Systematic Review and Meta-Analysis

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Prognostic significance of pulmonary hypertension in patients with cystic fibrosis

A systematic review and meta-analysis

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Abstract

Background and objective: Pulmonary hypertension (PH) is frequently found in advanced parenchymal lung diseases like cystic fibrosis (CF), but the role played by PH in the clinical outcome of CF patients remains unclear. The aim of this study is to determine the influence of PH on survival in the CF population by meta-analysis.

Methods: Publications addressing the associations between PH and overall survival (OS) or other clinical characteristics in CF patients were selected from electronic databases. Odds ratios (ORs) or mean differences (MDs) were used to estimate the association between PH and the clinical characteristics. The hazard ratios (HRs) with 95% confidence interval (CI) were abstracted or calculated to evaluate the association between PH and CF survival outcome. Subgroup analyses were also conducted.

Results: Seven studies including 2141 CF patients who met the inclusion criteria were included in our meta-analysis. With respect to clinical features, PH was significantly associated with lower PaO_2 ($P < .001$), higher $PaCO_2$ ($P = .02$), lower forced expiratory volume in 1 second percent ($P < .001$) and lower forced vital capacity percent ($P < .001$). However, PH had no significant impact on CF patients' OS (HR = 1.29, 95% CI 0.81 to 2.06, $P = .283$). Furthermore, subgroup analyses also showed no evidence of prognostic role of PH in CF patients (all P values $> .05$).

Conclusions: Our findings suggest that the presence of PH was strongly correlated with worse blood-gas parameters and worse lung function, but surprisingly had no significant prognostic value on survival among CF patients. Further large-scale and prospective studies are needed to confirm these findings.

Abbreviations: BMI = body mass index, CF = cystic fibrosis, DLCO = diffusion capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HR = hazard ratio, MD = mean difference, OR = odds ratio, OS = overall survival, PAP = pulmonary artery pressure, PH = pulmonary hypertension, PVR = pulmonary vascular resistance, RHC = right heart catheter.

Keywords: cystic fibrosis, meta-analysis, pulmonary circulation, pulmonary hypertension

1. Introduction

Cystic fibrosis (CF) is a life-shortening genetic disease affecting approximately 70,000 individuals worldwide.[1] Apart from chronic respiratory infections and the development of bronchiectasis, CF patients may also develop pulmonary hypertension (PH), which can in turn evolve into right ventricular dysfunction.[2,3] CF-associated PH has been incorporated in Group 3, namely "pulmonary hypertension due to lung diseases and/or hypoxia" of the latest clinical World Health Organization (WHO) classification of PH.[4] In this group of patients, PH is principally caused by chronic hypoxia, which leads to pulmonary arterial vasoconstriction and increased pulmonary vascular resistance (PVR). Moreover, in advanced lung disease, a progressive loss of pulmonary blood vessels due to the destruction of lung tissue may subsequently leads to increased resistance and pressure of pulmonary circulation.[5,6] Therefore, the prevalence of PH usually varies depending on the following factors: the age of the patients and the severity of lung disease. The methodology employed to detect PH and the criteria used to define patients may also account for the difference in prevalence of PH in different cohorts.[7] However, once PH presents in CF, it may negatively affect outcomes, as it does in other lung diseases such as chronic obstructive pulmonary disease and interstitial lung disease.[8] Therefore, evaluating PH may help guide treatment decisions in CF patients. However, up to now, studies on the prognostic value of PH in CF are scarce and most of them have small sample sizes. In 2 studies with 18 and 55 paticipants,[6,9] the 5-year mortality was higher in patients with PH than those without this condition, but the difference did not reach statistical significance. Later, in the largest study to date (866 cases), Singh et al[10] demonstrated that patients with PH did not have significantly decreased 1-year

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survival compared with normotensive patients, whereas multivariate Cox regression analysis using mPAP (cutoff of 25 mmHg) did not yield significant results either.

As meta-analysis is an important tool to reliably and accurately summarize the current evidence, we conducted this study to gain a better insight about the direct relationship between presence of PH and survival in CF. Furthermore, we also tried to investigate the correlations of PH with patients' clinical characteristics, which, to the best of our knowledge, has not been performed previously.

