


## SYSTEMATIC REVIEW AND META-ANALYSIS

# Mildly Elevated Pulmonary Arterial Pressure Is Associated With a High Risk of Progression to Pulmonary Hypertension and Increased Mortality: A Systematic Review and Meta-Analysis

Lin Xue, MD\*; Yicheng Yang, MD\*; Bo Sun, BE; Bingyang Liu, MD, PhD; Qixian Zeng, MD, PhD; Changming Xiong , MD, PhD

**BACKGROUND:** Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (PAP)  $\geq 25$  mm Hg measured by right heart catheterization. However, the upper limit of a normal mean PAP is 20 mm Hg. There is a gap between the upper limit of normal and the threshold for diagnosing PH. Therefore, we aimed to investigate whether individuals with a mildly elevated PAP, defined as 20 mm Hg < mean PAP < 25 mm Hg, are at an increased risk of progression to PH or mortality than those with a normal PAP.

**METHODS AND RESULTS:** We reviewed studies evaluating the risk of progression to PH and/or mortality in individuals with a mildly elevated PAP versus those with a normal PAP. The mean PAP value of each participant was confirmed by right heart catheterization. We reviewed 1213 studies and 8 fulfilled our inclusion criteria. Our results indicated that individuals with a mildly elevated PAP were 1.81 to 2.45 times more likely to progress to PH than individuals with a normal PAP. There was a statistically significant difference in mortality between the mildly elevated PAP and normal PAP groups (hazard ratio, 2.48; 95% CI, 1.69–3.64). We also pooled survival probabilities in each arm to obtain a summary survival curve for each group, and the pooled survival rates in the mildly elevated PAP group were numerically lower than those in the normal PAP group.

**CONCLUSIONS:** Our study revealed that individuals with a mildly elevated PAP were at an increased risk of progression to PH and mortality than those with a normal PAP.

**Key Words:** mildly elevated pulmonary arterial pressure ■ mortality ■ pulmonary hypertension

**P**ulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP)  $\geq 25$  mm Hg measured by right heart catheterization (RHC) in the supine position at rest, according to current guidelines.<sup>1</sup> However, the upper limit of normal for mPAP is 20 mm Hg, as reported by Paul Wood in 1956<sup>2</sup> and by the World Health Organization Expert Committee in 1961.<sup>3</sup> In 2009, a systemic review on the normal

mPAP value also showed that the mPAP at rest is  $14.0 \pm 3.3$  mm Hg and rarely exceeds 20 mm Hg.<sup>4</sup> There is a gap between the upper limit of normal and the threshold for diagnosing PH, and the clinical significance of a mildly elevated PAP is currently unknown.

At the 6th World Symposium on Pulmonary Hypertension, held in Nice, France, in 2018, a controversial hemodynamic definition of PH was

Correspondence to: Changming Xiong, MD, PhD, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Road, Xicheng District, Beijing 100037, China. E-mail: xiongcm2000@163.com

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018374>

\*Dr Xue and Dr Yang contributed equally and are co-first authors.

For Sources of Funding and Disclosures, see page 10.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- Individuals with mildly elevated pulmonary arterial pressure (PAP) had a higher risk of progression to pulmonary hypertension during follow-up than those with normal PAP.
- Mildly elevated PAP is associated with increased mortality compared with normal PAP.
- The pooled 1-, 3-, 5-, 7-, and 9-year survival rates in the mildly elevated PAP group (97.0%, 89.4%, 77.0%, 64.5%, and 49.6%, respectively) were lower than those in the normal PAP group (97.7%, 93.3%, 88.8%, 81%, and 74.9%, respectively).

### What Are the Clinical Implications?

- Individuals with a mildly elevated PAP should receive more attention and closer follow-up than they do currently.
- Further studies concerning the time-to-progression to pulmonary hypertension and proper management for individuals with a mildly elevated PAP are needed.

## Nonstandard Abbreviations and Acronyms

<b>mPAP</b>	mean pulmonary arterial pressure
<b>PAP</b>	pulmonary arterial pressure
<b>PH</b>	pulmonary hypertension
<b>RHC</b>	right heart catheterization

proposed; it suggested lowering the threshold from  $\geq 25$  to  $>20$  mm Hg.<sup>5</sup> This proposal might have been attributed to increasing evidence from studies suggesting that a mildly elevated PAP is associated with an increased risk of disease progression and poor survival.<sup>6–9</sup> However, those studies used different criteria for the lower limit of a mildly elevated PAP, varying from 19 to 21 mm Hg. Critical voices against this proposal were raised, arguing that the evidence for redefining PH was not enough and that the new definition might lead to overdiagnosis and overtreatment of PH.<sup>10</sup> Guidelines for the diagnosis of PH have not been updated since 2015, and further studies concerning individuals with a mildly elevated PAP (20 mm Hg  $<$  mPAP  $<$  25 mm Hg) are needed to support the new PH definition proposed at the 6th World Symposium on Pulmonary Hypertension.

We aimed to systematically investigate whether individuals with a mildly elevated PAP, defined as 20 mm Hg  $<$  mPAP  $<$  25 mm Hg in our study, are at an

increased risk of progression to PH, defined as mPAP  $\geq 25$  mm Hg according to the 2015 guidelines<sup>1</sup> or an increased risk of all-cause mortality than those with a normal PAP.

## METHODS

### Search Strategy and Data Sources

The data that support the findings of this study are available from the corresponding author upon reasonable request. This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines<sup>11</sup> and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines and was registered at PROSPERO (International Prospective Register of Systematic Reviews) (ID: CRD42020175897).

We reviewed studies evaluating the risk of developing PH and/or mortality in individuals with a mildly elevated PAP versus those with a normal PAP. The mPAP value of each participant was confirmed by RHC. The exposure of our study was a mildly elevated PAP, which was defined as 20 mm Hg  $<$  mPAP  $<$  25 mm Hg. The primary outcome of our study was all-cause mortality, and the secondary outcome was progression to PH.

A systematic search of articles published before March 31, 2020, was conducted through PubMed, EMBASE, Web of Science, the Cochrane Library, and Ovid. Other resources, including OpenGrey (unpublished grey literature) and the *European Respiratory Journal* (up-to-date literature), were also searched. The reference lists of key articles were also reviewed. The complete PubMed search is shown in Data S1.

### Study Selection and Data Collection

The inclusion criteria were as follows: (1) studies that included an identifiable study group with a mildly elevated PAP of  $>20$  and  $<25$  mm Hg; (2) the mPAP of each individual was measured by RHC; and (3) studies that provided the number of events or risk estimates for progression to PH and/or mortality in the mildly elevated PAP group versus the normal PAP group (mPAP  $\leq 20$  mm Hg). The exclusion criteria were as follows: (1) mildly elevated PAP or mild PH was defined as any value other than 20 mm Hg  $<$  mPAP  $<$  25 mm Hg; (2) studies without a reference group; (3) the mPAP was calculated by echocardiography instead of RHC; (4) follow-up data were incomplete; and (5) editorials, commentaries, opinions, and review articles.

Selection of studies: Two reviewers searched the database independently based on the same criteria. Two reviewers screened titles and abstracts

independently and ultimately examined the full texts of original articles for study inclusion. Any disagreements between reviewers were resolved by discussion and by a third reviewer when necessary.

**Data extraction and quality assessment:** Data that described the studies, participants, and outcomes were extracted. The study characteristics comprised the study design (prospective cohort and retrospective cohort), study year, country, and sample size. Participants' characteristics included the proportion of women and mean age. Follow-up duration and significant outcomes were also recorded. We contacted the study authors by e-mail when additional information was needed. Two investigators assessed study quality following the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

### Statistical Analysis

The pooled risk ratio (RR) for progression to PH and the corresponding 95% CI were calculated with a fixed-effects model (Mantel-Haenszel method) except when heterogeneity among studies was statistically significant (eg,  $I^2 > 50\%$ ). In that case, a random-effects model (DerSimonian-Laird method) was applied for estimation. The pooled hazard ratio (HR) for mortality and the corresponding 95% CI were estimated by the generic inverse variance method, using a fixed-effects or random-effects model as appropriate, according to the absence or existence of statistically significant heterogeneity. Subgroup analyses were conducted to identify subsets of individuals who were more likely to suffer from poor outcomes and to evaluate the efficacies of different studies.

For studies in which the numbers of at-risk participants during different time intervals or HRs and corresponding 95% CIs were not available, estimates were calculated using the method previously proposed by Williamson et al<sup>12</sup> and Tierney et al.<sup>13</sup> The survival probability at each time point was extracted using the R packages *ReadImage* and *digitize*. Summary survival curves were obtained using the R package *MetaSurv* provided by Combesure et al.<sup>14</sup>

Optimal method was used for estimating the mean value and SD from the sample size, median, and mid-quartile range if necessary.<sup>15</sup> For continuous data, the mean differences and the corresponding 95% CIs were used as the effect sizes.

