Mild Pulmonary Hypertension Is Associated With Increased Mortality: A Systematic Review and Meta-Analysis

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**Background**—Recent studies have demonstrated a continuum in clinical risk related to mean pulmonary artery pressure that begins at >19 mm Hg, which is below the traditional threshold used to define pulmonary hypertension (PH) of 25 mm Hg. Because of the implications on patient diagnosis and prognosis, the generalizability and validity of these data need further confirmation.

**Methods and Results**—Databases were searched from inception through January 31, 2018, to identify studies comparing all-cause mortality between patients with mildly elevated mean pulmonary artery pressure near but <25 mm Hg versus the referent group. The meta-analysis included 15 nonrandomized studies and 16 482 patients (7451 [45.2%] with measured or calculated mean pulmonary artery pressure of 19–24 mm Hg by right heart catheterization [n=6037] and echocardiography [n=1414] [mild PH]). The mean duration of follow-up was 5.2 years. Compared with the referent group, mild PH was associated with an increased risk of mortality (risk ratio, 1.52; 95% confidence interval, 1.32–1.74; P<0.001; I²=47%). Secondary analysis using risk-adjusted time-to-event estimates showed a similar result (hazard ratio, 1.19; 95% confidence interval, 1.09–1.31; P<0.001; I²=42%). The findings were consistent between subgroups of right heart catheterization and echocardiography studies (Pinteraction>0.05). There was evidence of publication bias; however, this did not influence the risk estimate (Duval and Tweedie’s trim and fill adjusted risk ratio, 1.34; 95% confidence interval, 1.15–1.56).

**Conclusions**—The risk of mortality is increased in patients with mild PH, defined as measured or calculated mean pulmonary artery pressure >19 mm Hg. These data emphasize a need for diagnosing patients with mild PH with consideration to enrollment in PH clinical studies investigating pharmacological and nonpharmacological interventions to attenuate clinical risk and improve outcomes. (*J Am Heart Assoc*. 2018;7:e009729. DOI: 10.1161/JAHA.118.009729.)

**Key Words:** echocardiography • mortality • pulmonary artery pressure • pulmonary hypertension • right heart catheterization
Mild Pulmonary Hypertension and Mortality

Kolte et al

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(1) included a clearly defined or identifiable study group with mildly elevated PA pressure and (2) provided the number of events and/or risk estimates for mortality in the mild PH versus referent group. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklists for the protocol of our meta-analysis.7, 8

What Are the Clinical Implications?

- Our data support efforts to update the current definition of PH and affirm the reproducibility of mean pulmonary artery pressure >19 mm Hg as an appropriate and clinically accessible level distinguishing patients with PH from patients without PH.
- Acknowledging this would identify previously undiagnosed patients with PH and provide a framework in clinical practice by which to initiate careful monitoring and efforts to modify risk factors and improve outcomes.

Methods

Data Sources

We searched PubMed (MEDLINE), CINHAL, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from inception through January 31, 2018, for English-language, peer-reviewed publications. The following keywords and Medical Subject Heading terms were used: “hypertension, pulmonary (Medical Subject Heading),” “pulmonary artery hypertension,” “pulmonary arterial hypertension,” “pulmonary artery pressure,” “pulmonary arterial pressure,” “pulmonary artery systolic pressure,” “right ventricular systolic pressure,” “mPAP,” “mortality (Medical Subject Heading),” and “death (Medical Subject Heading).” Reference lists of systematic reviews, meta-analyses, and original studies identified by the electronic search were reviewed to find other potentially eligible studies. The authors declare that all supporting data are available within the article and references.