2. Material and methods

2.1. Search strategy

Studies were identified via an electronic search of PubMed, Embase, Web of Science, and Cochrane Library (updated to January 31, 2016). The syntax used for search was ((((((prognosis) OR prognostic) OR survival)) AND ((cystic fibrosis) OR CF)) AND ((((((pulmonary hypertension) OR pulmonary arterial hypertension) OR PH) OR PAH) OR pulmonary vascular disease) OR pulmonary circulation)). The languages were limited to English. We also used a manual reference search for relevant articles, including original articles and reviews, to identify additional studies.

2.2. Selection criteria

The search results were screened according to the following inclusion criteria: the diagnosis of CF must have been confirmed clinically or genetically; the cutoff for PH diagnosis must have been defined; the correlation of PH with overall survival (OS) or other clinical characteristics in CF had to be evaluated; hazard ratios (HRs) with their 95% confidence intervals (95% CIs) for OS, odds ratios (ORs), or mean differences (MDs) with 95% CIs for clinical features must be provided or could be calculated from the data presented. To avoid duplicated publications, the most recent report or the most informative one was included. Reviews, conference abstracts, or comments were excluded due to insufficient data.

2.3. Data extraction and quality assessment

Data were extracted by 2 investigators (LD and LQ) independently. Disagreements between the reviewers were resolved by consensus. The following information was extracted from each study and used as a supplement if available: first author, year of publication, country, number of patients, pulmonary artery pressure (PAP) measurement method, cutoff, follow-up period, HR with 95% CI and clinical characteristics such as gender, body mass index (BMI), blood-gas data, and lung function parameters. If HR and 95% CI were not provided directly, 2 reviewers (LD and WB) extracted the data through the Kaplan–Meier curves using GetDataGraph Digitizer 2.24 (http://getdata-graph-digitizer.com) and then recalculated the HR and its variance (GraphPad Software, Inc, La Jolla, CA). The Newcastle–Ottawa scale was applied to evaluate the quality of included studies,[11] which consists of 8 items assessing 3 aspects of a study: patient selection, comparability, and ascertainment of outcome. Each item could be awarded 1 point except for the item on comparability, which is awarded 2 points. High-quality studies were those with scores of 5 to 9, whereas those with scores of 0 to 4 were considered low quality.

2.4. Statistical analysis

The ORs or MDs with 95% CIs were used to estimate the association between PH and clinical characteristics for CF, including age, gender, BMI, arterial blood gases (PaO_2 and $PaCO_2$) and parameters of lung function (forced expiratory volume in 1 second [FEV1]% and forced vital capacity [FVC]%). The HR with its 95% CI was abstracted or calculated to quantitatively evaluate the association between PH and CF survival outcome. To assess heterogeneity among the studies, Cochrane's Q test (χ^2 test) and inconsistency (I^2) statistics were used.[12] Where there was no heterogeneity ($P > .1$; $I^2 < 50\%$), the fixed-effects model analysis was made; otherwise, the random-effects model was used. One-way sensitivity analysis was conducted to assess the stability of the results by deleting 1 study each time to reflect the influence of the individual data set to the pooled HR.[13] The publication bias was tested by Begg's funnel plots, whose symmetry was further assessed by Egger's linear regression method.[14] For all analyses, a 2-sided P value <0.05 was considered as statistically significant. All analyses were performed by STATA version 12.0 (Stata Corporation, College Station, TX) and Revman5.3 software (Cochrane Collaboration, Oxford, UK). All analyses were based on previous published studies; thus, no ethical approval and consent from patients are required.

3. Results

3.1. Identification and characteristics of eligible studies

A total of 8663 CF-related citations were identified based on the initial search. After independent review, 4662 studies were excluded due to irrelevance to the current analysis. 3968 were excluded since they were reviews, letters to editor, editorials, case reports, conference abstracts or animal/in vitro studies, leaving 15 studies for retrieval of the full text (Fig. 1). After detailed evaluation, 8 studies were excluded for lacking sufficient data to extract (n = 6), associations between OS and PH not evaluated (n = 1) or duplicate study (n = 1). Ultimately, 7 studies with 2141 CF patients were included in this meta-analysis.[5,6,9,10,15–17] These studies were published between 1999 and 2015, among which 3 were conducted in the United States, whereas the other 4 were from Netherland, Canada, France, and Italy, respectively. Of the 7 studies, 6 with scores more than 5 were assessed as high-quality studies.[5,6,10,15–17] All studies collected data retrospectively, except for 2 studies.[9,15] Hazards ratios with 95% CIs were extracted directly from 3 studies and calculated for the remaining 4. Methods for measuring PAP were right heart catheter (RHC) (n = 3), echocardiograph (n = 3), or both (n = 1). The characteristics of these 7 studies included in the meta-analysis are presented in Table 1.