The Cochran Q-test and  $I^2$  and  $H^2$  statistics were used to evaluate heterogeneity among studies.<sup>16</sup> Leave-one-out sensitivity analyses were performed to determine the influence of individual studies. Publication bias was assessed with funnel plots by Egger's linear regression test.<sup>17</sup> The results with  $P < 0.05$  were considered "statistically significant." Analyses were performed using Review Manager version 5.3 (Cochrane

Collaboration, Oxford, UK), Stata/MP version 16.0 (Stata Corporation, College Station, TX), and R version 3.6.3 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

## RESULTS

### Characteristics of the Included Studies

We identified 1213 studies through the aforementioned search method, 8 of which fulfilled our inclusion criteria (study selection flow diagram is shown in Figure 1).<sup>18–25</sup> Four of the studies evaluated the risk of progression to PH in the mildly elevated PAP and normal PAP groups, and all 8 studies compared mortalities among different groups. The study characteristics of the included studies are summarized in Table 1. All 8 studies were published between 2012 and 2019; 3 were retrospective, 3 were prospective, and 2 were ambispective. Patients with cardiac and/or pulmonary comorbidities were included in 5 studies and excluded in the remaining 3 studies.

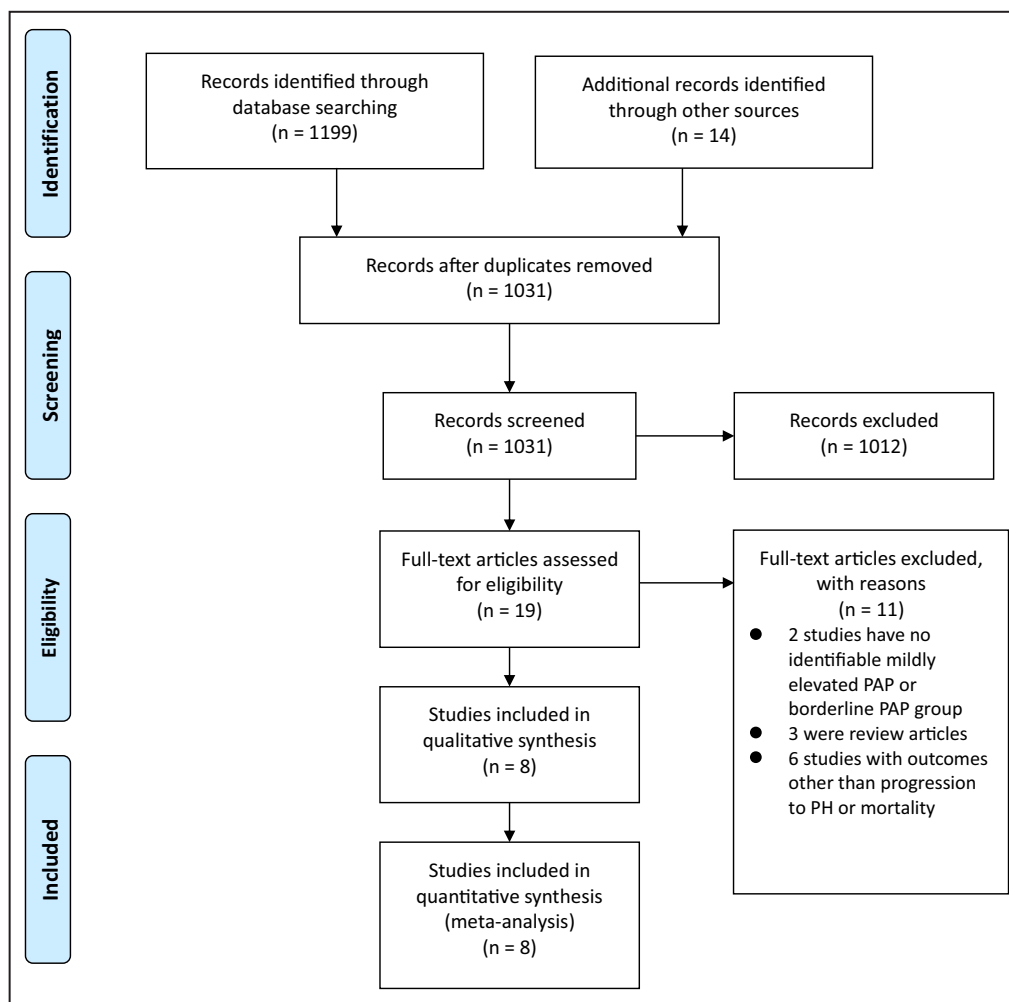
A total of 2015 participants were enrolled in the 8 studies (802 with a normal PAP, 333 with a mildly elevated PAP, and 880 diagnosed with PH). The mean/median age of the participants ranged from 56.2 to 71.2 years, and the female proportion ranged from 64.0% to 87.0% (1 study did not provide this information). The mean/median follow-up duration ranged from 2.1 to 4.2 years (not mentioned in 2 studies). Study quality, assessed using the Newcastle-Ottawa Quality Assessment Scale, is shown in Table S1.

### Risk of Progression to PH

Four studies investigated the incidences of progression to PH during follow-up in the mildly elevated PAP group versus the normal PAP group. Pooled analyses of the 4 studies showed a higher risk of progression to PH during follow-up in the mildly elevated PAP group than in the normal PAP group (RR, 1.81; 95% CI, 1.21–2.71;  $P = 0.0040$ ,  $I^2 = 0\%$ , when only participants who had repeated RHCs were included when calculating the incidence of progression to PH, Figure 2A; RR, 2.45; 95% CI, 1.55–3.87;  $P = 0.0001$ ,  $I^2 = 0\%$ , when all participants in each group were included, regardless of whether they had repeated RHCs, Figure 2B). Sensitivity analyses assessing the robustness and reliability of the merged results are shown in Figures S1 and S2. In these analyses, there were no statistically significant publication biases based on Egger's tests ( $P = 0.2180$  and  $P = 0.6950$ , Figures S3 and S4).

### Risk of All-Cause Mortality

Seven studies were included to analyze the HR for all-cause mortality, where the mildly elevated PAP group



**Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram.**

PAP indicates pulmonary artery pressure; and PH, pulmonary hypertension.

was compared with the normal PAP group. Valerio's study was excluded from the analysis because neither survival curves nor HRs were provided. Douschan et al subdivided the normal PAP group into lower-normal and upper-normal subgroups in their study. We pooled the survival curves of these subgroups to obtain the survival curve for the normal PAP group. We estimated the HR and corresponding CI using survival curves of the normal PAP and mildly elevated PAP groups. As illustrated in Figure 3, the pooled HR of the mildly elevated PAP group versus the normal PAP group was 2.48 (95% CI, 1.69–3.64;  $P < 0.0001$ ,  $I^2 = 26\%$ ).

Subgroup analyses were conducted based on baseline diseases (systemic sclerosis or others, Figure 3A) and underlying comorbidities (including or excluding patients with cardiac and/or pulmonary diseases, Figure 3B). The differences between subgroups were not statistically significant ( $P = 0.7900$  and  $P = 0.2700$ ). Sensitivity analyses indicated that no individual study significantly influenced the pooled HR (Figure S5). No

publication bias was detected based on Egger's test ( $P = 0.8610$ , Figure S6).

As Assad's research have a large number of participants, we added his study for supplementary analyses, although it defined the "mildly elevated PAP group" differently from our study (patients with mPAP values of 19 to 24 mm Hg were classified as borderline PH group in Assad's study). The pooled HR of the mildly elevated PAP group versus the normal PAP group was 1.73 (95% CI, 1.46–2.06;  $P < 0.0001$ ,  $I^2 = 43\%$ , Figure 4) when Assad's study was added. The mean difference of pulmonary vascular resistance between the mildly elevated PAP and normal PAP groups were compared and illustrated in Figure 5. Pulmonary vascular resistance of mildly elevated PAP group was 0.89 Wood units (95% CI, 0.72–1.07;  $P < 0.0001$ ,  $I^2 = 0\%$ , Figure 5A) higher than that of the normal PAP group and was 0.79 Wood units (95% CI, 0.50–1.09;  $P < 0.0001$ ,  $I^2 = 82\%$ , Figure 5B) when Assad's study was added.