Study Selection

Studies were included in the meta-analysis if they: (1) included a clearly defined or identifiable study group with mildly elevated PA pressure and (2) provided the number of events and/or risk estimates for mortality in the mild PH versus referent group. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklists for the protocol of our meta-analysis.7, 8

Data Extraction and Quality Assessment

Three physician reviewers (D.K., S.L., and G.C.) evaluated independently study eligibility and quality, and performed data extraction using standardized data collection sheets. Disagreements were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale, which assigns a star for 3 areas of study quality: selection (4 criteria), comparability (1 criterion), and outcome (3 criteria). A study can be awarded a maximum of 1 star for each numbered criterion within the selection and outcome categories. A maximum of 2 stars can be given for comparability. ◆ criterion not satisfied (star not awarded) ★ criterion satisfied (star awarded).

Exposure

The exposure was mild PH. Mild PH was defined as a lower limit mPAP of 19 to 21.5 mm Hg and an upper limit mPAP of ≈25 mm Hg, except some studies in which few patients (n=11 patients) with mPAP >25 mm Hg were also included in the mild PH group because of unavailability of mortality data.

Table 1. Assessment of the Quality of Nonrandomized Studies Included in the Meta-Analysis Using the Newcastle-Ottawa Scale

| Study | Selection | Comparability | Outcome |
|-------|-----------|---------------|---------|
| Valerio et al, 201315 | ★★★★ | ★ | ★★★ |
| Heresi et al, 201311 | ★★★★ | ★ | ★★★ |
| Kovacs et al, 20145 | ★★★★ | ★ | ★★★ |
| Suzuki et al, 201412 | ★★★★ | ★ | ★★★ |
| Maron et al, 20163 | ★★★★ | ★ | ★★★ |
| Takahashi et al, 201613 | ★★★★ | ★ | ★★★ |
| Douschan et al, 20184 | ★★★★ | ★ | ★★★ |
| Assad et al, 20172 | ★★★★ | ★ | ★★★ |
| Abramson et al, 199214 | ★★★★ | ★ | ★★★ |
| Kjaergaard et al, 200715 | ★★★★ | ★ | ★★★ |
| Shalaby et al, 200816 | ★★★★ | ★ | ★★★ |
| Lam et al, 200917 | ★★★★ | ★ | ★★★ |
| Damy et al, 201018 | ★★★★ | ★ | ★★★ |
| Cabrita et al, 201319 | ★★★★ | ★ | ★★★ |
| Choudhary et al, 201420 | ★★★★ | ★ | ★★★ |

Study quality was evaluated using the Newcastle-Ottawa Scale, which assigns a star for 3 areas of study quality: selection (4 criteria), comparability (1 criterion), and outcome (3 criteria). A study can be awarded a maximum of 1 star for each numbered criterion within the selection and outcome categories. A maximum of 2 stars can be given for comparability. ◆ criterion not satisfied (star not awarded) ★ criterion satisfied (star awarded).
Table 2. Characteristics of Studies Included in the Meta-Analysis

