

The Prognostic Significance of the Alterations of Cardiovascular Hemodynamics in Patients With Pulmonary Arterial Hypertension: A Meta-regression Analysis of Randomized Controlled Trials

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Research

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Abstract

Background:

Hemodynamic assessment in patients with pulmonary arterial hypertension (PAH) is essential for risk stratification and pharmacological management. However, the prognostic value of the hemodynamic changes after treatment is less well established.

Objectives:

We investigated the prognostic impacts of the changes in hemodynamic indices, including mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), right atrial pressure (RAP) and cardiac output index (CI). We conducted this systematic review with meta-regression analysis on existing clinical trials.

Methods:

We searched and identified all relevant randomized controlled trials from multiple databases. An analogous R^2 index was used to quantify the proportion of variance explained by each predictor in the association with PAH patients' prognosis. A total of 20 trials and 3,263 individuals were enrolled.

Results:

The changes in mPAP, PVR, RAP and CI were all significantly associated with the change in 6MWD (Δ 6MWD). The change in mPAP was with the highest explanatory power for Δ 6MWD (R^2 analog=0.739). Additionally, the changes in mPAP, PVR and CI were independently predictive of adverse clinical events. The change in mPAP had the highest explanatory power for the clinical events (R^2 analog =0.911). Furthermore, the change in PVR was with the highest explanatory power for total mortality of PAH patients (R^2 analog =0.594).

Conclusion:

Hemodynamic changes after treatment, including mPAP, PVR, CI and RAP, were significantly associated with adverse clinical events or mortality in treated PAH patients. It is recommended that further studies be conducted to evaluate the changes in hemodynamic indices to guide drug titration.

Trial registration number: PROSPERO; No.: CRD42019125157; URL: <https://www.crd.york.ac.uk/PROSPERO/> (Date of registration: 14/03/2019)

Introduction

Although there have been significant advances of pharmacological therapies in the past decade, pulmonary arterial hypertension (PAH) remains a progressive and fatal disease. The 2015 ESC/ERS

Pulmonary Hypertension guidelines have strongly recommended comprehensive screening protocols for high-risk populations and subsequent early intervention. [1] In addition, upfront combination therapy and aggressive medical escalations were also suggested in the treatment of PAH patients. Given the variable long-term survival rates between patients, risk stratification has been endorsed in the clinical management of PAH. While the European guideline has proposed a risk prediction algorithm, comprising 9 measures [1], Benza et al. also computed a risk score calculator for 1-year survival in 504 individuals from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry). [2] However, the routine clinical application was limited due to the complexity of these predictive algorithms. Hoeper et al. therefore validated a simplified risk stratification strategy for mortality, including World Health Organization functional class (WHO Fc), 6-min walking distance (6WMD), brain natriuretic peptide or its N-terminal fragment, right atrial pressure (RAP) and cardiac index (CI) in a cohort of 1,588 PAH patients. [3] Despite the existing prediction models, the prognostic significance of the changes of these parameters during treatment for patients with PAH have not been systematically examined.

The pathophysiology of PAH is characterized by increased pulmonary vascular resistance (PVR) at the beginning, followed by elevated pulmonary arterial pressure (PAP), decreased cardiac output and increased RAP. The published data have supported that the hemodynamic indices, including PVR, cardiac output and RAP were predictive of clinical outcomes among PAH patients. [4, 5] However, it remains debated whether the changes in the hemodynamic parameters are predictive of clinical outcomes. Although the non-invasive variables have been widely recommended to assess the risks in PAH, the mismatch between pulmonary resistance and RV contractility remains the main cause of mortality. We therefore conducted a systemic review to investigate the prognostic values of the changes in hemodynamic indices in PAH.

Methods

Search strategy

All relevant studies from EMBASE, MEDLINE, Cochrane Library, and PubMed through May 2020, were searched and identified using the following keywords and the Medical Subject Headings (MeSH) terms: Pulmonary hypertension, Pulmonary Arterial Hypertension, PH and PAH. No language restrictions were applied on any of these searches. We limited our searches to randomized controlled trials (RCTs) that compare either the effects of any of the 9 drug classes (ERA, PDE5, PDGFR, Prostacyclin, Prostacyclin plus ERA, Rho-kinase, TXSI/TXRA, sGC) with placebo or the effects between 2 drug classes.