3.2. Meta-analysis results

3.2.1. PH and clinical features of CF patients. The prevalence of PH in the 7 included studies ranged from 14.9% to 63.2%, depending on the clinical characteristics of study patients. Totally, for these studies included in the meta-analysis, PH was present in 806 CF patients (38%). Several studies independently evaluated associations between PH and gender,[5,6,15–17] BMI,[6,15–17] PaO_2,[6,9,15,17] $PaCO_2$,[6,9,15,17] FEV1%,[6,9,15–17] and FVC %.[6,9,16,17] As expected, our analyses suggested that PH was significantly associated with lower PaO_2 (MD = −5.63, 95% CI −8.01 to −3.25; $P < .001$), higher $PaCO_2$ (MD = 3.98, 95% CI 0.73 to 7.24; $P = .02$), declined FEV1% (MD = −4.45, 95% CI −6.14 to −2.76; $P < .001$), and FVC % (MD = −8.87, 95% CI −11.00 to −6.74; $P < .001$) (Table 2), indicating that higher PAP

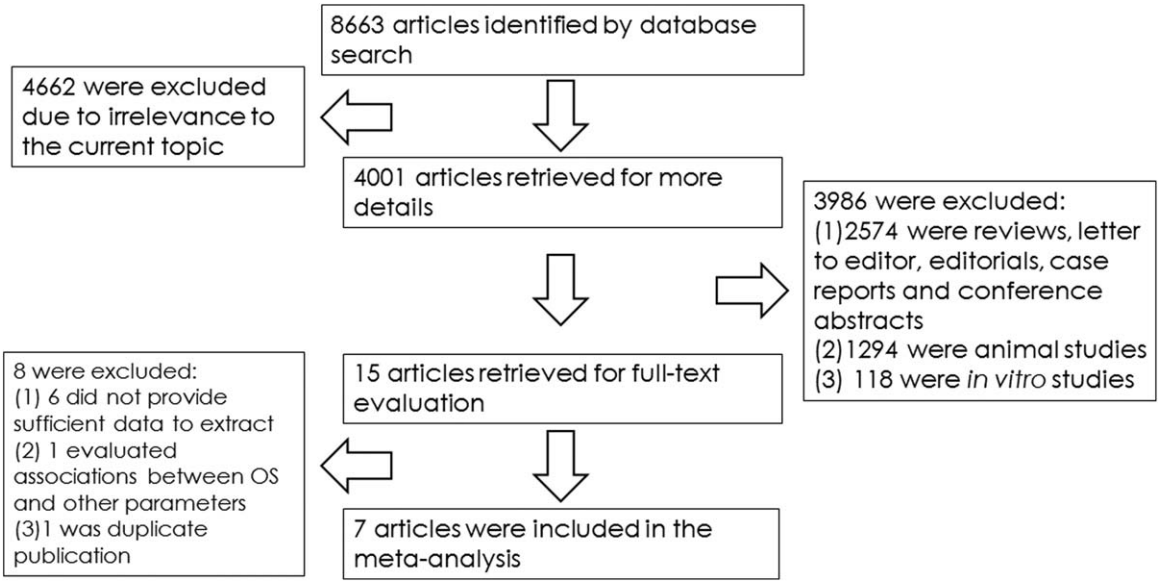

Figure 1. Flow chart of selection process for eligible articles.

had close association with ventilation and gas exchange dysfunction, rather than gender and BMI in CF patients.