| Study               | Study Design         | Data Source                        | Study Population                  | N*  | RHC or Echocardiographic Index | Study Groups                               | Follow-Up Duration, y |
|---------------------|----------------------|------------------------------------|----------------------------------|-----|-------------------------------|---------------------------------------------|-----------------------|
| Valerio et al, 2013 | Retrospective        | The Royal Free Hospital Pulmonary Hypertension Database | Systemic sclerosis               | 199 | RHC mPAP                       | mPAP 21–24 mm Hg                            | 5                     |
| Heresi et al, 2013  | Retrospective        | Cleveland Clinic Pulmonary Hypertension Registry | Cardiac disease (16.2%), pulmonary disease (29.7%), CTD (18.9%), other (6.1%) | 82  | RHC mPAP                       | mPAP 21–24 mm Hg                            | 5                     |
| Kovacs et al, 2014  | Retrospective        | Single center                       | Cardiac disease (23%), pulmonary disease (23%), CTD (43%) | 141 | RHC mPAP                       | mPAP 21–24 mm Hg                            | 4.2                   |
| Suzuki et al, 2014  | Retrospective        | Single center                       | LD-CTD                           | 100 | RHC mPAP                       | mPAP ≥20 mm Hg                              | 5                     |
| Maron et al, 2016   | Retrospective        | VA-CART                             | US Veterans (HF [38.7%], pulmonary disease [27.8%], CTD [4.6%])            | 9237| RHC mPAP                       | mPAP 19–24 mm Hg                            | 5                     |
| Takahashi et al, 2016 | Retrospective        | Single center                       | CTD-ILD                          | 68  | RHC mPAP                       | mPAP ≥20 mm Hg                              | 7                     |
| Douschan et al, 2018 | Retrospective Prospective | Single center                                | Patients with cardiopulmonary disease with unexplained dyspnea and/or at risk of PH referred for RHC | 257 | RHC mPAP                       | mPAP 20.6–24.9 mm Hg                          | 5                     |
| Assad et al, 2017   | Retrospective        | Single center                       | Patients referred for RHC (HF [32.1%], pulmonary disease [14.3%], CTD [2.0%]) | 1659| RHC mPAP                       | mPAP 19–24 mm Hg                            | 5                     |
| Abramson et al, 1992 | Retrospective        | Single center                       | Ischemic or idiopathic dilated cardiomyopathy | 87  | Echocardiographic TRV           | TRV 2.6–3.0 m/s (mPAP 21.5–27.0 mm Hg)      | 2.3                   |
| Kjaergaard et al, 2007 | Post hoc analysis of RCT | ECHOS                              | Heart failure                     | 194 | Echocardiographic RVSP         | RVSP 31–38 mm Hg (mPAP 20.9–25.2 mm Hg)     | 4                     |
| Shalaby et al, 2008  | Retrospective        | Multicenter                         | CRT recipients                   | 176 | Echocardiographic PASP         | PASP 30–44 mm Hg (mPAP 20.3–28.5 mm Hg)     | 1.6                   |
| Lam et al, 2009     | Prospective          | Olmsted County                      | Random sample of the Olmsted County population ≥45 y | 1234| Echocardiographic PASP         | PASP 30–32 mm Hg (mPAP 20.1–21.5 mm Hg)     | 8                     |

Continued
separately for these patients (Table 2). For echocardiography studies that reported only the tricuspid regurgitation velocity or gradient (n=3), pulmonary artery systolic pressure (PASP) was calculated as tricuspid regurgitation gradient plus an assumed right atrial pressure of 5 mm Hg. This approach has been used in prior studies.\textsuperscript{17,20–22} mPAP was calculated using the following formula: \((0.61 \times \text{PASP}) + 2 \text{ mm Hg}\).\textsuperscript{21}

**Outcomes**

The primary outcome of interest was all-cause mortality.

**Statistical Analysis**

Random-effects models of DerSimonian and Laird were used to calculate pooled risk ratio (RR) and corresponding 95% confidence interval (CI) for mortality. For studies that reported risk-adjusted time-to-event estimates (adjusted hazard ratio [HR]) and the corresponding 95% CI, we performed secondary analyses using the generic inverse variance method to estimate pooled HR using a random-effects model. Secondary analyses were also performed using fixed-effect models. Heterogeneity was assessed using the Higgins I\textsuperscript{2} statistic, with values <25% and >75% considered indicative of low and high heterogeneity, respectively. Pooled estimates were calculated for all studies as well as the a priori defined subgroups of echocardiography and RHC studies. Publication bias was assessed visually by asymmetry in funnel plots and formally using Egger’s regression test and the Begg-Mazumdar rank correlation test. To assess the impact of publication bias on the risk estimate, we used Duval and Tweedie’s Trim and Fill as well as cumulative meta-analysis (after sorting the included studies from largest to smallest size).\textsuperscript{24,25}

All tests were 2 tailed, with a \(P<0.05\) considered statistically significant. Analyses were performed using the Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark) and Comprehensive Meta-Analysis Version 3.0 (Biostat, Englewood, NJ).