Inclusion and exclusion criteria

Studies were eligible only if they reported any or all of the following outcomes: hospitalization for PAH, death due to PAH, total mortality, all adverse events of hospitalization and all-cause death, and exercise capacity (as measured by a 6-minute walk distance, 6MWD). Additional studies were retrieved by manually checking the reference lists of reviews, meta-analyses, and original publications. Finally, we excluded RCT studies investigating pediatric PAH (age < 12) and those did not report sequential

measurements of cardiopulmonary hemodynamics, including mPAP, PVR, RAP, CI, or pulmonary artery wedge pressure (PAWP). For studies with more than one publication, only the studies with the largest number of participants in the trial were retained. Of 601 articles identified by the initial search, 37 were retrieved for more detailed evaluation, and 20 trials were included in the study. The selection process of the literature search is shown in Fig. 1. The International prospective register of systematic reviews (PROSPERO) registration number of this study is CRD42019125157 (URL:

<https://www.crd.york.ac.uk/PROSPERO/>).

Data extraction

In order to calculate the unit consistency, the standard deviations were all converted to standard error (divided by the square root of the sample number), 95% confidence intervals were converted to standard errors (= [upper limit-lower limit]/3.92). If the actual data is not presented in the study and only graphically, we use WebPlotDigitizer version 4.1 [6] to interpolate the approximate data. In addition, for studies reporting PVR in Woods units, we multiplied this value by 80 to obtain the PVR in dyne-sec/cm⁵.

Data were extracted from papers by 2 investigators (W. Y. Yeh and C. J. Huang) independently, and differences in data extraction were resolved through discussions with the third investigator (H.M. Cheng).

Quality assessment

The quality of studies was assessed by using the Cochrane Risk of Bias tool to assess the quality of these randomized controlled trials. The following 7 main domains are used in the assessment: (1) Bias arising from the randomization; (2) Bias due to inappropriate allocation process; (3) Bias due to blinding of participants or outcome data assessment; (4) Bias due to missing outcome data; (5) Bias in measurement of the outcome; (6) Bias in selection of the reported result; (7) Other bias that may significantly affect the interpretation of the results. Bias is assessed as a judgment of high, low, or unclear. Trials with high or unclear risk for bias were considered to be having high risk of bias (Supplemental Figure S1).

Data synthesis and statistical analysis

Weighted meta-regression analysis was performed to examine the relationship between hemodynamics changes before/after the interventions and outcome variables included in this study by Comprehensive Meta-Analysis version 2.2.064. [7] For this analysis, the achieved differences between the changes in 6MWD (Δ 6MWD), and the event numbers of hospitalization and deaths in active treatment and control groups were considered.

For the assessment of the regression coefficient of each hemodynamic parameter with Δ 6MWD and clinical outcomes, and changes in mPAP (Δ mPAP), PVR (Δ PVR), RAP (Δ RAP), and CI (Δ CI), were entered into the meta-regression model separately with the adjustment of age, sex, and baseline WHO function class. The prognostic values of Δ mPAP, Δ PVR, Δ RAP, Δ CI and Δ 6MWD were evaluated by using the univariate meta-regression model. For all meta-regression analyses, a random-effects model was used, and the analogous R square value (R^2 analog) was adopted to quantify the proportion of variance

explained by the entered covariate(s) in meta-regression. Tau² and the restricted maximum likelihood (REML) methods were used to explain residual heterogeneity not explained by the covariate(s). [7, 8] If there were missing values of the hemodynamic parameters or outcomes in the enrolled studies, the missing data were excluded from the meta-regression analysis.

The present study is the secondary analysis of the published data without any human primary data. It has been waived for the review by our ethical committee according to the regulation of our hospital.

Results

Characteristics of the included studies

A total of 20 RCTs and 3,263 PAH patients, published between 1996 and 2013 were recruited in this analysis. Supplemental Table S1 has shown the characteristics of each RCT, and the mean age of the study population ranged from 29 to 56 years. Of all the participants, 1,097 received placebo, and 2,166 were treated with active drugs. The changes in hemodynamics indices, including Δ mPAP, Δ PVR, Δ RAP and Δ CI, Δ 6MWD, and the adverse events of mortality, death due to PAH and hospitalization for PAH were summarized in Supplemental Table S2.

