($I^2 = 33.7\%$, $p = 0.113 > 0.1$). The pooled results indicated that the CI in BMPR2 mutation carriers was significantly lower compared to non-carriers (WMD=-0.38, 95% CI: -0.45 ~ -0.32, $P = 0.000 < 0.05$) (Fig. 5).

CO (cardiac output)

Eight studies, involving 611 patients, reported the CO of patients with BMPR2 mutation and those without. Given the presence of heterogeneity, a random-effects model was applied in the meta-analysis ($I^2 = 47.2\%$, $p = 0.066 > 0.1$). The pooled results indicated that the CO in BMPR2 mutation carriers was significantly lower compared to non-carriers (WMD=-0.60, 95% CI: -0.99 ~ -0.21, $P = 0.003 < 0.05$) (Fig. 6).

RAP (right atrial pressure)

Nine studies that included 1,531 patients, reported the RAP for both BMPR2 mutation carriers and non-carriers. Since heterogeneity was found, a random effects model was applied in the meta-analysis ($I^2 = 58.6\%$, $p = 0.013 < 0.1$). The analysis showed that the difference in RAP between carriers and non-carriers of the BMPR2 mutation was not statistically significant (WMD = 0.13, 95% CI: -0.73 ~ 1.00, $P = 0.762$) (Fig. 7).

PAWP (pulmonary artery wedge pressure)

Thirteen studies with a total of 1,729 patients, included the PAWP of patients with BMPR2 mutation and those without. Because significant heterogeneity was found, a random-effects model was applied in the meta-analysis ($I^2 = 71.0\%$, $p = 0.000 < 0.1$). The combined results revealed that the difference in PAWP values between BMPR2 mutation carriers and non-carriers was not statistically significant (WMD=-0.55, 95% CI: -1.21 ~ 0.12, $P = 0.107$) (Fig. 8).

Subgroup analysis

mPAP

We further investigated whether different ethnicities were associated with differences in mPAP between patients with and without BMPR2 mutations. The pooled results indicated that mPAP was significantly higher in BMPR2 mutation carriers compared to both Asian and Caucasian patients without the mutation. The difference in mPAP between Asian patients (WMD = 6.42, 95% CI: 3.97 ~ 8.86, $P = 0.000$; $I^2 = 0.0\%$, $p = 0.593 > 0.1$) and Caucasian patients (WMD = 6.41, 95% CI: 4.80 ~ 8.02, $P = 0.000$; $I^2 = 40.0\%$, $p = 0.101 > 0.1$) was not statistically significant ($P = 0.994$) (Fig. 9).

PVR

We also examined whether ethnicity influenced PVR differences between BMPR2 mutation carriers and non-carriers. The overall results showed significantly higher PVR