**Table 1. Characteristics of the Included Studies**

Study	Study Design	Data Source	Country	Study Population	Sample Size, n	Age, y	Follow-Up Duration, y	Pulmonary vascular resistance, Wood units	Outcomes	
									Progression to PH, n (Repeated RHCs, n)	Survival Rates, %
Assad et al, <sup>9</sup> 2017*	Retrospective	Single center	USA	All patients undergoing routine RHC for clinical indication	4343	Reference: 59 (47–68) Borderline PH: 62 (52–71) PH: 61 (50–69)	/	Reference: 1.40 (0.90–1.90) Borderline PH: 1.80 (1.20–2.40) PH: 3.20 (2.10–5.30)	Borderline PH: 43 (70)	5-y survival rates: <sup>†</sup> Reference: 83% Borderline PH: 75% PH: 59%
Bae et al, <sup>18</sup> 2012	Prospective	Multiple centers	USA	Patients with SSC “at risk” or recently diagnosed with resting PH on RHC (PHAROS [ Pulmonary Hypertension Registry of Scleroderma] Registry)	206	57.2±11.6	2.1±1.4	Normal PAP: 1.71±0.93 boPAP: 2.63±1.38	Normal PAP: 4 (13) boPAP: 6 (11)	3-y survival rates: <sup>†</sup> Normal PAP: 87% boPAP: 83%
Heresi et al, <sup>19</sup> 2013	Retrospective and prospective	Single center	USA	People (without left heart or respiratory disease) seen at the clinic	469	Normal PAP: 51±17 Borderline PAP: 59±14 PAH: 54±15	/	Normal PAP: 1.46±0.61 Borderline PAP: 2.22±1.00 PAH: 10.99±6.45	/	5-y survival rates: <sup>†</sup> Normal PAP: 97.8% Borderline PAP: 80.9% PAH: 53.4%
Valerio et al, <sup>20</sup> 2013	Retrospective	Single center	UK	Patients with SSC and suspected PAH undergoing RHC (those with ILD and PH were excluded)	228	59±11	4.0±2.9	/	Normal mPAP: 11 (38) Borderline mPAP: 18 (38)	5-y survival rates: <sup>†</sup> Normal mPAP: 89.7% Borderline mPAP: 87.7%
Kovacs et al, <sup>21</sup> 2014	Retrospective	Single center	Austria	Patients underwent RHC for symptoms indicative of PH or due to underlying disease associated with an increased risk for PH	141	59.2±13.0	4.2 (1.5–7.5)	Normal mPAP: 1.80±0.80 Borderline mPAP: 2.70±0.70	Normal mPAP: 3 (29) Borderline mPAP: 4 (8)	7-y survival rates: <sup>†</sup> Normal resting mPAP: 96% Borderline resting mPAP: 72%
Coghlan et al, <sup>22</sup> 2018	Prospective	Two centers	UK and Germany	Patients with SSC and a DL <sub>CO</sub> <60% predicted (patients with PH at baseline or receiving any targeted PAH therapy were not included)	96	56.2±12.0	2.95±0.7	Normal PAP: 1.47±0.49 boPAP: 2.35±0.79	Normal PAP: 11 (50) boPAP: 7 (21)	5-y survival rates: <sup>†</sup> Normal PAP: 91% boPAP: 100%
Douschan et al, <sup>23</sup> 2018	Retrospective and prospective	Single center	Austria	Patients referred to the clinic with unexplained dyspnea and/or at risk for PH	547	Lower-normal: 56 (45–66) Upper-normal: 64 (55–72) Borderline mPAP: 67 (58–75) Manifest PH: 68 (58–74)	3.8 (1.8–6.4)	Lower-normal: 1.45 (1.10–1.93) Upper-normal: 1.89 (1.35–2.55) Borderline mPAP: 2.68 (1.89–3.33) Manifest PH: 6.09 (3.71–9.92)	/	5-y survival rates: <sup>†</sup> Lower-normal: 92% Upper-normal: 79% Borderline mPAP: 71% Manifest PH: 58%

(Continued)

**Table 1. Continued**

Study	Study Design	Data Source	Country	Study Population	Sample Size, n	Age, y	Follow-Up Duration, y	Pulmonary vascular resistance, Wood units	Outcomes	
									Progression to PH, n (Repeated RHCs, n)	Survival Rates, %
Nemoto et al. <sup>24</sup> 2019	Retrospective	Single center	Japan	Patients with ILD who underwent RHC (those with CTD-PAH were excluded)	80	71.2±10.3	/	No-PH: 2.25 (1.81–2.63) bo-PH: 3.51 (2.64–3.96) PH: 4.73 (4.00–6.18)	/	1-y survival rates: <sup>‡</sup> No-PH: 87.5% bo-PH: 77.8% PH: 83.3%
Xanthouli et al. <sup>25</sup> 2019	Prospective	Multiple centers	Germany and Switzerland	Patients with SSC (without significant lung or left heart disease)	248	57.5±12.7	3.7±3.7	/	/	7-y survival rates: <sup>‡</sup> Normal mPAP: 84% Mildly elevated mPAP: 56% Manifest PH: 59%

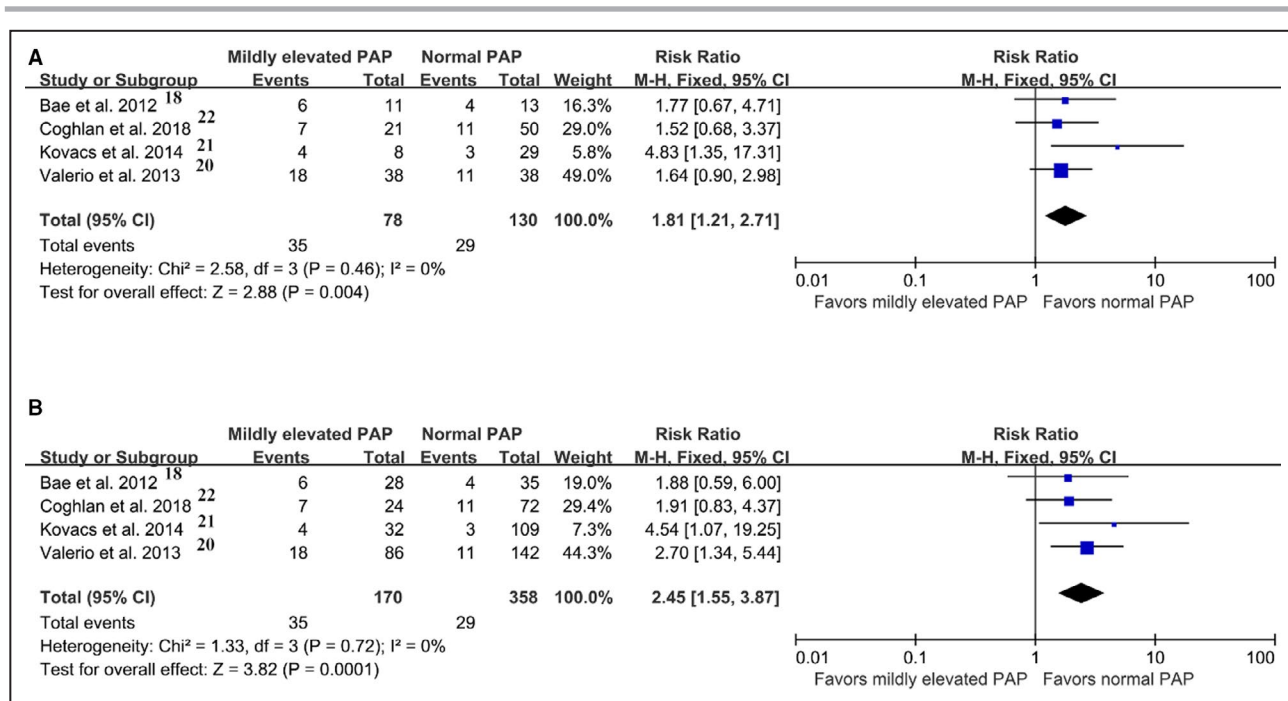
/ indicate the study did not provide that information.

Half of the studies were on individuals with SSC. boPAP indicates borderline pulmonary artery pressure; bo-PH, borderline pulmonary hypertension; CTD, connective tissue disease; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; DL<sub>CO</sub>, lung diffusion of carbon monoxide; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RHC, right heart catheterization; and SSC, systemic sclerosis.

\*Assad's study did not fulfill our inclusion criteria but was included for supplementary analyses.

<sup>†</sup>The survival rates were reported in published studies.

<sup>‡</sup>The survival rates were extracted from survival curves.



**Figure 2. Risk of progression to PH in the mildly elevated PAP group vs the normal PAP group (fixed-effects model).** **A**, Only participants who had repeated RHCs were included in the calculation of the incidence of progression to PH; **(B)** all participants in each group were included in the total number. M-H indicates Mantel-Haenszel; PAP, pulmonary artery pressure; PH, pulmonary hypertension; and RHC, right heart catheterization.

Furthermore, participants of Nemoto’s study had different underlying etiologies of elevated PAP compared with that of other included studies. We also conducted supplementary analyses which excluded Nemoto’s study (HR, 2.54; 95% CI, 1.71–3.75;  $P < 0.0001$ ,  $I^2 = 36\%$ , when Nemoto’s study was excluded, Figure S7A; HR, 2.24; 95% CI, 1.43–3.49;  $P = 0.0004$ ,  $I^2 = 51\%$ , when Assad’s study was added whereas Nemoto’s study was excluded, Figure S7B).