Risks of bias among the included studies

The risk of bias among the 20 RCTs were evaluated in 7 categories, and researches presented higher or uncertain risk aspects including: (1) allocation concealment: 18 articles had no detailed description; (2) blinding of outcome assessment: 15 article had no clear description, but the 6MWD, hospitalizations, and mortality were objectively evaluated indicators, which were less susceptible to human subjective assessment; (3) selective reporting: 13 articles unlisted study protocol to check the reported and unreported findings, nor special statement about the containment of all expected outcomes. Because the main purpose of this study was to investigate the predictive effect of hemodynamic parameters on the disease course of PAH, the investigators suggested that it should be less susceptible to the above risk of bias, so 20 studies were all included in the subsequent meta-regression analysis.

Meta-regression of the hemodynamic parameters on clinical outcomes

The meta-regression analysis demonstrated that all of the changes in hemodynamic indices, including Δ mPAP, Δ PVR, Δ RAP and Δ CI, correlated with the Δ 6MWD, after accounting for age, sex and baseline functional class (Table 1, Fig. 2). Patients with increasing mPAP, PVR and RAP were independently associated with less improvement of 6MWD (β = -7.1067, -0.1261 and - 18.1120, respectively), and increasing change in CI was independently related to better improvement of 6MWD (β = 43.1253). With regard to the clinical outcomes, after accounting for age, sex and baseline functional class, Δ mPAP, and Δ PVR were positively and Δ CI was negatively related to the adverse clinical events (β = 0.1794, 0.0031 and - 1.7544, respectively) (Fig. 2). While Δ mPAP was the variable with the highest explanatory power for

$\Delta 6MWD$ (R^2 analog = 0.74), it also had the highest explanatory power for the incident adverse events (R^2 analog = 0.91) among the 4 hemodynamic indices. On the other hand, ΔPVR was positively and ΔCI was negatively related to the total mortality ($\beta = 0.0022$ and $- 1.2035$, respectively). In addition, none of the changes in hemodynamic indices was significantly related to the hospitalizations for PAH or death due to PAH in multivariate meta-regression analysis. Moreover, $\Delta 6MWD$ didn't correlate with any adverse event, neither.

Table 1
 Meta-regression analysis of the relationship between the hemodynamic parameters and PAH prognostic outcomes

Outcomes	Predictors	Coefficient [#]	p-value [#]	R ² analog [†]
(Y1) Δ 6MWD	(X1) Δ mPAP	-7.1067	< .0001	.7397
	(X2) Δ PVR	-0.1261	< .0001	.6837
	(X3) Δ RAP	-18.1120	< .0001	.6459
	(X4) Δ CI	43.1253	< .0001	.4123
(Y2) All adverse events	(X1) Δ mPAP	0.1794	.0048	.9111
	(X2) Δ PVR	0.0031	.0015	.8217
	(X3) Δ RAP	0.2191	.1109	.5224
	(X4) Δ CI	-1.7544	.0004	.7701
	(X5) Δ 6MWD	-0.0141	.1195	.6511
(Y3) Total mortality	(X1) Δ mPAP	0.1143	.0932	.5498
	(X2) Δ PVR	0.0022	.0409	.5943
	(X3) Δ RAP	0.2762	.0529	.5487
	(X4) Δ CI	-1.2035	.0293	.5867
	(X5) Δ 6MWD	-0.0077	.2906	.6894
(Y4) Hospitalization for PAH	(X1) Δ mPAP	0.1420	.0519	.2792
	(X2) Δ PVR	0.0024	.1174	.5761
	(X3) Δ RAP	0.3741	.2162	.0000
	(X4) Δ CI	-0.6668	.3520	.0000
	(X5) Δ 6MWD	-0.0079	.2847	.0704
(Y5) Death due to PAH	(X1) mPAP	0.0548	.6496	.0000
	(X2) Δ PVR	0.0020	.4698	.0000
	(X3) Δ RAP	0.0593	.8449	.0000
	(X4) Δ CI	-0.6998	.5650	.0000
	(X5) Δ 6MWD	0.0019	.8909	.0000
#Adjusted for age, sex, and baseline WHO function class.				
†Results of univariate regression analysis.				