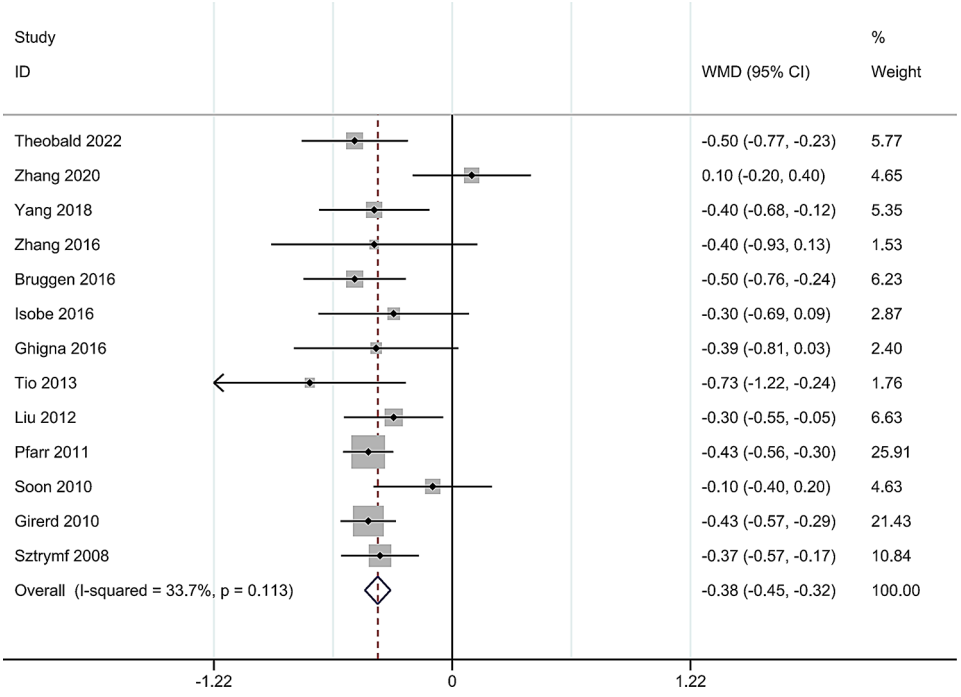

Fig. 5 CI in PAH patients with and without BMPR2 mutation

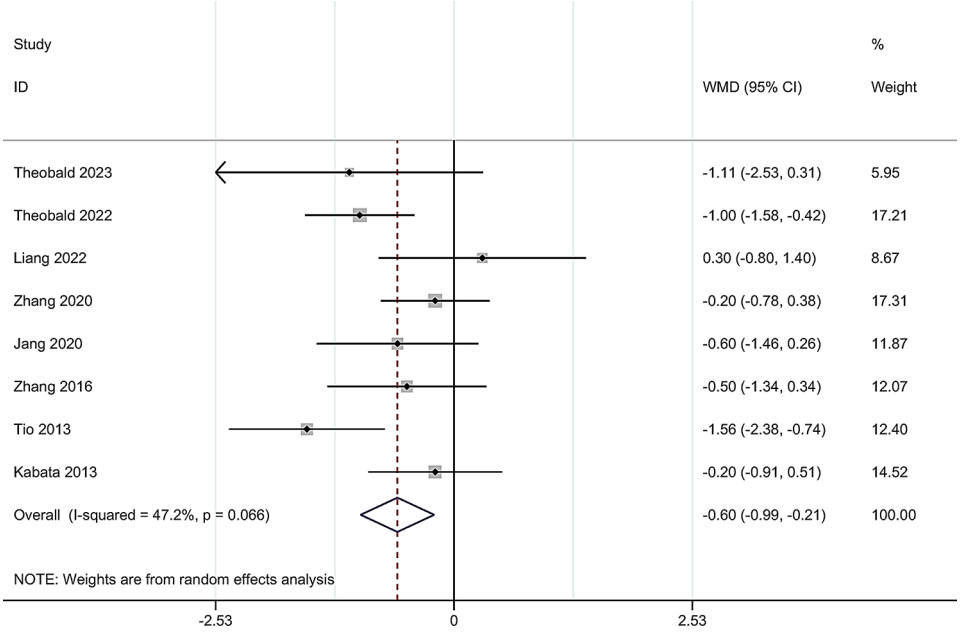

Fig. 6 CO in PAH patients with and without BMPR2 mutation

in mutation carriers among both Asian and Caucasian patients. Although the difference in PVR between Asian patients (WMD = 3.03, 95% CI: 1.83 ~ 4.24, $P = 0.000$; $I^2 = 0.0\%$, $p = 0.848 > 0.1$) and Caucasian patients (WMD = 4.33, 95% CI: 3.08 ~ 5.59, $P = 0.000$; $I^2 = 33.1\%$, $p = 0.176 > 0.1$) was not statistically significant ($P = 0.143$), the PVR of Asians was still relatively lower than that of Caucasians (Fig. 10).

CI

We evaluated whether ethnicity influenced CI differences between BMPR2 mutation carriers and non-carriers, and found that carriers had notably lower CI in both Asian and Caucasian groups. Furthermore, CI in Asian patients (WMD=-0.24, 95% CI: -0.39 ~ -0.10, $P = 0.001$; $I^2 = 40.7\%$, $p = 0.150 > 0.1$) was statistically significant higher ($P = 0.033 < 0.05$) than in Caucasian patients