3.2.2. PH and OS of CF patients. The pooled outcome data of this meta-analysis are summarized in Table 3. Six studies had sufficient data for estimating HR and 95% CI, including 1964 patients. All of the studies had a maximum follow-up period exceeding 1 year. Notably, 2 of the 6 included studies suggested that high PAP was significantly associated with poorer OS,[5,16] whereas others reported negative associations, implying controversial results among current studies. By pooling the data using a random-effects model, as shown in Figure 2, the results suggested that the OS for CF patients with PH was lower than those without, but this did not reach statistical significance (HR = 1.29, 95% CI 0.81 to 2.06, $P = .283$), indicating that presence of PH might not predict the risk of mortality for CF.

Table 1

Characteristics of eligible studies.

First author	Year	Country	Method of PAP measurement	Number of Patients	Number with PH	Duration of follow-up, mo	Cutoff value for PH, mmHg	HR estimate	HR (95% CI)	Study design	Quality score*
Belle-van Meerkerk G	2013	Netherlands	RHC	93	24	60	mean PAP ≥ 25	Sur. Curve	3.2 (1.16, 8.4)	R	5
Damy T	2012	France	Echo	67	10	60	sPAP ≥ 35	Sur. Curve	3.78 (0.25, 56.77)	P	5
Fraser KL	1999	Canada	Echo	18	7	50	sPAP ≥ 35	Sur. Curve	27.63 (0, ∞)	P	4
Hayes D.Jr	2014	USA	RHC	899	465	36	mean PAP ≥25	HR 95% CI	1.75 (1.39, 2.2)	R	5
Scarsini R	2015	Italy	RHC	141	79	60	mean PAP ≥ 25	HR 95% CI	0.95 (0.49, 1.85)	R	6
Singh VK	2015	USA	NA	866	185	12	TPG ≥ 20	HR 95% CI	0.88 (0.54, 1.45)	R	5
Tonelli AR	2010	USA	RHC/Echo	57	36	60	mean PAP ≥ 25	Sur. Curve	0.49 (0.13, 1.78)	R	5

CI = confidence interval, Echo = echocardiogram, HR = hazard ratio, NA = not available, P = prospective, PAP = pulmonary artery pressure, PH = pulmonary hypertension, R = retrospective, RHC = right heart catheter, sPAP = systolic pulmonary artery pressure, Sur. = survival.

* Quality scores range from 0 to 9. Quality of included studies was assessed using the Newcastle–Ottawa scale.[11]

Table 2

Meta-analysis of the association between PH and clinical features in patients with CF.

Clinical features	Number of studies	Number of patients		OR (95% CI)	MD (95% CI)	*P*	I^2 (%)	P_{het}
		PH	Non-PH					
Gender	5	246	994	1.18 (0.87 to 1.62)	—	.29	0	.82
BMI	4	222	925	—	0.50 (−0.05 to 1.04)	.07	0	.75
PaO_2	4	132	133	—	−5.63 (−8.01 to −3.25)	<.001	0	.45
$PaCO_2$	4	132	133	—	3.98 (0.73 to 7.24)	.02	55	.08
FEV1%	5	229	935	—	−4.45 (−6.14 to −2.76)	<.001	48	.1
FVC%	4	219	895	—	−8.87 (−11.00 to −6.74)	<.001	46	.13

BMI = body mass index, CI = confidence interval, FEV1 = force expiratory volume in 1 second, FVC = forced vital capacity, MD = mean difference, OR = odds ratio, PH = pulmonary hypertension, P_{het} = *P* value for heterogeneity.

Table 3

Estimated effect of PH on OS in CF patients.

Subgroups	Number of studies	Number of patients	HR (95% CI)	*P*	I^2, %	P_{het}
Total	6	1964	1.29 (0.81 to 2.06)	.28	62.9	.02
Follow-up period, mo						
≥60	4	334	1.32 (0.55 to 3.16)	.53	55.4	.08
<60	2	1630	1.27 (0.66 to 2.51)	.46	83.5	.01
PAP detection methods						
Right heart catheterization	4	1859	1.38 (0.85 to 2.24)	.19	70.6	.16
Echocardiograph	2	105	0.95 (0.15 to 6.19)	.96	43.4	.91
Cutoff value, mmHg						
Mean PAP ≥ 25	4	1048	1.4 (0.8 to 2.47)	.24	62.1	.05
sPAP ≥ 35	1	50	3.78 (0.25 to 56.96)	.34	Not applicable	Not applicable
Sample size						
≥100	3	1771	1.62 (0.39 to 6.7)	.5	62.8	.07
<100	3	193	1.2 (0.72 to 2)	.5	74.8	.02

CI = confidence interval, HR = hazard ratio, PAP = pulmonary artery pressure, P_{het} = *P* value for heterogeneity, sPAP = systolic pulmonary artery pressure.