Discussion

In this meta-regression analysis of 20 RCTs and 3,263 participants, we demonstrated all the changes in hemodynamic indices, including mPAP, PVR, RAP and CI were associated with Δ 6MWD, independent of age, sex and baseline functional class. However, only Δ mPAP, Δ PVR and Δ CI, but not Δ RAP or Δ 6MWD were related to clinical adverse events, after accounting for age, sex and functional class. In addition, only Δ PVR and Δ CI were the hemodynamic parameters to be independently predictive of total mortality. But none of the changes in hemodynamic indices was correlated with PAH hospitalization or death due to PAH. The study results may support the use of the changes in the hemodynamic parameters, including Δ mPAP, for the risk assessment in the management of PAH.

Hemodynamic indices and the prognosis

Although elevated mPAP is essential in the diagnosis of PAH and small increases in mPAP are independently associated with increased mortality in patients with borderline pulmonary hypertension, [9, 10] several studies did not demonstrate any association between mPAP and the survival in PAH patients. [4, 5] Benza et al. have shown RAP but not mPAP were associated with 1-year survival in REVEAL registry of 2,716 subjects. [11] In contrast, CI among the hemodynamic indices was suggested to be predictive of clinical outcomes in European cohorts of PAH. [3, 12] Since the difference between mPAP and PAWP is the product of cardiac output multiplied by PVR, the increase in PVR and the decrease in cardiac output along with the progression of PAH could partially cancel their effects on mPAP. Conversely, an increase in mPAP could result from an augment in cardiac output due to improving PAH, and might not be due to a raise in PVR from deteriorating PAH. Therefore, the determinants of mPAP could vary on different stages of right ventricular failure, and the prognostic value of mPAP in PAH patients is expected to be low. However, D'Alonzo et al. showed that a higher mPAP at the diagnosis of PAH conferred a greater risk of early death in a cohort of 194 patients. [13] Moreover, Sitbon et al. identified an apparently paradoxical correlation between low baseline mPAP and mortality in 178 patients with PAH in WHO functional class III or IV. [14] In patients with severe PAH and right ventricular failure, low mPAP may better correlate with low cardiac output rather than low PVR, indicating worse outcomes. [14] On the other hand, few studies have investigated the association between the changes in hemodynamic indices and outcomes in patients with PAH. Weatherald et al. presented a PAH cohort of 981 patients who had undergone repeated hemodynamic surveys in a mean time of 4.6 months. [15] The results suggested that Δ mPAP and Δ PVR were significantly associated with death or lung transplantation in the whole study population, while Δ CI was only predictive of clinical outcomes in the subgroup of severe PAH patients. [15]

In the present study, we have shown that Δ mPAP, Δ PVR, Δ RAP and Δ CI were all crudely correlated with clinical adverse events. After accounting for age, sex and WHO functional class, Δ mPAP, Δ PVR and Δ CI remained significantly related to clinical outcomes. The study results may support the inclusion of these indices in the simplified risk score for the prediction of disease outcomes. [12]

The 6-minute walk distance

The change from baseline in 6MWD has long-term served as the surrogate endpoint in the clinical trials of PAH to evaluate the therapeutic efficacy of the study drugs. It is expected the indirect measure of 6MWD may reflect the clinically meaningful endpoints, such as quality of life and survival. The SERAPHIN study may have firstly endorsed the directly clinical outcomes as the primary endpoint to demonstrate macitentan significantly reduced morbidity and mortality among patients with PAH. [16] However, the change in 6MWD was not associated with the long-term outcomes. [17] In a meta-analysis of 16 short-term RCTs, Macchia et al. have shown the change in 6MWD was not predictive of a survival benefit or adverse clinical events. [18] The updated meta-analyses have demonstrated again that the change in 6MWD didn't correlate with any of the composite clinical events, including mortality, hospitalization for PAH, lung transplantation, or initiation of rescue therapy. [19, 20] The present study also found that Δ 6MWD was not associated with clinical outcomes. The results support the use of morbidity and mortality rather than Δ 6MWD as the primary endpoint in the RCTs for PAH patients.