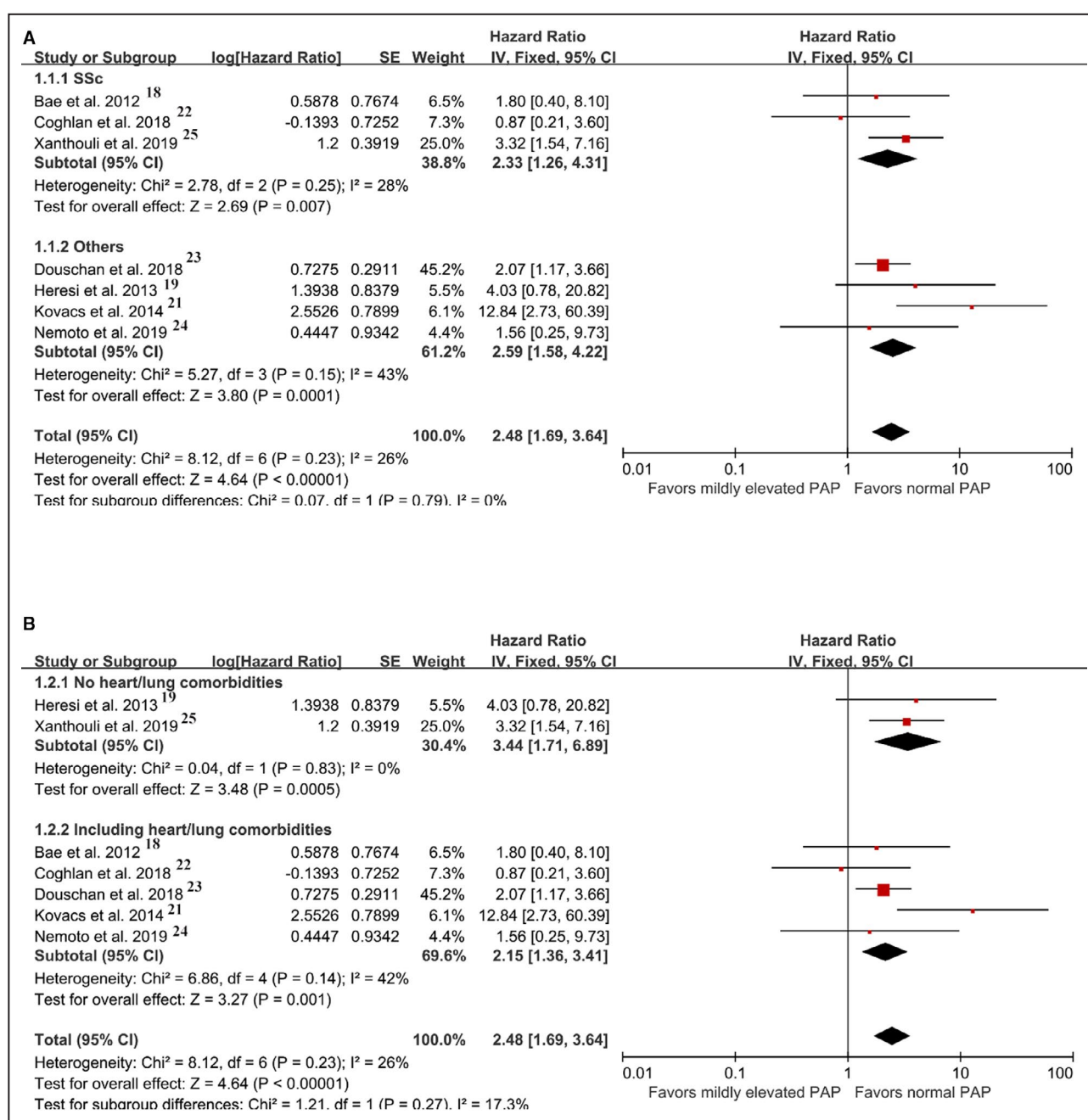
### Summary Survival Curves

Survival curves for different groups were provided in 6 studies (all 6 studies contained the normal PAP and mildly elevated PAP groups, and 4 of 6 contained the PH group), and we pooled survival probabilities in each arm to obtain a summary survival curve for each group (Figure 6). The pooled survival rates and 95% CIs for each group are shown in Table S2. The pooled 1-, 3-, 5-, 7-, and 9-year survival rates in the mildly elevated PAP group (97.0% [95% CI, 93.7–100.0], 89.4% [95% CI, 84.0–95.2], 77.0% [95% CI, 67.2–88.3], 64.5% [95% CI, 55.4–75.0], and 49.6% [95% CI, 35.5–69.4], respectively) were numerically lower than those in the normal PAP group (97.7% [95% CI, 95.4–100.0], 93.3% [95% CI, 90.2–96.5], 88.8% [95% CI, 83.4–94.6], 81% [95% CI, 72.3–90.7], and 74.9% [95% CI, 67.8–82.8], respectively).

### DISCUSSION

A mildly elevated PAP has been a heated topic especially since the proposal of lowering the hemodynamic definition of PH at the 6th World Symposium on Pulmonary Hypertension in 2018.<sup>5</sup> The threshold value of mPAP that should be used for diagnosing PH is still under debate.<sup>10,26,27</sup> We aimed to evaluate the prognostic effects of mildly elevated PAP, and the results showed that participants with a mildly elevated PAP were at a higher risk of progression to PH and mortality than those with a normal PAP.

In the first part of our analyses, we assessed the risk of progression to PH between the mildly elevated PAP group and the normal PAP group. As RHC is an invasive operation, not all participants underwent repeated RHCs during follow-up. The criteria for repeated RHCs also varied among the 4 studies. Patients had repeated RHCs if they were suspected of having overt PH clinically or on noninvasive examinations in the studies of Bae et al<sup>18</sup> and Valerio et al.<sup>20</sup> Repeated RHCs were performed in all participants in Coghlan’s study at the 3-year follow-up after excluding those who refused the invasive operation.<sup>22</sup> Kovacs et al<sup>21</sup> did not declare the criteria for repeated RHCs. All these factors might have affected the results. Thus, we calculated the incidences of progression to PH among participants who underwent repeated RHCs or among all participants in each group, and the pooled RRs were similar (shown in



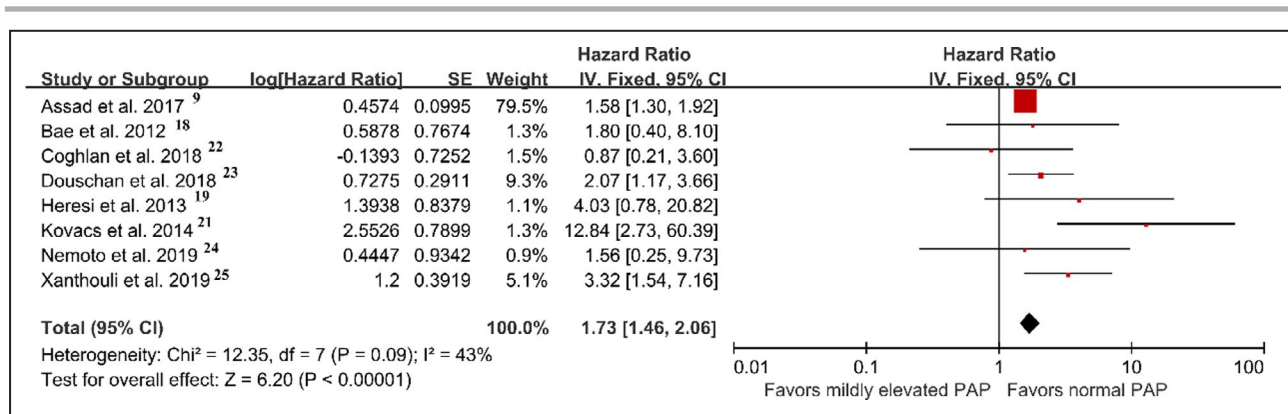
**Figure 3. Pooled hazard ratio for mortality in the mildly elevated PAP group vs the normal PAP group (fixed-effects model).** **A**, Subgroup analysis based on baseline diseases; **B** subgroup analysis based on underlying comorbidities. IV indicates inverse variance; PAP, pulmonary artery pressure; and SSc, systemic sclerosis.

Figure 2). Individuals in the mildly elevated PAP group were 1.81 to 2.45 times more likely to progress to PH than individuals in the normal PAP group, indicating that a mildly elevated PAP might be an intermediate stage between a normal PAP and PH. As progression to PH is also time dependent, further studies investigating the time-to-progression to PH are needed to better evaluate its risk in the population with a mildly elevated PAP.