**Results**

The database search yielded 11 184 articles. After removing duplicates, 7920 articles were screened at the title/abstract level and 7880 were excluded for various reasons (eg, systematic reviews, case reports, studies that included only patients with known PH, and studies with no data on mortality). Forty full-text articles were assessed for eligibility (Figure 1). Fifteen (8 RHC and 7 echocardiography) studies were included in the meta-analysis.\textsuperscript{2–5,10–20} The characteristics of the included studies are shown in Table 2. Of the 15 studies, 12 were retrospective, 1 was prospective, 1 was ambispective, and 1 was a post hoc analysis of a randomized
controlled trial. The 15 studies included 16,482 patients (7,451 [45.2%] with mild PH [6,037 diagnosed by RHC, and 14,141 diagnosed by echocardiography] and 9,031 [56.4%] in the referent group). The mean duration of follow-up weighted for the sample size was 5.2 years. The studies included in the meta-analysis encompassed a broad spectrum of the patient population at risk of PH, including those with cardiac, pulmonary, connective tissue, and hematologic diseases. Table 3 shows the characteristics of patients in the 2 groups in the included studies. The mean/median age of patients ranged from 41 to 77 years, and the proportion of women ranged from 3.5% to 90%.

Compared with the referent group, mild PH was associated with significantly increased risk of mortality (random-effects model: RR, 1.52; 95% CI, 1.32–1.74; P<0.001; $I^2=47$%; fixed-effect model: RR, 1.34; 95% CI, 1.27–1.43; P<0.001; $I^2=47$%) (Figures 2 and 3). Secondary analysis using risk-adjusted time-to-event estimates showed results consistent with the direction of primary finding (random-effects model: HR, 1.19; 95% CI, 1.09–1.31; P<0.001; $I^2=42$%; fixed-effect model: HR, 1.17; 95% CI, 1.11–1.23; P<0.001; $I^2=42$%) (Figures 4 and 5). The findings were consistent between RHC and echocardiography studies ($P_{\text{interaction}}>0.05$). The results were unchanged in a sensitivity analysis, excluding 2 studies that accounted for >70% of the patients (RR, 1.64; 95% CI, 1.36–1.97; P<0.001; $I^2=47$%; and HR, 1.22; 95% CI, 1.07–1.39; $P=0.004$; $I^2=45$%)$^{3,20}$

There was evidence of publication bias on the basis of asymmetry in the funnel plot as well as results of the Egger’s regression test and the Begg-Mazumdar rank correlation test (Figure 6). However, the presence of publication bias did not influence the risk estimate and overall result (Duval and Tweedie’s Trim and Fill adjusted RR, 1.34; 95% CI, 1.15–1.56) (Figure 7). Similarly, cumulative meta-analysis demonstrated that the RR had stabilized with the inclusion of the larger studies and did not shift significantly with the addition of smaller studies, suggesting that the inclusion of smaller studies did not introduce bias (Figure 8).

**Discussion**

Data from this study address controversy on the mPAP level required to capture clinical risk in patients referred for RHC or...
Table 3. Baseline Characteristics of Patients in the Included Studies