Study limitations The long-term prognostic values of hemodynamic changes haven't been evaluated in large cohorts yet. Although meta-regression analysis may improve our understandings for the associations between hemodynamic indices and the long-term clinical outcomes, the variances of baseline characteristics, study designs, and background therapies across the enrolled RCTs can cause biased study findings. Some RCTs were undertaken to prove the short-term effects of a novel drug mainly on exercise capacity. Although the others might have been designed to evaluate the therapeutic effects on long-term mortality and morbidities, caution should be exercised to interpretate the correlations between hemodynamic changes and clinical outcomes. For patients with early PAH and preserved right ventricular function, the therapeutic changes in CI might be subtle, and the changes in mPAP may reflect the changes in PVR. In patients with PAH and profound right ventricular failure, improvement of CI followed by increased mPAP may indicate significant amelioration of right ventricular dysfunction and better long-term outcomes were expected. While connective tissue disease is the second common etiologies of PAH, it may cause direct damage on myocardium rather than through PAH. The inclusion of these subjects with distinct pathophysiology in the previously published RCTs may influence the findings observed in the present meta-regression analysis. Moreover, the study results are based on published RCTs, in some of which currently available PAH drugs were not commercially available. Future studies are needed to evaluate the prognostic impacts of hemodynamic indices, stratified by PAH etiologies and right ventricular function.

Conclusions

Progression of PAH is usually characterized by increasing mPAP, PVR and RAP, and decreasing CI. In addition to the baseline and on treatment hemodynamic measures, the present study demonstrates that Δ mPAP, Δ PVR, Δ RAP and Δ CI were all significantly associated with the prognosis of PAH patients. Given the risk stratification is essential in the management of PAH, further studies are warranted to evaluate whether the changes in the hemodynamic indices could be used to evaluate the therapeutic effects, in addition to the clinical risk factors, including functional class, 6MWD and NT-proBNP.

Abbreviations

pulmonary arterial hypertension (PAH)

pulmonary artery pressure (mPAP)

pulmonary vascular resistance (PVR)

right atrial pressure (RAP)

cardiac output index (CI)

6-min walking distance (6WMD)

Medical Subject Headings (MeSH)

Declarations

Ethics approval and consent to participate

The present study is the secondary analysis of the published data without any human primary data. It has been waived for the review by our ethical committee (Taipei Veterans General Hospital) according to the regulation of our hospital.

Consent for publication

Not applicable. (Our manuscript does not contain data from any individual person)

Availability of data and material

The database of the present study can be made available on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing financial interests.

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Authors' contributions

All authors have drafted the work or revising it critically for important intellectual content; given final approval of the version to be published; and provided Agreement to be accountable for all aspects of the

work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The individual contributions of each authors are detailed as below:

Shih-Hsien Sung: conception or design of the work; the acquisition, analysis, and interpretation of data for the work

Wan-Yu Yeh: analysis, and interpretation of data for the work

Chern-En Chiang: analysis, and interpretation of data for the work

Chi-Jung Huang: analysis, and interpretation of data for the work

Wei-Ming Huang: acquisition and interpretation of data for the work

Chen-Huan Chen: acquisition and interpretation of data for the work

Hao-Min Cheng: conception or design of the work; the acquisition, analysis, and interpretation of data for the work