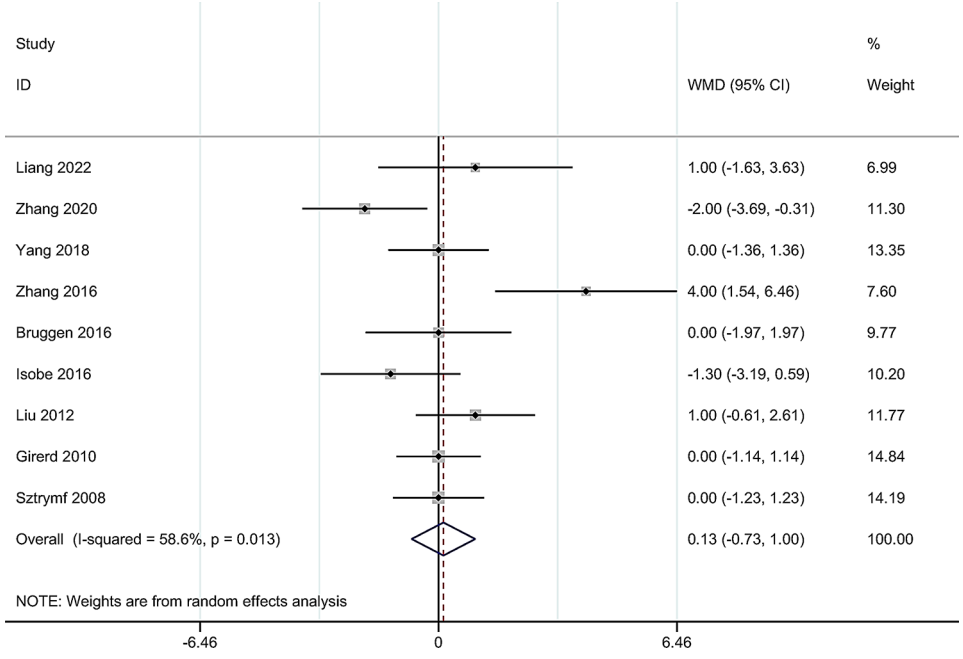

Fig. 7 RAP in PAH patients with and without BMPR2 mutation

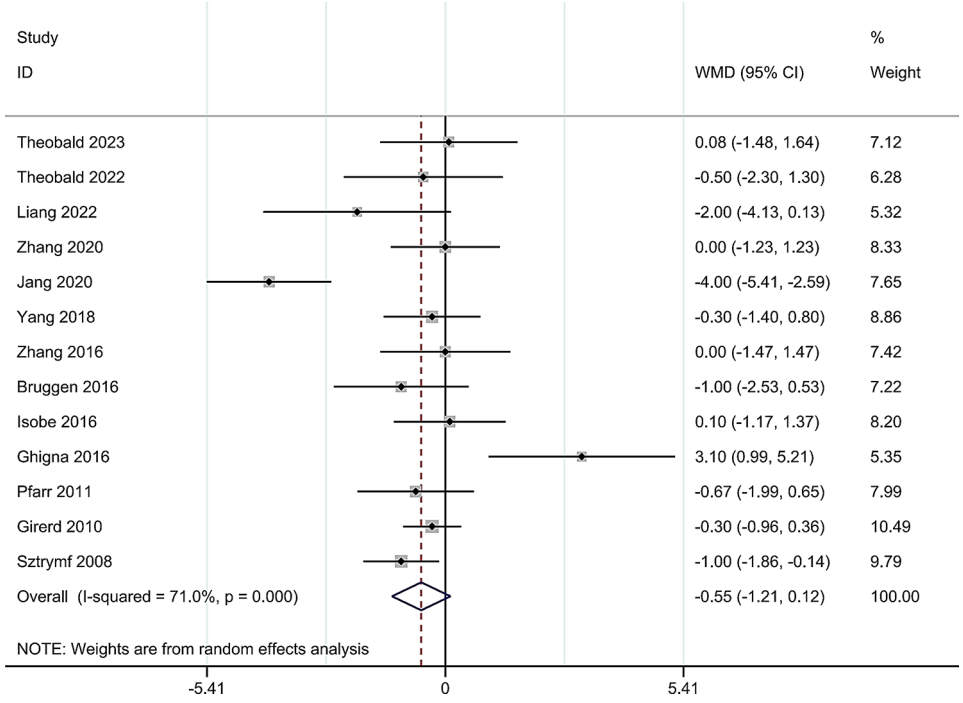

Fig. 8 PAWP in PAH patients with and without BMPR2 mutation

(WMD=-0.42, 95% CI: -0.49 ~ -0.35, $P = 0.000$; $I^2 = 0.0\%$, $p = 0.451 > 0.1$) (Fig. 11).

CO

We also assessed whether ethnicity influenced CO differences between BMPR2 mutation carriers and non-carriers, finding that carriers had notably lower CO in both Asian and Caucasian groups, despite the presence of slight heterogeneity. After subgroup analyses, the heterogeneity disappeared. The difference in CO between Asian patients (WMD=-0.26, 95% CI: -0.60 ~ 0.08, $P = 0.129$; $I^2 = 0.0\%$, $p = 0.739 > 0.1$) and Caucasian patients (WMD=-1.18, 95% CI: -1.63 ~ -0.73, $P = 0.000$;

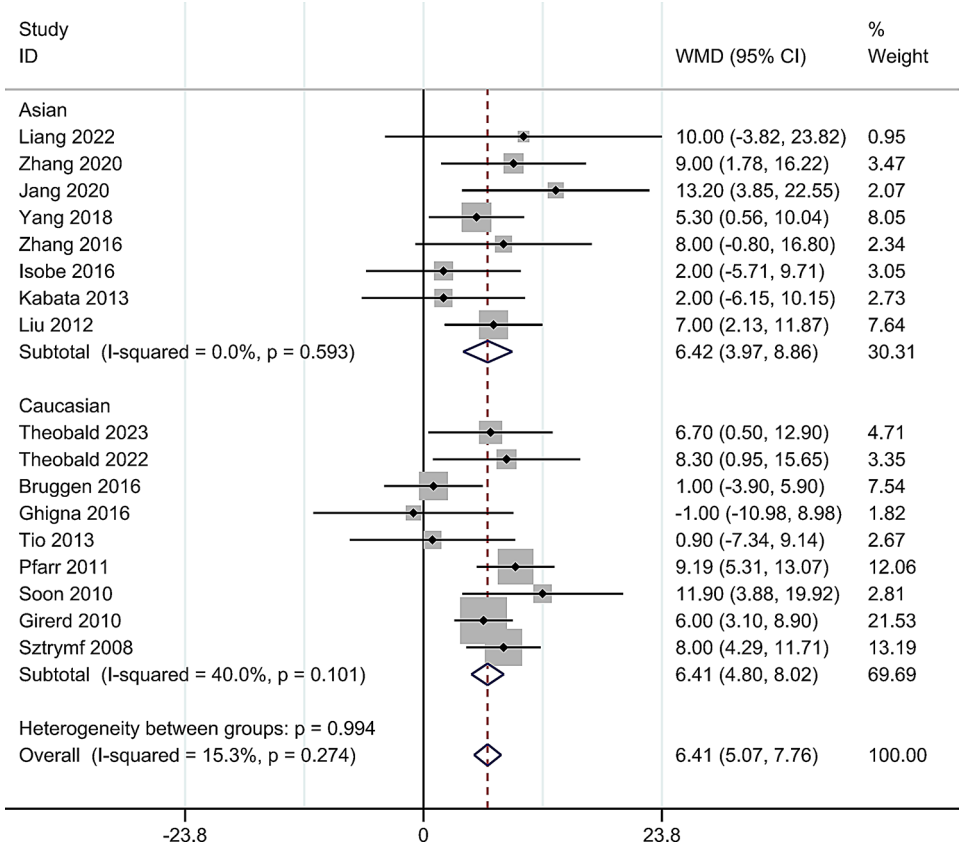

Fig. 9 Impact of ethnicity on mPAP differences among BMPR2 mutation carriers and non-carriers

$I^2 = 0.0\%$, $p = 0.550 > 0.1$) was statistically significant ($P = 0.001 < 0.05$) (Fig. 12).