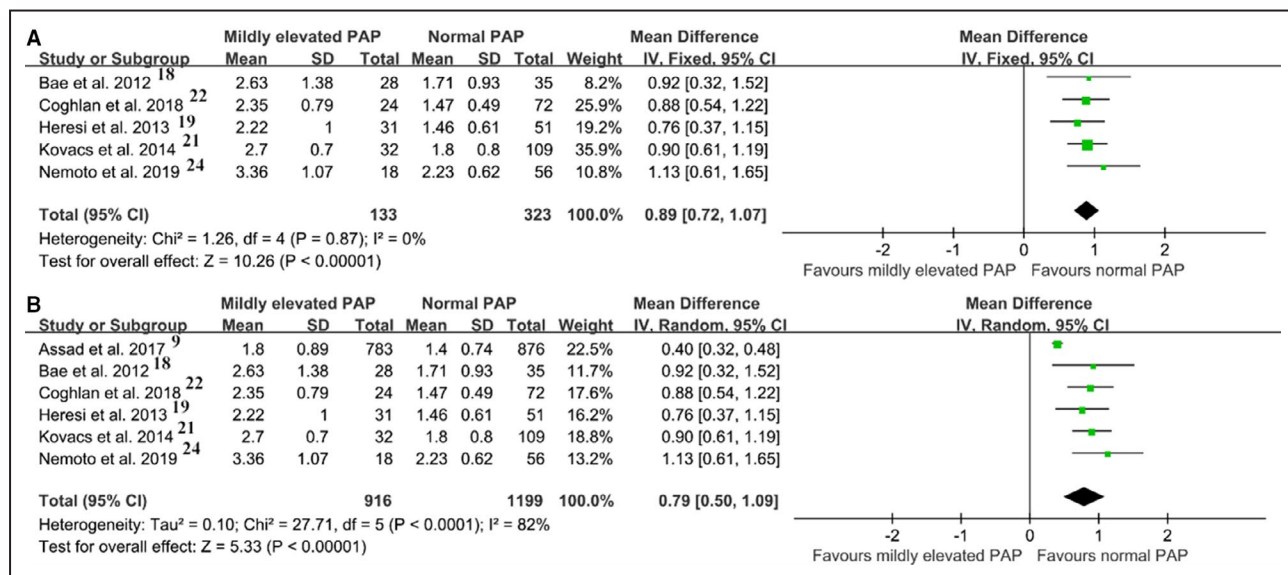
The primary outcome of our study was all-cause mortality, because for patients who died from other

diseases, an elevated PAP might have aggravated their clinical conditions and worsened their prognoses. In 2018, Kolte et al<sup>28</sup> reported an increased risk of mortality in patients with mild PH, defined as a measured or calculated mPAP >19 mm Hg by RHC or echocardiography, in a meta-analysis. However, the studies included in the meta-analysis used different criteria for the lower limit of a mildly elevated PAP, which varied from 19 to 21 mm Hg, and would lead to misclassification: participants with an mPAP of 19 to 20 mm Hg





**Figure 4. Supplementary analysis of pooled hazard ratio for mortality in the mildly elevated PAP group vs the normal PAP group when Assad's study was added (fixed-effects model).** IV indicates inverse variance; and PAP, pulmonary artery pressure.

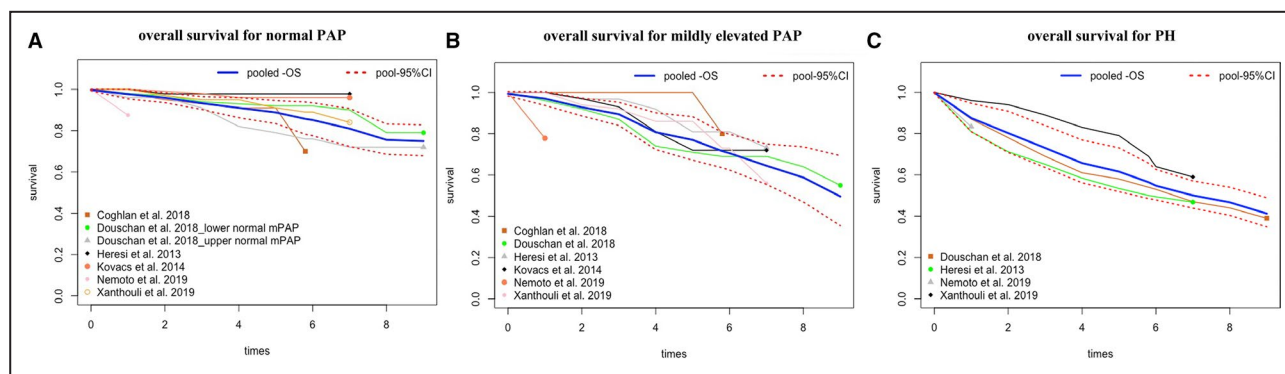


**Figure 5. Mean difference of PVR between the mildly elevated PAP group vs the normal PAP group.** A, Analysis of PVR of included studies (fixed-effects model); (B) supplementary analysis of PVR when Assad's study was added (random-effects model). IV indicates inverse variance; PAP, pulmonary artery pressure; and PVR, pulmonary vascular resistance.

might be assigned to the normal PAP group in some studies but assigned to the mild PH group in others, which may have reduced the credibility of the results. Moreover, echocardiography is useful for screening for PH but is not precise enough for an individual diagnosis of PH.<sup>29–31</sup> In our study, the mPAP of participants was measured by RHC, and the hemodynamic criteria for different groups were clear: mPAP ≤20 mm Hg for the normal PAP group, 20 mm Hg < mPAP <25 mm Hg for the mildly elevated PAP group, and mPAP ≥25 mm Hg for the PH group. The pooled HR for mortality in our study suggested increased mortality for the mildly elevated PAP group (Figure 3), consistent with the study by Kolte et al.<sup>28</sup> Subgroup analyses based on baseline diseases and comorbidities showed no statistically

significant differences between subgroups, which suggested that increased mortality was a general phenomenon in the population with a mildly elevated PAP. Another essential achievement of this meta-analysis is the summary survival curves for different groups, especially the curve for the mildly elevated PAP group, which offered complementary information illustrating the risk of death over time (Figure 6). There was no evidence of statistically significant heterogeneities or publication biases in our analyses.

As poor prognoses (risk of progression to PH and mortality) were observed in the population with a mildly elevated PAP, we need to know how to better manage this population to improve their outcomes. It is universally acknowledged that early treatment is beneficial



**Figure 6. Summary survival curves for different groups (random-effects model).**

**A**, Summary survival curve for the normal PAP group ( $I^2=14\%$ ,  $H^2=1.16$ ); **(B)** summary survival curve for the mildly elevated PAP group ( $I^2=0\%$ ,  $H^2=0.807$ ); **(C)** summary survival curve for the PH group ( $I^2=4\%$ ,  $H^2=1.04$ ). The thick blue lines represent the summary survival curves with the 95% CI (dashed lines). Other solid fine lines represent the survival curve from each study; the end of the follow-up period is marked. mPAP indicates mean pulmonary artery pressure; OS, overall survival; PAP, pulmonary artery pressure; PH pulmonary hypertension.

in patients with pulmonary arterial hypertension, while the management of individuals with a mildly elevated PAP has not yet been verified. Whether this population with a mildly elevated PAP would benefit from pulmonary arterial hypertension targeted therapies and other nonpharmaceutical interventions still requires further randomized controlled trials before revising the definition of PH.

## Limitations

First, restricted by the nature of the meta-analysis, we were unable to obtain individual participant data from each study, which might have influenced the precision of the pooled estimates and survival curves. Additionally, the criteria used for repeated RHC varied among studies, which could have led to an overestimation or underestimation of the incidence of progression to PH. Moreover, the time intervals between the first and the second RHCs were not provided in most of the studies, which made it impossible to pool the risk of progression to PH at the same time point. In addition, any retrospective study is subject to selection bias. Three of our included studies were retrospective and might have affected our results. Last but not least, the clinical phenotypes of participants varied among studies. Even though we conducted subgroup and sensitivity analyses, there might still be some effects.

## CONCLUSIONS

Our study revealed that individuals with a mildly elevated PAP (20 mm Hg < mPAP < 25 mm Hg) were at a higher risk of progression to PH and increased mortality (HR, 2.48; 95% CI, 1.69–3.64) than those with a normal PAP. The pooled 1-, 3-, 5-, 7-, and 9-year survival rates in the mildly elevated PAP group were 97.0% (95% CI,

93.7–100.0), 89.4% (95% CI, 84.0–95.2), 77.0% (95% CI, 67.2–88.3), 64.5% (95% CI, 55.4–75.0), and 49.6% (95% CI, 35.5–69.4), respectively. Our results suggest that individuals with a mildly elevated PAP should receive more attention and closer follow-up than they do currently. Further studies concerning the time-to-progression to PH and proper management for individuals with a mildly elevated PAP are needed.

## ARTICLE INFORMATION

Received July 7, 2020; accepted February 1, 2021.

### Affiliations

From the Department of Cardiology, Center for Diagnosis and Management of Pulmonary Vascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases (L.X., Y.Y., B.L., Q.Z., C.X.) and Department of Information Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (B.S.).

### Sources of Funding

This work was supported by the Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine (CAMS-I2M) (grant number 2016-I2M-3-006) and the Capital's Funds for Health Improvement and Research (CFH) (grant number 2020-4-4035).

### Disclosures

None.