| Characteristics | Valerio et al<sup>10</sup> | Heresi et al<sup>11</sup> | Kovacs et al<sup>5</sup> | Suzuki et al<sup>12</sup> | Maron et al<sup>3</sup> | Takahashi et al<sup>13</sup> | Douschan et al<sup>15</sup> | Assad et al<sup>2</sup> |
|-----------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                 | (Ref. Mild PH) (n=136)   | (Ref. Mild PH) (n=63)    | (Ref. Mild PH) (n=109)   | (Ref. Mild PH) (n=32)    | (Ref. Mild PH) (n=18)    | (Ref. Mild PH) (n=4207)  | (Ref. Mild PH) (n=109)   | (Ref. Mild PH) (n=32)    |
| Age, y          | 51±17                    | 59±14                    | 57.3±12.5                | 65.8±12.5                | 64.3±8.3                 | 67.9±6.4                 | 64.3 (59.6–73.0)         | 65.2 (60.3–73.5)         |
| Female          | 88.2                     | 90                       | 37.8                     | 27.8                     | 3.5                      | 3.4                      | 58.6                     | 43.8                     |
| Race (nonwhite) |                          |                          | 20.9                     | 20.7                     |                          |                          | 10                       | 15                       |
| BMI, kg/m<sup>2</sup> |                |                          | 25.6±4.5                 | 27.5±5.9                 | 23.5±3.8                 | 24.8±4.6                 | 28 (24.6–31.5)           | 29.6 (26–34)             |
| Hypertension    |                          |                          |                          |                          | 82.3                     | 86                       |                          |                          |
| DM              |                          |                          |                          |                          | 33.4                     | 40.6                     |                          |                          |
| Smoking         |                          |                          | 58.5                     | 72.2                     |                          |                          | 37.9                     | 56.3                     |
| Obesity         | 29.4                     | 30                       | 33.7                     | 47.3                     |                          |                          | 29                       | 43                       |
| CAD             |                          |                          | 78.6                     | 82.4                     |                          |                          | 72                       | 76                       |
| Atrial fibrillation |                        |                          |                          |                          |                          |                          |                          |                          |
| COPD            |                          |                          | 23                       | 30.8                     |                          |                          | 5                        | 14                       |
| ILD             |                          |                          | 100                      | 100                      | 0.4                      | 0.7                      |                          |                          |
| OSA             |                          |                          | 7.3                      | 10.2                     |                          |                          | 5                        | 10                       |
| Anemia          |                          |                          |                          |                          | 36                       | 44                       |                          |                          |
| Heart failure   |                          |                          | 34.1                     | 42.7                     |                          |                          | 25                       | 39                       |
| CTD             |                          |                          | 100                      | 100                      | 4.9                      | 4.3                      | 2                        | 2                        |
| CKD             |                          |                          |                          |                          | 17.6                     | 21.2                     |                          |                          |
| HIV             |                          |                          | 0.5                      | 0.3                      |                          |                          |                          |                          |
| Sickle cell disease |                    |                          | 0                        | 0                        |                          |                          |                          |                          |
| Cirrhosis       |                          |                          | 9.7                      | 8.1                      |                          |                          |                          |                          |
|                 | Abramson et al<sup>14</sup> | Kjaergaard et al<sup>13</sup> | Shalaby et al<sup>16</sup> | Lam et al<sup>17</sup> | Damy et al<sup>18</sup> | Cabrilla et al<sup>19</sup> | Choudhary et al<sup>20</sup> |                  |
|                 | (Ref. Mild PH) (n=80)    | (Ref. Mild PH) (n=7)     | (Ref. Mild PH) (n=97)    | (Ref. Mild PH) (n=86)    | (Ref. Mild PH) (n=956)   | (Ref. Mild PH) (n=212)   | (Ref. Mild PH) (n=86)    |                  |
| Age, y          | 66.7                     | 72 (65–81)               | 77 (68–81)               | 65±12                    | 65±12                    | 73±10                    | 77±9                     | 41±12                    |
| Female          | 15                       | 36                       | 41                       | 6                        | 16                       | 36                       | 55                       | 35.6                     |
| Race (nonwhite) |                          |                          | 4                        | 6                        |                          |                          |                          |                          |