Sensitivity analysis

A sensitivity analysis was performed to evaluate whether any single study had a disproportionate impact on the overall meta-analysis results. In this analysis, each included study was removed one by one, followed by a summary analysis of the remaining studies to further validate our findings. The results indicated that removing individual studies did not significantly affect the meta-analysis outcomes, suggesting that the results of the remaining studies were both consistent and robust (Figure S1-S6).

Discussion

This study utilized databases including PubMed-MEDLINE, EMBASE, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials. A total of 1,363 studies were retrieved from inception through June, 2024. After removing duplicates, 679 studies remained. Following a review of titles and abstracts, 639 studies were excluded, leaving 40 for full-text review. Ultimately, 17 studies, comprising a total of 2,190 patients, were selected for meta-analysis (Fig. 1). The study results did not indicate any publication bias (Fig. 1). Among the hemodynamic variables, patients with BMPR2 mutations exhibited significantly differences in mPAP, PVR, CI, and CO at diagnosis compared to those without BMPR2 mutations, while there were no significant differences in RAP and PAWP (Figs. 3, 4, 5, 6, 7 and 8). Furthermore, subgroup analysis was conducted on data showing significant differences, revealing no significant differences in mPAP and PVR between Asian and Caucasian patients with BMPR2 mutations, however, the PVR of Asians was still relatively lower than that of Caucasians (Figs. 9 and 10). Last but not least, significant differences in CI and CO were observed between these two ethnic groups, with CI and CO in Caucasians being more affected by BMPR2 mutations and decreasing more than in Asians (Figs. 11 and 12). Sensitivity analysis confirmed that the meta-analysis results remained consistent and robust even when individual studies were removed (Fig. S1-6). In summary, there is a statistically significant difference in the hemodynamic variables of PAH between BMPR2 mutation carriers and non-carriers, highlighting the mutation's impact on PAH severity. This influence is not associated with ethnicity in mPAP and PVR; however, it is associated with ethnicity in CI and CO, with Caucasians being more affected by BMPR2 mutations than

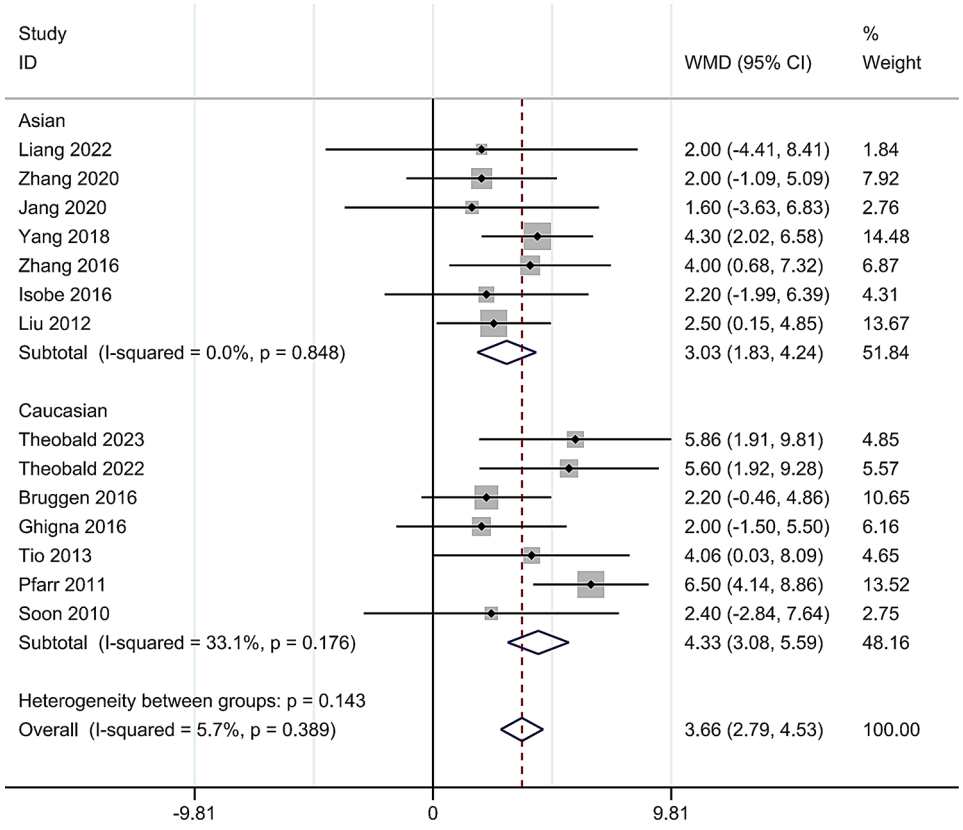

Fig. 10 Impact of ethnicity on PVR differences among BMPR2 mutation carriers and non-carriers