### Supplementary Material

Data S1  
Tables S1–S2  
Figures S1–S7

## REFERENCES

- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by:

- Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119. DOI: 10.1093/eurheartj/ehv317.
2. Wood P. *Disease of the Heart and Circulation*. 2nd, revised ed. London: Eyre & Spottiswoode; 1956:828–848.
  3. Chronic cor pulmonale. Report of an expert committee. *World Health Organ Tech Rep Ser*. 1961;213:35.
  4. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34:888–894. DOI: 10.1183/09031936.00145608.
  5. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. DOI: 10.1183/13993003.01913-2018.
  6. Maron BA, Hess E, Maddox TM, Opatowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation*. 2016;133:1240–1248. DOI: 10.1161/CIRCULATIONAHA.115.020207.
  7. Suzuki A, Taniguchi H, Watanabe N, Kondoh Y, Kimura T, Kataoka K, Matsuda T, Yokoyama T, Sakamoto K, Nishiyama O, et al. Significance of pulmonary arterial pressure as a prognostic indicator in lung-dominant connective tissue disease. *PLoS One*. 2014;9:e108339. DOI: 10.1371/journal.pone.0108339.
  8. Takahashi K, Taniguchi H, Ando M, Sakamoto K, Kondoh Y, Watanabe N, Kimura T, Kataoka K, Suzuki A, Ito S, et al. Mean pulmonary arterial pressure as a prognostic indicator in connective tissue disease associated with interstitial lung disease: a retrospective cohort study. *BMC Pulm Med*. 2016;16:55. DOI: 10.1186/s12890-016-0207-3.
  9. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol*. 2017;2:1361–1368. DOI: 10.1001/jamacardio.2017.3882.
  10. Gibbs JSR, Torbicki A. Proposed new pulmonary hypertension definition: is 4 mm(Hg) worth re-writing medical textbooks? *Eur Respir J*. 2019;53:1900197.
  11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. DOI: 10.1136/bmj.b2535.
  12. Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. *Stat Med*. 2002;21:3337–3351. DOI: 10.1002/sim.1303.
  13. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16. DOI: 10.1186/1745-6215-8-16.
  14. Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. *Stat Med*. 2014;33:2521–2537. DOI: 10.1002/sim.6111.
  15. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785–1805. DOI: 10.1177/0962280216669183.
  16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. DOI: 10.1002/sim.1186.
  17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634. DOI: 10.1136/bmj.315.7109.629.
  18. Bae S, Saggarr R, Bolster MB, Chung L, Csuka ME, Derk C, Domsic R, Fischer A, Frech T, Goldberg A, et al. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. *Ann Rheum Dis*. 2012;71:1335–1342. DOI: 10.1136/annrheumdis-2011-200546.
  19. Heresi GA, Minai OA, Tonelli AR, Hammel JP, Farha S, Parambil JG, Dweik RA. Clinical characterization and survival of patients with borderline elevation in pulmonary artery pressure. *Pulm Circ*. 2013;3:916–925. DOI: 10.1086/674756.
  20. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. *Arthritis Rheum*. 2013;65:1074–1084. DOI: 10.1002/art.37838.
  21. Kovacs G, Avian A, Tscherner M, Foris V, Bachmaier G, Olschewski A, Olschewski H. Characterization of patients with borderline pulmonary arterial pressure. *Chest*. 2014;146:1486–1493. DOI: 10.1378/chest.14-0194.
  22. Coghlan JG, Wolf M, Distler O, Denton CP, Doelberg M, Harutyunova S, Marra AM, Benjamin N, Fischer C, Grunig E. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. *Eur Respir J*. 2018;51:1701197. DOI: 10.1183/13993003.01197-2017.
  23. Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, Olschewski H. Mild elevation of pulmonary arterial pressure as a predictor of mortality. *Am J Respir Crit Care Med*. 2018;197:509–516. DOI: 10.1164/rccm.201706-1215OC.
  24. Nemoto K, Oh-ishi S, Akiyama T, Yabuuchi Y, Goto H, Nonaka M, Sasatani Y, Tachi H, Arai N, Ishikawa H, et al. Borderline pulmonary hypertension is associated with exercise intolerance and increased risk for acute exacerbation in patients with interstitial lung disease. *BMC Pulm Med*. 2019;19:167. DOI: 10.1186/s12890-019-0932-5.
  25. Xanthouli P, Jordan S, Milde N, Marra A, Blank N, Egenlauf B, Gorenflo M, Harutyunova S, Lorenz H-M, Nagel C, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. *Ann Rheum Dis*. 2020;79:370–378. DOI: 10.1136/annrheumdis-2019-216476.
  26. Hoeper MM, Humbert M. The new haemodynamic definition of pulmonary hypertension: evidence prevails, finally!. *Eur Respir J*. 2019;53:1900038. DOI: 10.1183/13993003.00038-2019.
  27. Simonneau G, Hoeper MM. The revised definition of pulmonary hypertension: exploring the impact on patient management. *Eur Heart J Suppl*. 2019;21:K4–K8. DOI: 10.1093/eurheartj/suz211.
  28. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e009729. DOI: 10.1161/JAHA.118.009729.
  29. Fisher MR, Forfia PR, Chamera E, Houston-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179:615–621. DOI: 10.1164/rccm.200811-1691OC.
  30. Kaymaz C, Akbal OY, Hakgor A, Tokgoz HC, Tanboga IH, Aktemur T, Turkday S, Tanyeri S, Poci N, Keskin B, et al. Reappraisal of the reliability of Doppler echocardiographic estimations for mean pulmonary artery pressure in patients with pulmonary hypertension: a study from a tertiary centre comparing four formulae. *Pulm Circ*. 2018;8:2045894018762270. DOI: 10.1177/2045894018762270.
  31. D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Corra A, Bossone E, Sarubbi B, Calabrò R, Russo MG, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol*. 2013;168:4058–4062. DOI: 10.1016/j.ijcard.2013.07.005.

# **SUPPLEMENTAL MATERIAL**





Fatality[Title/Abstract]) OR Rates, Case Fatality[Title/Abstract]) OR Mortality,  
Excess[Title/Abstract]) OR Excess Mortalities[Title/Abstract]) OR Mortalities,  
Excess[Title/Abstract]) OR Excess Mortality[Title/Abstract]) OR Decline,  
Mortality[Title/Abstract]) OR Declines, Mortality[Title/Abstract]) OR Mortality  
Declines[Title/Abstract]) OR Mortality Decline[Title/Abstract]) OR Mortality  
Determinants[Title/Abstract]) OR Determinant, Mortality[Title/Abstract]) OR Mortality  
Determinant[Title/Abstract]) OR Determinants, Mortality[Title/Abstract]) OR Mortality,  
Differential[Title/Abstract]) OR Differential Mortalities[Title/Abstract]) OR Mortalities,  
Differential[Title/Abstract]) OR Differential Mortality[Title/Abstract]) OR Age-Specific  
Death Rate[Title/Abstract]) OR Age-Specific Death Rates[Title/Abstract]) OR Death Rate,  
Age-Specific[Title/Abstract]) OR Death Rates, Age-Specific[Title/Abstract]) OR Rate, Age-  
Specific Death[Title/Abstract]) OR Rates, Age-Specific Death[Title/Abstract]) OR Age  
Specific Death Rate[Title/Abstract]) OR Death Rate[Title/Abstract]) OR Death  
Rates[Title/Abstract]) OR Rate, Death[Title/Abstract]) OR Rates, Death[Title/Abstract]) OR  
Mortality Rate[Title/Abstract]) OR Mortality Rates[Title/Abstract]) OR Rate,  
Mortality[Title/Abstract]) OR Rates, Mortality[Title/Abstract]) OR survival[Title/Abstract])  
OR pulmonary hypertension[Title/Abstract]) OR hazard ratio[Title/Abstract]) OR  
""Mortality""[Mesh]) OR ""Survival""[Mesh]) OR ""Hypertension,  
Pulmonary""[Mesh]),248

**Table S1. Quality assessment of the cohort studies included in the meta-analysis using the Newcastle Ottawa Scale (NOS).** A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Study		Selection				Outcome				Total Score
Author	Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	outcome of interest was not present at start of study	Comparability	Assessment of outcome	Adequate follow-up period for outcome	Adequacy of follow up of cohorts	
Bae et al. <sup>18</sup>	2012	*	*	*	*	*	*	*	*	8
Heresi et al. <sup>19</sup>	2013	*	*	*	*	**	*	*	*	9
Valerio et al. <sup>20</sup>	2013	*	*	*	*	*	*	*	*	8
Kovacs et al. <sup>21</sup>	2014	*	*	*	*		*	*	*	7
Coghlan et al. <sup>22</sup>	2018	*	*	*	*		*	*	*	7
Douschan et al. <sup>23</sup>	2018	*	*	*	*		*	*	*	7
Nemoto et al. <sup>24</sup>	2019	*	*	*	*	**	*	*	*	8
Xanthouli et al. <sup>25</sup>	2019	*	*	*	*	**	*	*	*	9