Continued
|                        | Abramson et al\textsuperscript{14} | Kjaergaard et al\textsuperscript{15} | Shalaby et al\textsuperscript{16} | Lam et al\textsuperscript{17} | Damy et al\textsuperscript{18} | Cabrita et al\textsuperscript{19} | Choudhary et al\textsuperscript{20} |
|------------------------|------------------------------------|------------------------------------|------------------------------------|--------------------------------|---------------------------------|---------------------------------|----------------------------------|
| Ref.                   | Ref.                               | Ref.                               | Ref.                               | Ref.                           | Ref.                            | Ref.                            | Ref.                             |
| (n\textsuperscript{=80}) | (n\textsuperscript{=7})             | (n\textsuperscript{=97})           | (n\textsuperscript{=86})           | (n\textsuperscript{=90})       | (n\textsuperscript{=278})      | (n\textsuperscript{=212})       | (n\textsuperscript{=795})        |
| **BMI, kg/m\textsuperscript{2}** | 26 (23–29) | 26 (21–28) | 27 ± 5 | 26 ± 6 | 25 ± 5 | 24 ± 6 | 30.5 ± 6.6 | 31.8 ± 6.9 |
| **Hypertension**       | 18                                 | 30                                 | 71                                 | 60                             | 42.9                            | 50                              | 52.7                             | 65.6 |
| **DM**                 | 10                                 | 12                                 | 47                                 | 39                             | 9.9                             | 16                              | 20.2                             | 24.9 |
| **Smoking**            | 29                                 | 29                                 | 22                                 | 18                             | 15.6                            | 12                              | 29.3                             | 34.4 |
| **Obesity**            | 41                                 | 43                                 |                                    |                                |                                 |                                 | 46.1                             | 54.2 |
| **CAD**                |                                    |                                    |                                    |                                |                                 |                                 | 6.1                              | 9    |
| **Atrial fibrillation**|                                    |                                    | 34                                 | 49                             | 44.5                            | 55                              |                                   |      |
| **COPD**               | 18                                 | 24                                 | 34                                 | 27                             | 43                              | 50                              |                                   |      |
| **ILD**                |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **OSA**                |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **Anemia**             |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **Heart failure**      | 76                                 | 68                                 |                                    |                                |                                 | 1.4                             | 3.1                              |      |
| **CTD**                |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **CKD**                | 5                                  | 9                                  |                                    |                                |                                 |                                 |                                   |      |
| **HIV**                |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **Sickle cell disease**|                                    |                                    |                                    |                                |                                 |                                 |                                   |      |
| **Gastroisis**         |                                    |                                    |                                    |                                |                                 |                                 |                                   |      |

Continuous variables are presented as mean±SD or median (interquartile range), and categorical variables are presented as percentages. Empty cells indicate data not available. BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CTD, connective tissue disease; DM, diabetes mellitus; ILD, interstitial lung disease; OSA, obstructive sleep apnea; PH, pulmonary hypertension; Ref., referent group.
echocardiography using a meta-analysis, which is the optimal research tool for determining aggregate risk across study populations.\textsuperscript{26} We report that mildly elevated PA pressures, estimated by either echocardiography or invasive catheterization, are associated with 19\% increased risk of mortality over 5 years. Despite analyzing both community-based and referral populations with varying underlying comorbidities, there was only mild statistical heterogeneity of risk across the included studies. This suggests a truly generalizable association between mild PH and mortality. These data support the ongoing efforts to identify optimal cutoffs for hemodynamic parameters in PH, including pulmonary arterial hypertension, to identify at-risk populations earlier.\textsuperscript{27}

A notable finding of this study is the consistent association between mild PH and increased mortality when PA pressure was measured by either RHC or echocardiography. Although RHC is the only test available to diagnose PH, echocardiography is the preferred screening test for at-risk patients.\textsuperscript{6} Current guidelines recommend further evaluation of patients for PH if the tricuspid regurgitation velocity is $>2.9$ m/s (corresponding to PASP $>40$ mm Hg).\textsuperscript{6} However, our findings demonstrate that PA pressure assessed by echocardiography, at levels considered currently to be below the range of clinical significance (tricuspid regurgitation velocity $>2.5$ m/s, PASP $>35$ mm Hg) across both community-based and referral populations, is, in fact, a valid predictor of mortality. Thus, our data suggest that when PA pressure can be measured by echocardiography, this is an effective screening tool for detecting patients at risk for mild PH who may benefit from further evaluation, close follow-up, and risk reduction interventions.\textsuperscript{17,20} Nonetheless, a recent study in patients with PH (mPAP $>25$ mm Hg) demonstrated modest correlation and poor agreement between echocardiography-derived and RHC-measured PASP and mPAP.\textsuperscript{28} Fisher et al\textsuperscript{29} showed that approximately half of the cases of PASP overestimation are related solely to right atrial pressure overestimation by echocardiography. Thus, although we used an assumed right atrial pressure of $5$ mm Hg for calculating PASP in echocardiography studies that reported only tricuspid regurgitation velocity or gradient, concern for