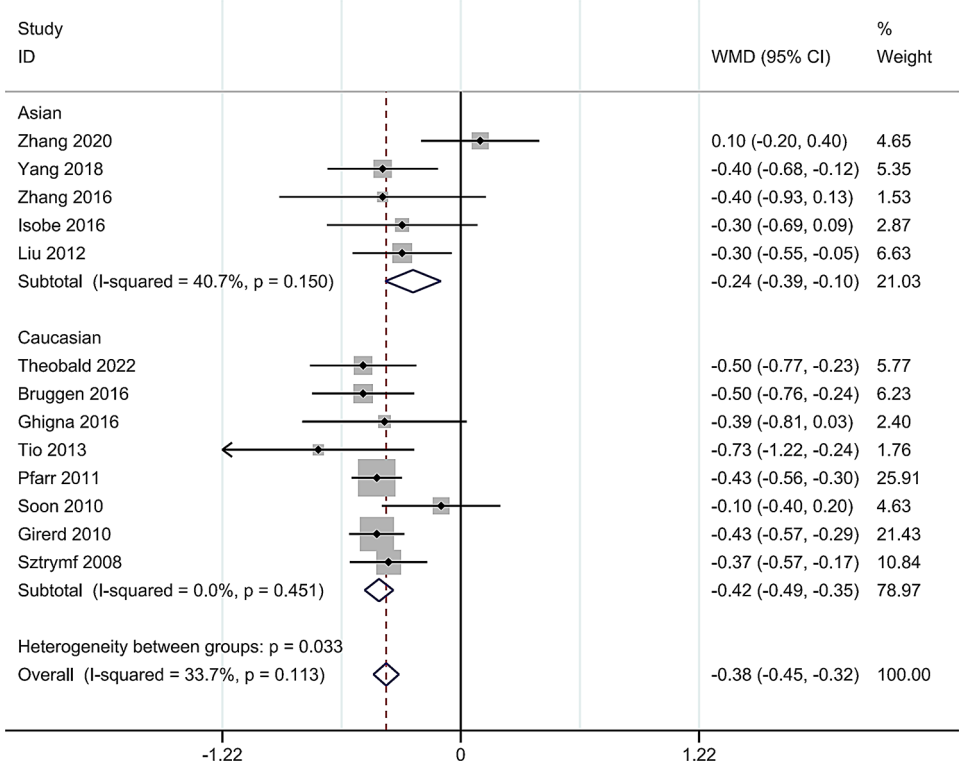

Fig. 11 Impact of ethnicity on CI differences among BMPR2 mutation carriers and non-carriers

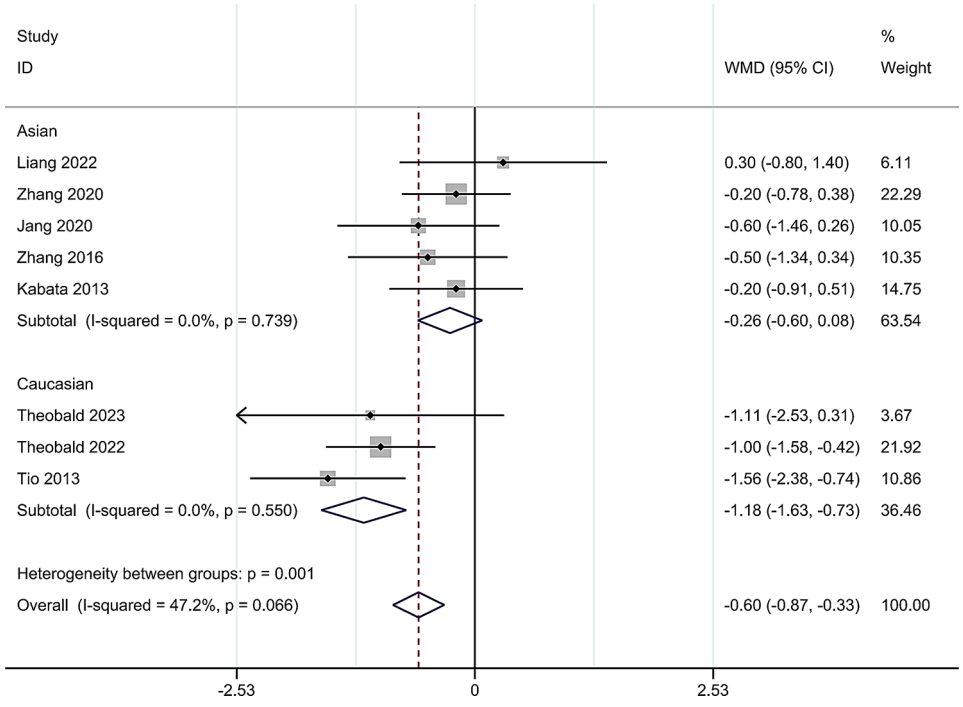

Fig. 12 Impact of ethnicity on CO differences among BMPR2 mutation carriers and non-carriers

Asians. This suggests that Caucasians may be more sensitive to BMPR2 mutations. These findings underscore the necessity of genetic testing for PAH patients, particularly among the Caucasian population. Given the poorer clinical phenotype and prognosis of BMPR2 mutation carriers, closer follow-up may be required.

PAH is a serious, progressive vascular disease with a poor prognosis, and its exact cause and pathogenesis are not yet fully understood. However, the past decades have seen remarkable progress in understanding its hereditary background, pathophysiology and treatment options [10, 37, 38]. The discovery of the link between BMPR2 gene mutations and various forms of PAH represents a significant breakthrough in our understanding of the disease. This research searched a total of 1,363 studies from inception through June 2024, ultimately screening 17 for inclusion (Fig. 1). No publication bias was found in this study (Fig. 2). Key information from these studies was extracted and summarized in Table 1. Through our review of the literature, we found that the BMPR2 mutation is the most extensively studied mutation in PAH and the first mutation identified within the BMPR family. BMPR2 gene mutations have been identified in 70-80% of patients with familial PAH (FPAH). Other studies have also found that approximately 10–40% of IPAH patients also carry this mutation [5, 10, 11]. Furthermore, the same mutations have also been discovered in 10–26% of patients with sporadic PAH [9]. Although BMPR2 mutations appear to play a crucial role in the pathogenesis of PAH, their functional consequences remain to be fully elucidated.