There was obvious heterogeneity among studies (P_{het} = .019 and I^2 = 62.9%), so we conducted subgroup analyses according to confounders, such as follow-up period (≥60 months or <60 months), PAP detection methods (RHC or echocardiograph), cutoff values for PH diagnosis (mean PAP ≥ 25 mmHg or systolic PAP ≥ 35 mmHg), and sample size (≥100 or <100). Consistent with the overall data, the results revealed that HRs in all of the subgroups did not differ significantly between the 2 groups (PH and non-PH), as shown in Table 3.

3.3. Sensitivity analyses and publication bias

For sensitivity analyses, we omitted 1 study per time to check if individual study affected the final results. All the results were not materially altered. Test of publication bias in current meta-analysis was performed by Begg's funnel plot and Egger's test. In all included studies, there was no funnel plot asymmetry observed, with *P* = .58 in the Egger's test (Fig. 3), indicating no evidence of significant publication bias.

4. Discussion

The present meta-analysis summarized the results of 7 clinical studies representing 2141 CF patients. By pooling all the studies and comparing the survival outcome of patients according to PH status, we observed that the OS was lower in CF patients with PH than those without, but the difference was not statistically significant. However, presence of PH markedly correlated with worse blood-gas parameters and worse lung function in CF patients. To the best of our knowledge, this is the most comprehensive meta-analysis to assess the prognostic value of PH in CF.

PH in patients with CF and end-stage lung disease has been frequently found nowadays as more cases can survive to

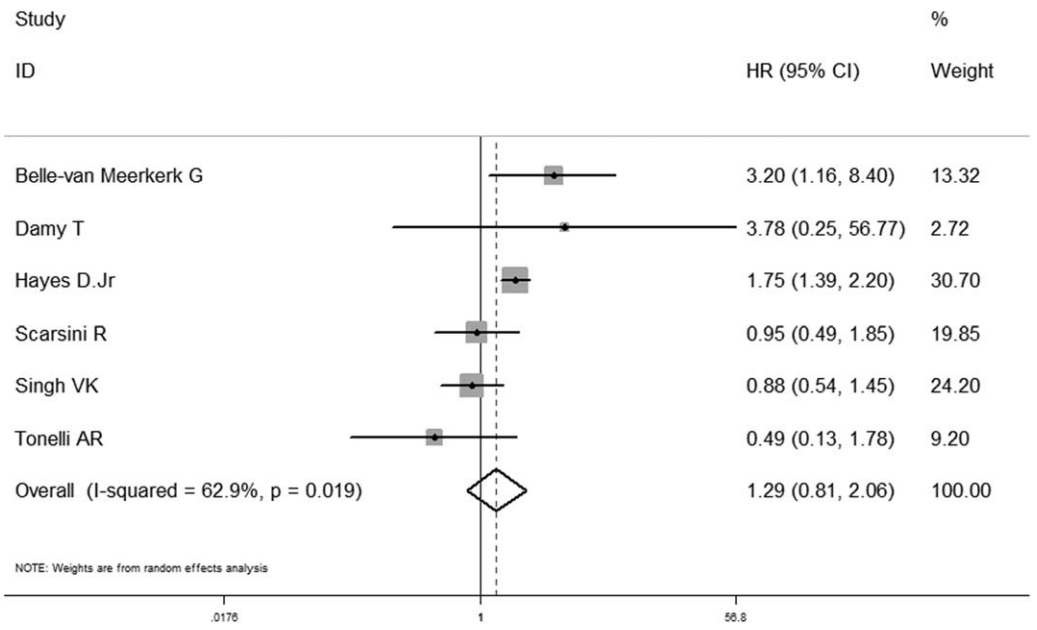

Figure 2. The association between presence of PH and OS of CF stratified by HR estimation. The summary HR and 95% CIs were shown (according to the random-effects estimations). CF = cystic fibrosis, CI = confidence interval, HR = hazard ratio, OS = overall survival, PH = pulmonary hypertension.