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Figures

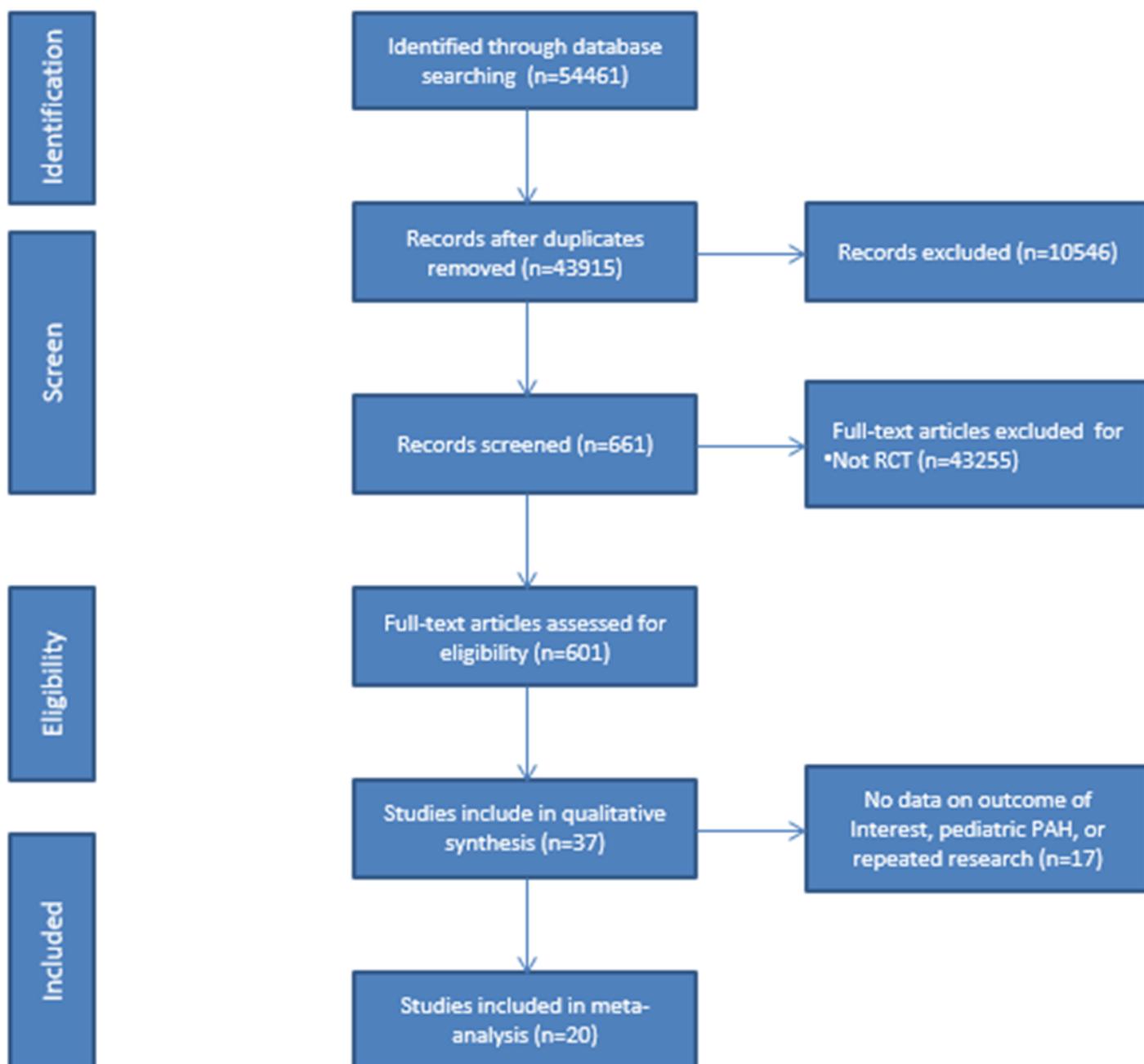
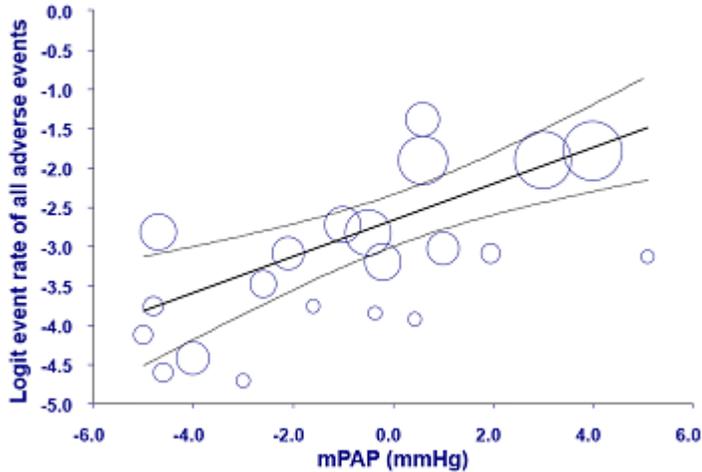