Many studies have suggested that PAH patients with BMPR2 mutations tend to be in poorer clinical condition and may develop symptoms at a younger age compared to those without the mutation [13, 23, 25, 32, 35, 36]. However, these studies typically involve relatively small cohorts. To further validate the clinical conditions of these patients on a larger scale, a meta-analysis was conducted to assess the relationship between PAH severity and BMPR2 mutation status, based on hemodynamic variables. Furthermore, changes in hemodynamic parameters are closely linked to the progression and duration of PAH. Theoretically, the mPAP is typically the earliest change in PAH development. As the disease progresses, pulmonary vascular remodeling increases PVR, a key feature of PAH. In the early stages, the heart compensates for rising mPAP and PVR to maintain CI and CO. However, as PVR exceeds the right ventricle's capacity, it loses the ability to sustain normal CI and CO, signaling a decline in right heart function. Increased RAP usually appears later and indicates right ventricular failure. While the trend of PAWP is unclear, its rise suggests left heart disease or mixed pulmonary hypertension.

The results of this meta-analysis revealed that patients with BMPR2 mutations had significantly higher mPAP, PVR, CI, and CO, compared to those without mutations (Figs. 3, 4, 5 and 6). Other studies have validated these parameters as survival predictors and incorporated them into a survival probability model, which can be directly

used for prognosis determination [14, 39, 40]. Our results demonstrate that BMPR2 mutations in PAH are associated with less favorable hemodynamic profiles, which could potentially infer poorer prognosis [12, 35, 41]. In the present meta-analysis, other hemodynamic variables, including RAP and PAWP, did not exhibit statistically significant differences between BMPR2 mutation carriers and non-carriers (Figs. 7 and 8). Multiple studies have demonstrated consistent results [12, 13, 33].

Furthermore, subgroup analyses were conducted to investigate whether differences existed between patients with and without BMPR2 mutations across different ethnicities. The subgroup analysis in this study primarily explored whether differences in hemodynamic parameters at diagnosis existed between mutation carriers and non-carriers in Asian and Caucasian populations. The results indicated that there were no significant differences in mPAP and PVR between Asian and Caucasian patients with BMPR2 mutations (Figs. 9 and 10). However, there were significant differences in CI and CO between Asian patients and Caucasian patients (Figs. 11 and 12).

The mPAP and PVR reflect pulmonary vascular changes, primarily due to remodeling and stenosis, and these changes are similar across different races in PAH patients according to our study. The absence of statistical differences in these indicators between the two groups suggests that the pathological process of pulmonary vasculature is highly consistent across ethnic groups. While patients with BMPR2 mutations typically show more severe vascular remodeling, the mutation's effects may follow similar pathophysiological mechanisms regardless of ethnicity, explaining the lack of significant differences in mPAP and PVR. Overall, both BMPR2 mutation carriers and non-carriers exhibit similar pulmonary vascular changes, resulting in no significant differences in the trends of increasing mPAP and PVR.

However, the CI and CO reflect the ventricle's response to the pathological load of PAH, with right ventricular function playing a critical role in PAH progression. Although there are no reports on racial differences in mPAP and PVR, racial variations may affect the compensatory capacity of the ventricle and, consequently, CI and CO. Studies suggest structural and functional differences in the heart between different races [42–44]. This could explain the more significant drop in CI and CO in Caucasians. Beyond anatomical differences, environmental factors and genetic backgrounds, such as BMPR2 mutations, may also affect the right heart's compensatory processes. These mutations may have a more pronounced negative impact on right ventricular function in Caucasians, leading to a greater decline in CI and CO. Our research indicates that Caucasians may experience more rapid or severe declines in RV function in response to BMPR2 mutations in PAH. These differences could be related to variations in RV remodeling, suggesting that the impact of BMPR2 mutations is greater in Caucasians than in Asians. Consequently, Caucasians may experience quicker right heart decline due to BMPR2 mutations.

BMPR2 mutation carriers are at an increased risk of developing pulmonary arterial hypertension (PAH), and recent studies suggest that these mutations may have an impact even before clinical PAH manifests. Bogaard et al. [45] report that BMPR2 mutation carriers can exhibit subclinical cardiac and pulmonary vascular changes, including reduced cardiac output and altered right ventricular function, prior to PAH onset. Similarly, Montani et al. [46] identify subclinical manifestations in BMPR2 carriers, including reduced pulmonary vascular distensibility and impaired exercise hemodynamics, detectable through advanced diagnostic tools. These findings indicate a preclinical phase in BMPR2 carriers, emphasizing the importance of early screening and monitoring, and reinforcing the value of genetic screening and early intervention in high-risk populations.

Overall, this meta-analysis further confirms the association between BMPR2 mutations and disease severity. These hemodynamic variables are valuable for assessing the response to PAH-targeted treatment and guiding clinical decisions. There is a statistically significant difference in the hemodynamic variables of PAH between BMPR2 mutation carriers and non-carriers. However, this effect is not linked to ethnicity in mPAP and PVR, but it is associated with ethnicity in CI and CO, with Caucasians being more affected by BMPR2 mutations than Asians. This underscores the clinical importance of genetic testing for PAH patients. Given the poorer ventricular compensatory function in Caucasian BMPR2 mutation carriers compared to Asians, closer follow-up may be necessary for Caucasian patients.