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**Figure 2.** Association between mild pulmonary hypertension (PH) and mortality (random-effects model). Studies included in this analysis are Valerio et al,\textsuperscript{10} Heresi et al,\textsuperscript{11} Kovacs et al,\textsuperscript{5} Suzuki et al,\textsuperscript{12} Maron et al,\textsuperscript{3} Takahashi et al,\textsuperscript{13} Douschan et al,\textsuperscript{4} Assad et al,\textsuperscript{2} Abramson et al,\textsuperscript{14} Kjaergaard et al,\textsuperscript{15} Shalaby et al,\textsuperscript{16} Lam et al,\textsuperscript{17} Damy et al,\textsuperscript{18} Cabrita et al,\textsuperscript{19} and Choudhary et al.\textsuperscript{20} CI indicates confidence interval; M-H, Mantel-Haenszel; RHC, right heart catheterization.

| Study or Subgroup | Mild PH | Normal | Risk Ratio | Risk Ratio |
|-------------------|---------|--------|------------|------------|
|                   | Events  | Total  | Weight     | M-H, Random, 95\% CI |
| 1.3.1 RHC         |         |        |            | Year       |
| Valerio et al. 2013 | 8       | 63     | 14         | 2.5\% |
| Heresi et al. 2013 | 6       | 31     | 1          | 51\% 0.4\% |
| Kovacs et al. 2014 | 6       | 32     | 4          | 109\% 1.3\% |
| Suzuki et al. 2014 | 9       | 18     | 15         | 82\% 3.8\% |
| Maron et al. 2016 | 1504    | 5030   | 980        | 4207\% 20.6\% |
| Takahashi et al. 2016 | 10 | 16      | 15         | 58\% 4.5\% |
| Douschan et al. 2017 | 17     | 64     | 24         | 193\% 4.9\% |
| Assad et al. 2017  | 196     | 783    | 149        | 876\% 15.4\% |
| Subtotal (95\% CI) | 6037    | 9712   | 53.5\%     | 1.78 [1.38, 2.29] |
| Total events      | 1756    | 1202   |            |            |
| Heterogeneity: Tau$^2 = 0.06$; Chi$^2 = 22.15$, df = 7 (P = 0.002); P = 68\% |
| Test for overall effect: Z = 4.44 (P < 0.0001) |

| 1.3.2 Echo        |         |        |            | M-H, Random, 95\% CI |
| Abramson et al. 1992 | 2     | 7      | 14         | 80\% 1.1\% |
| Kjaergaard et al. 2007 | 49    | 97     | 44         | 97\% 11.0\% |
| Shalaby et al. 2008 | 16      | 90     | 10         | 86\% 3.1\% |
| Lam et al. 2009   | 28      | 278    | 62         | 956\% 7.1\% |
| Damy et al. 2010  | 55      | 99     | 88         | 212\% 13.3\% |
| Cabrita et al. 2013 | 8   | 48     | 8          | 116\% 2.1\% |
| Choudhary et al. 2014 | 48  | 795    | 70         | 1772\% 8.9\% |
| Subtotal (95\% CI) | 1414    | 3319   | 46.5\%     | 1.36 [1.18, 1.58] |
| Total events      | 206     | 296    |            |            |
| Heterogeneity: Tau$^2 = 0.00$; Chi$^2 = 4.40$, df = 6 (P = 0.62); P = 0\% |
| Test for overall effect: Z = 4.12 (P < 0.0001) |

| Total (95\% CI) | 7451    | 9031   | 100.0\%    | 1.52 [1.32, 1.74] |
| Total events    | 1962    | 1498   |            |            |
| Heterogeneity: Tau$^2 = 0.02$; Chi$^2 = 26.44$, df = 14 (P = 0.02); P = 47\% |
| Test for overall effect: Z = 5.91 (P < 0.00001) |
| Test for subgroup differences: Chi$^2 = 3.17$, df = 1 (P = 0.08); P = 68.4\% |