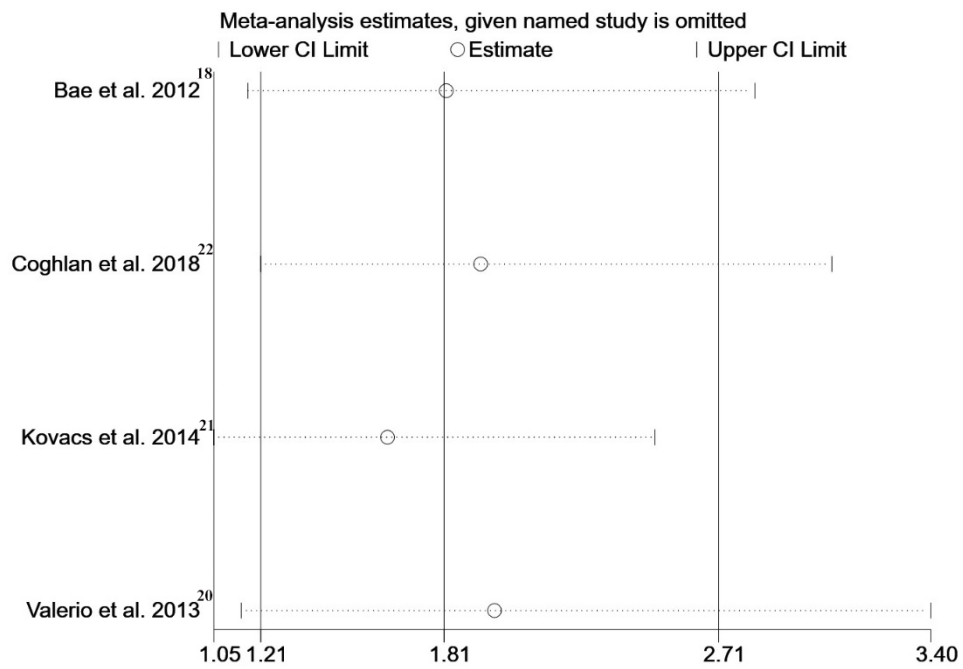


**Table S2. The pooled survival rates and their 95% CIs of the normal PAP, mildly elevated PAP and PH groups.**

Year	The Pooled Survival Rates (95%CI), %		
	Normal PAP	Mildly elevated PAP	PH
1	97.7 (95.4-100.0)	97.0 (93.7-100.0)	87.5 (80.9-94.7)
2	95.9 (93.6-98.4)	92.8 (88.6-97.2)	80.2 (70.8-90.8)
3	93.3 (90.2-96.5)	89.4 (84.0-95.2)	73.0 (63.6-83.9)
4	91.0 (86.2-96.0)	80.7 (72.3-90.1)	65.7 (56.2-76.9)
5	88.8 (83.4-94.6)	77.0 (67.2-88.3)	61.6 (51.9-73.1)
6	85.2 (77.5-93.5)	70.6 (62.4-79.8)	54.8 (47.9-62.6)
7	81.0 (72.3-90.7)	64.5 (55.4-75.0)	50.0 (43.9-57.1)
8	75.5 (68.5-83.3)	58.8 (46.9-73.6)	46.7 (40.4-54.0)
9	74.9 (67.8-82.8)	49.6 (35.5-69.4)	41.3 (34.8-48.9)

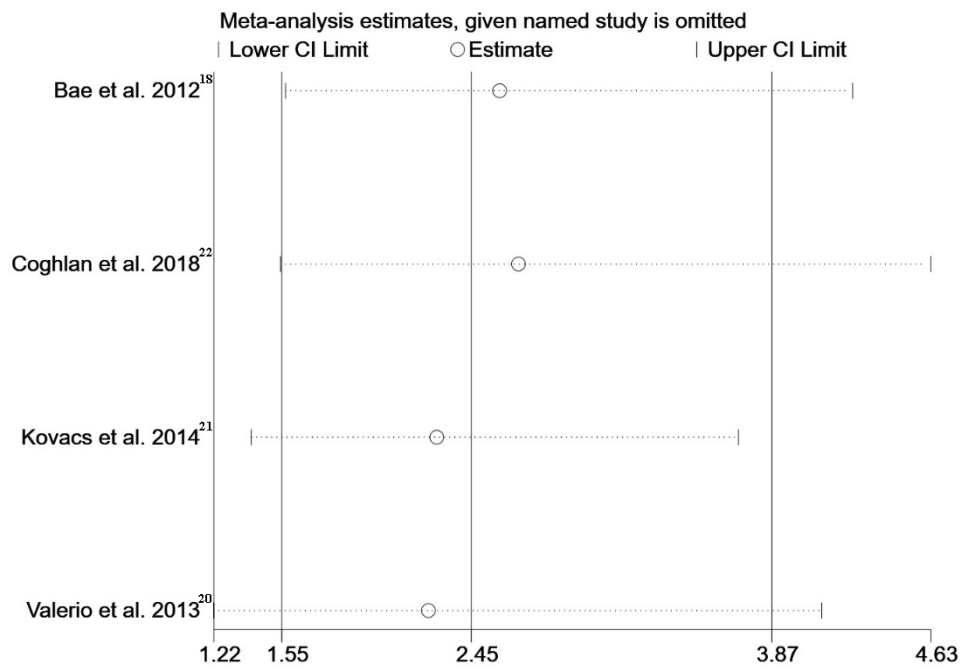
PAP: pulmonary artery pressure; PH: pulmonary hypertension; CI: confidence interval.

**Figure S1. Sensitivity analysis for the meta-analysis of risk of progression to PH in the mildly elevated PAP group versus the normal PAP group when only participants who had repeated RHCs were included in the calculation of the incidence of progression to PH (the analysis shown in Figure 2A).**



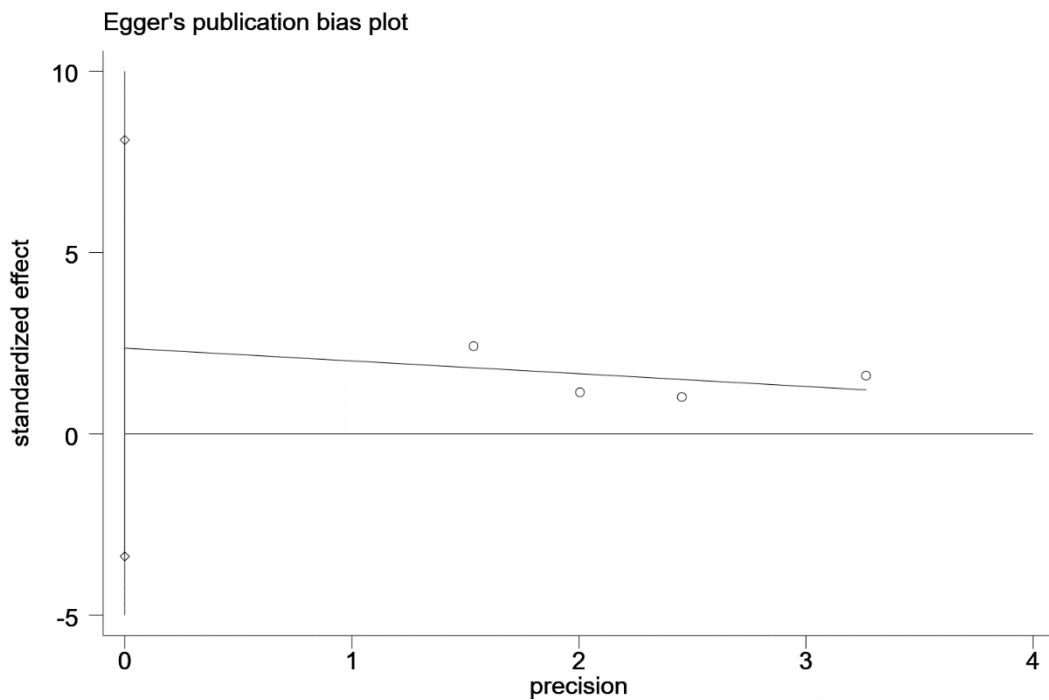
PH: pulmonary hypertension; PAP: pulmonary artery pressure; RHC: right heart catheterization.

**Figure S2. Sensitivity analysis for the meta-analysis of risk of progression to PH in the mildly elevated PAP group versus the normal PAP group when all participants in each group were included in the total number (the analysis shown in Figure 2B).**



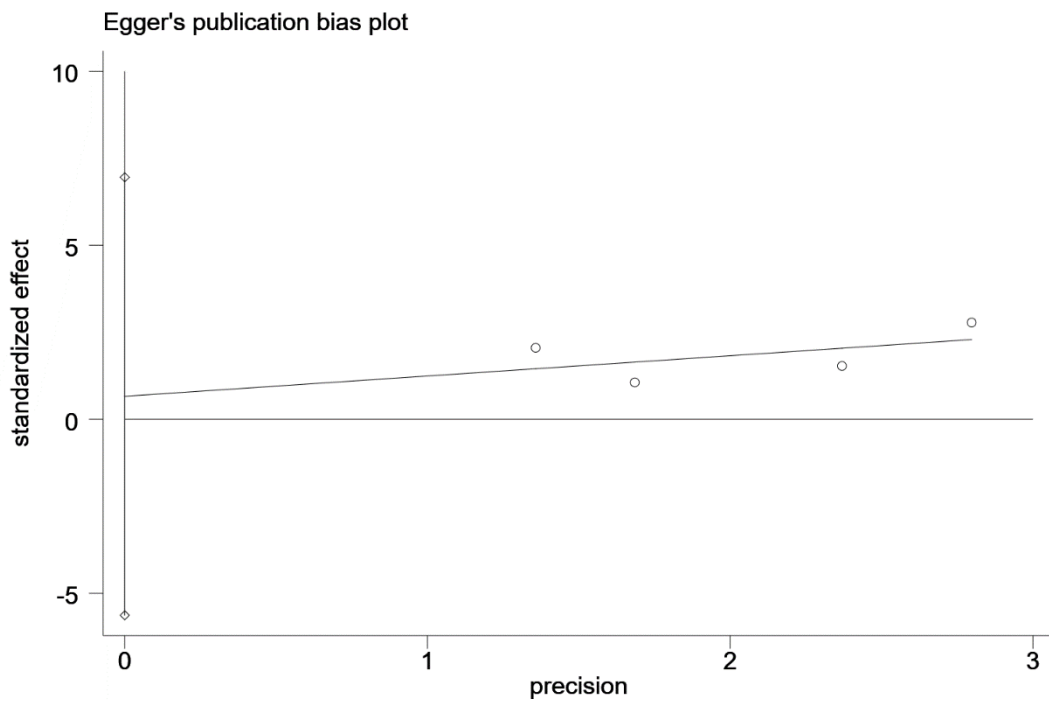
PH: pulmonary hypertension; PAP: pulmonary artery pressure.