The current meta-analysis has several limitations that should be acknowledged. First, as it includes only non-randomized studies, it inherits the typical limitations of observational research, such as confounding and selection bias. However, our meta-analysis offers greater statistical power compared to a single retrospective study. Second, the studies used varying methods for recruitment and data collection, with differing ratios of familial and sporadic BMPR2 mutation cases, potentially contributing to heterogeneity, though it was generally limited and acceptable. Third, most included studies lacked detailed therapy data, including triple therapy information, and did not consistently report correlations with hemodynamic parameters. This limits our ability to assess the impact of advanced therapies, highlighting the need for standardized data in future studies. Additionally, further studies with larger sample sizes and extended follow-up are needed to evaluate the causal mechanisms

underlying the association between BMPR2 mutations, disease severity, and prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03145-5 .

Supplementary Material 1: **Figure S1**: Sensitivity analysis for RAP in PAH patients with and without BMPR2 mutations.

Supplementary Material 2: **Figure S2**: Sensitivity analysis for mPAP in PAH patients with and without BMPR2 mutations.

Supplementary Material 3: **Figure S3**: Sensitivity analysis for PAWP in PAH patients with and without BMPR2 mutations.

Supplementary Material 4: **Figure S4**: Sensitivity analysis for PVR in PAH patients with and without BMPR2 mutations.

Supplementary Material 5: **Figure S5**: Sensitivity analysis for CI in PAH patients with and without BMPR2 mutations.

Supplementary Material 6: **Figure S6**: Sensitivity analysis for CO in PAH patients with and without BMPR2 mutations.

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Author contributions
JW made significant contributions to the work, including the conception, study design, data acquisition, analysis, and interpretation. JW wrote the main manuscript and prepared Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12, Figures S1-S6, and Table 1. JX and YG assisted with the study design, data acquisition, and analysis, and contributed to the review and revision of the manuscript. QH, YZ, ZD, HF, and YZ contributed to the analysis and review of the manuscript. All authors approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
The publication of details regarding this study has received approval from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Consent to publish
Not applicable.

Consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61.
2. Prins KW, Thenappan T. World Health Organization Group I pulmonary hypertension: epidemiology and pathophysiology. Cardiol Clin. 2016;34:363–74.
3. Chang KY, Duval S, Badesch DB, Bull TM, Chakinala MM, De Marco T, et al. Mortality in pulmonary arterial hypertension in the modern era: early insights from the pulmonary hypertension association registry. J Am Heart Assoc. 2022;11:e024969.
4. Wang LY, Lee KT, Lin CP, Hsu LA, Wang CL, Hsu TS, et al. Long-term survival of patients with pulmonary arterial hypertension at a single center in Taiwan. Acta Cardiol Sin. 2017;33:498–509.
5. Cuthbertson I, Morrell NW, Caruso P. BMPR2 mutation and metabolic reprogramming in pulmonary arterial hypertension. Circ Res. 2023;132:109–26.
6. Zhai Z, Wang J, Zhao L, Yuan JX, Wang C. Pulmonary hypertension in China: pulmonary vascular disease: the global perspective. Chest. 2010;137:69S–77S.
7. Medrek SK, Sahay S. Ethnicity in pulmonary arterial hypertension: possibilities for novel phenotypes in the age of personalized medicine. Chest. 2018;153:310–20.
8. Frump AL, Datta A, Ghose S, West J, de Caestecker MP. Genotype-phenotype effects of Bmpr2 mutations on disease severity in mouse models of pulmonary hypertension. Pulm Circ. 2016;6:597–607.
9. Soon E, Crosby A, Southwood M, Yang P, Tajsic T, Toshner M, et al. Bone morphogenetic protein receptor type II deficiency and increased inflammatory cytokine production. A gateway to pulmonary arterial hypertension. Am J Respir Crit Care Med. 2015;192:859–72.
10. Morrell NW, Aldred MA, Chung WK, Elliott CG, Nichols WC, Soubrier F, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J. 2019;53.
11. Cogan JD, Pauciulo MW, Batchman AP, Prince MA, Robbins IM, Hedges LK, et al. High frequency of BMPR2 exonic deletions/duplications in familial pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006;174:590–98.
12. Evans JD, Girerd B, Montani D, Wang XJ, Galie N, Austin ED, et al. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. Lancet Respir Med. 2016;4:129–37.
13. Pfarr N, Szamalek-Hoegel J, Fischer C, Hinderhofer K, Nagel C, Ehlken N, et al. Hemodynamic and clinical onset in patients with hereditary pulmonary arterial hypertension and BMPR2 mutations. Respir Res. 2011;12:99.
14. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343–9.
15. Pagnamenta A, Lador F, Azzola A, Beghetti M. Modern invasive hemodynamic assessment of pulmonary hypertension. Respiration. 2018;95:201–11.
16. Chemla D, Castelain V, Hervé P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J. 2002;20:1314–31.
17. Weatherald J, Boucly A, Chemla D, Savale L, Peng M, Jevnikar M, et al. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. Circulation. 2018;137:693–704.
18. Rich S. The current treatment of pulmonary arterial hypertension: time to redefine success. Chest. 2006;130:1198–202.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
20. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
21. Theobald V, Grunig E, Benjamin N, Seyfarth HJ, Halank M, Schneider MA, et al. Is iron deficiency caused by BMPR2 mutations or dysfunction in pulmonary arterial hypertension patients? Pulm Circ. 2023;13:e12242.
22. Theobald V, Benjamin N, Seyfarth HJ, Halank M, Schneider MA, Richtmann S, et al. Reduction of BMPR2 mRNA expression in peripheral blood of pulmonary arterial hypertension patients: a marker for disease severity? Genes (Basel). 2022;13.
23. Liang KW, Chang SK, Chen YW, Lin WW, Tsai WJ, Wang KY. Whole exome sequencing of patients with heritable and idiopathic pulmonary arterial hypertension in Central Taiwan. Front Cardiovasc Med. 2022;9:911649.
24. Zhang R, Wang L, Zhao QH, Jiang R, Gong SG, Jiang X, et al. Alteration of extracellular superoxide dismutase in idiopathic pulmonary arterial hypertension. Front Med (Lausanne). 2020;7:509.
25. Jang AY, Kim BG, Kwon S, Seo J, Kim HK, Chang HJ, et al. Prevalence and clinical features of bone morphogenetic protein receptor type 2 mutation