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misclassification remains when relying on echocardiography alone for the diagnosis of PH (or mild PH). Furthermore, the effect sizes of mild PH, as estimated by RHC and echocardiography on mortality, although different, are not directly comparable to suggest different clinical recommendations for patients with mild PH diagnosed via these 2 modalities.

Our meta-analysis, together with findings from the individual studies analyzed, provides comprehensive evidence in support of defining PH in contemporary and clinically relevant terms. Specifically, these data affirm the reproducibility across selected and unselected populations for mPAP > 19 mm Hg as an appropriate and clinically accessible level distinguishing patients with PH from patients without PH. Acknowledging this would identify previously undiagnosed patients with PH and provide a framework in clinical practice by which to initiate careful monitoring and efforts to modify risk factors. These patients should also be considered for enrollment in ongoing and future PH clinical trials investigating pharmacological and nonpharmacological (eg, exercise program and weight loss) interventions to attenuate risk and improve outcomes in this population. Indeed, randomized controlled trials examining the efficacy and safety of established pulmonary artery hypertension therapies in patients with mild mPAP are already underway.

Limitations

First, this is a meta-analysis of nonrandomized studies and has all limitations of observational data, including selection bias and unmeasured confounding variables. Second, restricted by the nature and characteristics of this meta-analysis, we did not have access to patient-level data. Therefore, we are unable to characterize covariates that modulate risk within the mild PH group, such as elevated pulmonary vascular resistance. This is a particularly important limitation, because the addition of pulmonary vascular resistance to analysis of cardiopulmonary hemodynamic data is needed to exclude mildly increased PA pressure that is

Figure 3. Association between mild pulmonary hypertension (PH) and mortality (fixed-effect model). Studies included in this analysis are Valero et al,10 Heresi et al,11 Kovacs et al,9 Suzuki et al,14 Maron et al,3 Takahashi et al,13 Douschan et al,4 Assad et al,2 Abramson et al,14 Kjaergaard et al,15 Shalaby et al,16 Lam et al,17 Damy et al,18 Cabrita et al,19 and Choudhary et al. Cl indicates confidence interval; M-H, Mantel-Haenszel; RHC, right heart catheterization.
physiologic in the setting of increased cardiac output or cor pulmonale from a diagnosis of mild PH. Similarly, although we performed analysis using adjusted HRs, the precise impact of comorbidities cannot be readily assessed across studies in the absence of patient-level data. Third, the possibility that differences in cardiopulmonary comorbidities and not PA...
pressure were responsible for differences in clinical outcome in this group cannot be excluded. However, pooled HRs derived from risk-adjusted time-to-event estimates demonstrated a 19% increased risk of mortality in patients with mild PH compared with the referent group. Fourth, the association of mild PH and mortality in the subgroups of patients with cardiac, pulmonary, hematologic, or connective tissue disease could not be determined because of unavailability of mortality data in these different subgroups. Last, the mortality estimates are based on an mPAP cutoff of \( \approx 19 \) to 20 mm Hg that was selected from prior published data, although a lower cutoff may yield slightly different results.

**Conclusion**

In a meta-analysis of 15 nonrandomized studies, mild PH was associated with an increased risk of all-cause mortality compared with the referent group. This finding was consistent...
in the subgroups of RHC and echocardiography studies. These
data add to the growing body of literature on the hemody-
namic range and prognostic significance of mild PH. Overall,
our data affirm efforts to update the current PH definition
and provide definitive data in support of future clinical trials
to improve outcome in this vulnerable patient subgroup.

Disclosures
None.

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