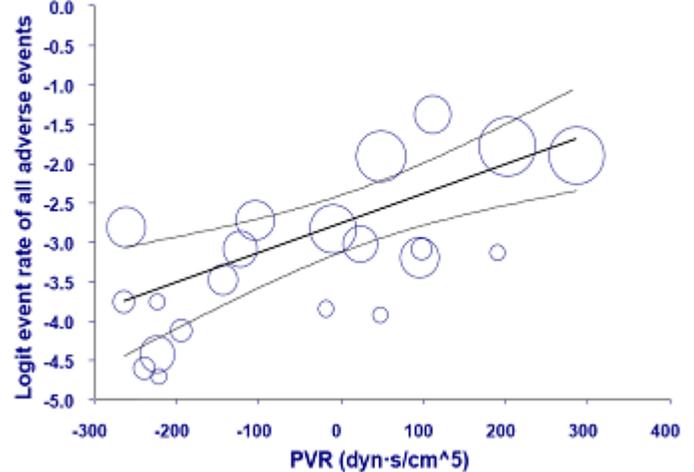
Figure 1

Flow chart of the literature search for studies investigating the effects of drugs on PAH including hemodynamic parameters. RCT stands for randomized controlled trials

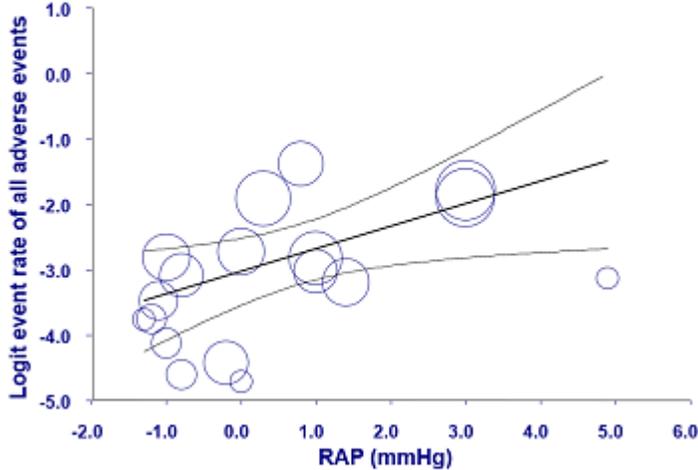
Logit event rate(Y)=-2.6699+0.2306*mPAP
(p=.0000, R² analog=.9111)



Logit event rate(Y)=-2.7671+0.0037*PVR
(p=.0000, R² analog=.8217)



Logit event rate(Y)=-3.0334+0.3457*RAP
(p=.0052, R² analog=.5224)



Logit event rate(Y)=-2.5735-2.0812*CI
(p=.0000, R² analog=.7701)

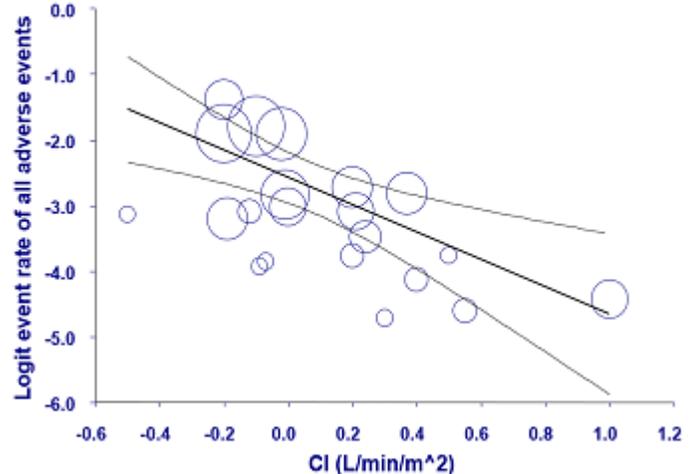


Figure 2

Univariate meta-regression analysis between changes in (1) mPAP, (2) PVR, (3) RAP, (4) CI and All adverse events (Y). Only statistically significant relationships in Table are plotted in this Figure.

Supplementary Files

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