in Korean idiopathic pulmonary arterial hypertension patients: the PILGRIM explorative cohort. PLoS One. 2020;15:e0238698.
26. Yang H, Zeng Q, Ma Y, Liu B, Chen Q, Li W, et al. Genetic analyses in a cohort of 191 pulmonary arterial hypertension patients. Respir Res. 2018;19:87.
27. Zhang R, Wang XJ, Zhang HD, Sun XQ, Zhao QH, Wang L, et al. Profiling nitric oxide metabolites in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2016;48:1386–95.
28. van der Bruggen CE, Happe CM, Dorfmuller P, Trip P, Spruijt OA, Rol N, et al. Bone morphogenetic protein receptor type 2 mutation in pulmonary arterial hypertension: a view on the right ventricle. Circulation. 2016;133:1747–60.
29. Isobe S, Kataoka M, Aimi Y, Gamou S, Satoh T, Fukuda K. Improved survival of patients with pulmonary arterial hypertension with BMPR2 mutations in the last decade. Am J Respir Crit Care Med. 2016;193:1310–4.
30. Ghigna MR, Guignabert C, Montani D, Girerd B, Jais X, Savale L, et al. BMPR2 mutation status influences bronchial vascular changes in pulmonary arterial hypertension. Eur Respir J. 2016;48:1668–81.
31. Tio D, Leter E, Boerrigter B, Boonstra A, Vonk-Noordegraaf A, Bogaard HJ. Risk factors for hemoptysis in idiopathic and hereditary pulmonary arterial hypertension. PLoS One. 2013;8:e78132.
32. Kabata H, Satoh T, Kataoka M, Tamura Y, Ono T, Yamamoto M, et al. Bone morphogenetic protein receptor type 2 mutations, clinical phenotypes and outcomes of Japanese patients with sporadic or familial pulmonary hypertension. Respirology. 2013;18:1076–82.
33. Liu D, Wu WH, Mao YM, Yuan P, Zhang R, Ju FL, et al. BMPR2 mutations influence phenotype more obviously in male patients with pulmonary arterial hypertension. Circ Cardiovasc Genet. 2012;5:511–8.
34. Soon E, Holmes AM, Treacy CM, Doughty NJ, Southgate L, Machado RD, et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation. 2010;122:920–7.
35. Girerd B, Montani D, Eyries M, Yaici A, Sztrymf B, Coulet F, et al. Absence of influence of gender and BMPR2 mutation type on clinical phenotypes of pulmonary arterial hypertension. Respir Res. 2010;11:73.
36. Sztrymf B, Coulet F, Girerd B, Yaici A, Jais X, Sitbon O, et al. Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. Am J Respir Crit Care Med. 2008;177:1377–83.
37. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. 2017;14:603–14.
38. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, et al. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62:D13–21.
39. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J. 2010;35:1079–87.
40. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest. 2019;156:323–37.
41. Andruska A, Spiekerkoetter E. Consequences of BMPR2 deficiency in the pulmonary vasculature and beyond: contributions to pulmonary arterial hypertension. Int J Mol Sci. 2018;19.
42. Parke KS, Brady EM, Alfuhied A, Motiwale RS, Razieh CS, Singh A, et al. Ethnic differences in cardiac structure and function assessed by MRI in healthy South Asian and White European people: a UK Biobank Study. J Cardiovasc Magn Reson. 2024;26:100001.
43. Kawut SM, Lima JA, Barr RG, Chahal H, Jain A, Tandri H, et al. Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study. Circulation. 2011;123:2542–51.
44. Skowronski J, Cho I, Mintz GS, Wolny R, Opolski MP, Cha MJ, et al. Inter-ethnic differences in normal coronary anatomy between Caucasian (Polish) and Asian (Korean) populations. Eur J Radiol. 2020;130:109185.
45. Tóth EN, Celant LR, Niglas M, Jansen S, Tramper J, Baxan N, et al. Deep phenotyping of unaffected carriers of pathogenic BMPR2 variants screened for pulmonary arterial hypertension. Eur Respir J. 2024;64.
46. Gerges C, Beurnier A, Jaïs X, Hervé P, Lau EMT, Girerd B, et al. Role of exercise hemodynamics in the prediction of pulmonary arterial hypertension in BMPR2 mutation carriers. Chest. 2024;166:1173–83.

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