**Figure S3. Egger's test for the meta-analysis of risk of progression to PH in the mildly elevated PAP group versus the normal PAP group when only participants who had repeated RHCs were included in the calculation of the incidence of progression to PH (the analysis shown in Figure 2A),  $P=0.218$ .**



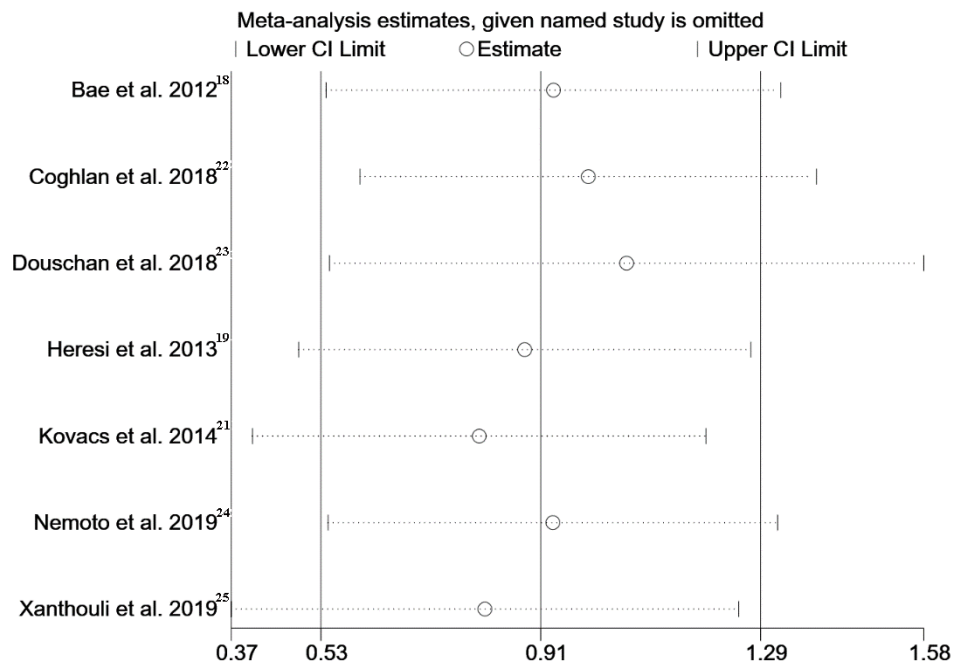
PH: pulmonary hypertension; PAP: pulmonary artery pressure; RHC: right heart catheterization.

**Figure S4. Egger's test for the meta-analysis of risk of progression to PH in the mildly elevated PAP group versus the normal PAP group when all participants in each group were included in the total number (the analysis shown in Figure 2B),  $P=0.695$ .**



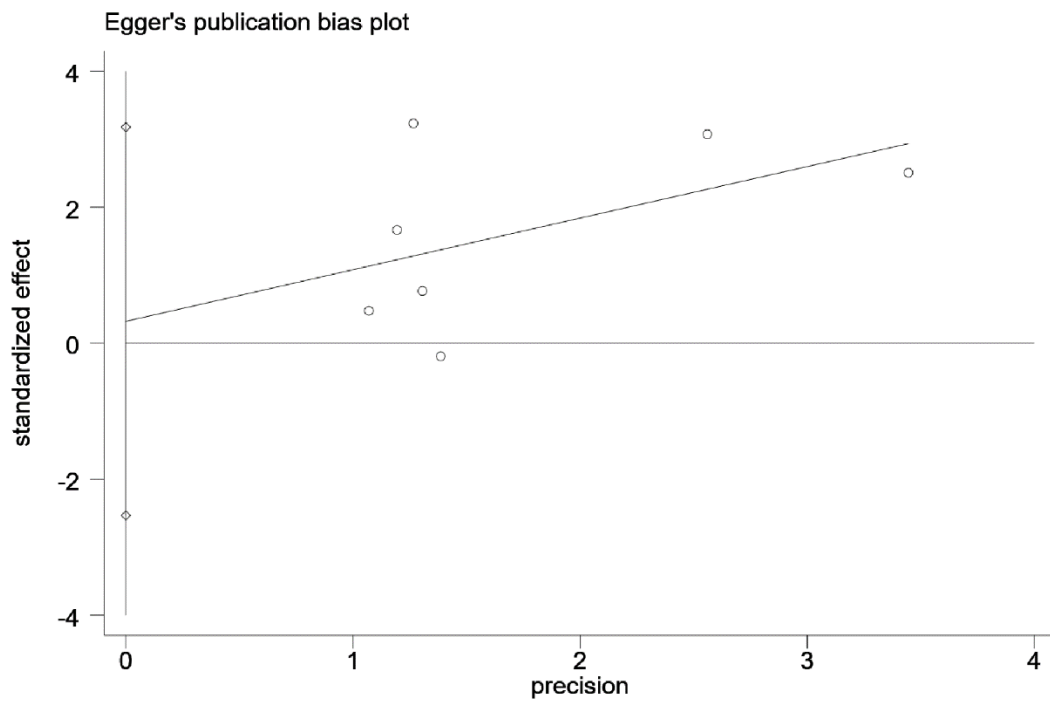
PH: pulmonary hypertension; PAP: pulmonary artery pressure.

**Figure S5. Sensitivity analysis for the meta-analysis of pooled hazard ratio for mortality in the mildly elevated PAP group versus the normal PAP group (the analysis shown in Figure 3).**



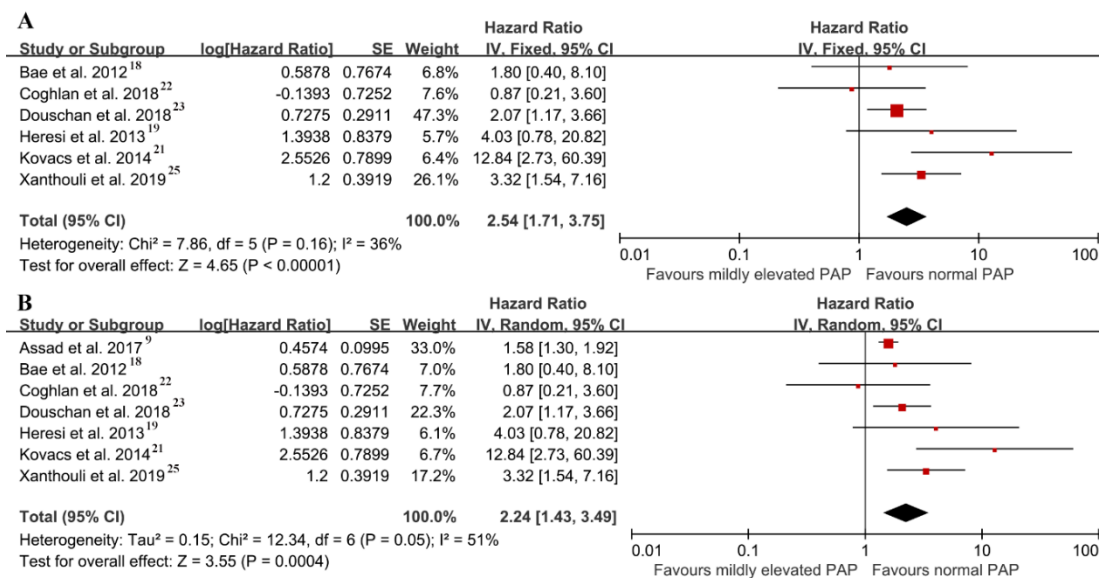
PAP: pulmonary artery pressure.

**Figure S6. Egger's test for the meta-analysis of pooled hazard ratio for mortality in the mildly elevated PAP group versus the normal PAP group (the analysis shown in Figure 3),  $P=0.861$ .**



PAP: pulmonary artery pressure.

**Figure S7. Supplementary analyses of pooled hazard ratio for mortality in the mildly elevated PAP group versus the normal PAP group.**



A: Supplementary analysis when Nemoto's study was excluded (fixed-effects model);

B: Supplementary analysis when Assad's study was added while Nemoto's study was excluded (random-effects model). PAP: pulmonary artery pressure; IV: inverse variance; CI: confidence interval.