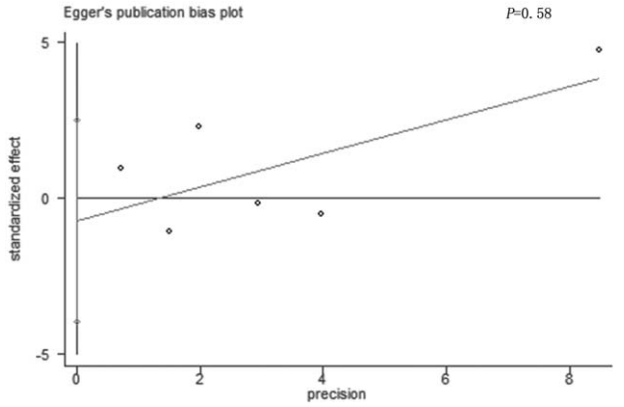

Figure 3. Egger's plot to detect publication bias on overall estimate.

adulthood. Nevertheless, how PH develops in CF patients has not been fully elucidated yet. It likely involves chronic alveolar hypoxia,[18] hypercapnia,[19] and endothelial dysfunction caused by vessel inflammation.[20] Previous work has demonstrated that arterial hypoxemia is the major cause of PH in CF patients,[21] because hypoxemia is a powerful pulmonary vasoconstrictor,[22,23] which occurs due to ventilation/perfusion (V/Q) mismatch, lung destruction, and right-to-left shunt.[24,25] Consistent with these studies, our results showed that patients with PH were more hypoxemic and hypercapnic than patients without PH, implying that PAP and PaO_2 are closely and negatively correlated in PH associated with CF.

Although the abnormalities of the cardiovascular system in PH are well described,[26] it is unclear to what extent the pulmonary vasculature is affected in CF. If the pulmonary vessels were affected in addition to the airways, this could provide another treatment strategy for a subset of advanced CF that remains difficult to treat despite the availability of novel drugs. In our study, CF patients with PH had poorer lung function, measured as FEV1% and FVC%, indicating that PH is related to the severity of the lung function loss in CF. Meanwhile, as FVC% is believed to be physiologically correlated with the extent of fibrosis, we speculate that tissue fibrosis may play a role in the genesis of PH in CF. However, due to lack of necessary data from original studies, we could not further explore whether the severity of PH (such as cardiac index or systolic pulmonary artery pressure) correlated with the severity of the lung function as assessed by flows and lung volumes. Because of the same reason, we were also unable to investigate the associations of PH with lung function parameters other than FEV1% and FVC%. It has been suggested that the development of PH in chronic lung diseases (Group 3) may be disproportionate to lung function, while reduced diffusion capacity for carbon monoxide (DLCO) is a more consistent finding in PH associated with chronic lung diseases.[27] DLCO may thus help to identify patients with PH who deteriorate, and such data would be important to abstract and report in future studies of PH in CF.

The prognostic relevance of PH in patients affected by CF has been discussed in a few studies, but these results remain inconsistent. Venuta et al[28] found that CF patients who died awaiting lung transplantation had a significantly higher mean PAP (35 ± 12 mmHg) compared with those who were alive at the end of the study (23 ± 6 mmHg). However, in another retrospective analysis of CF patients on the lung transplantation list, there was no difference in the mean PAP between patients who were alive at the end of the study and those who died awaiting lung transplantation (26 ± 5 vs 28 ± 7 mmHg, $P = .15$).[29] A cutoff of 25 mmHg or higher only had a sensitivity 70.2% and specificity 69.7% for predicting mortality in CF patients at 1 year.[28] Hence, these findings have begun a debate on whether PH needs to be diagnosed and treated earlier in the CF population. In our efforts to quantify the overall impact of PH on CF prognosis, we identified that the presence of PH in CF did not predict worse outcome. As most of the included studies were retrospective and differed in their study designs, moderately significant heterogeneity was found in the present meta-analysis ($I^2 = 62.9\%$, $P = .17$) for OS. To adjust for this, we performed the analysis using a random-effects model, which considers the between-study heterogeneity. Furthermore, a stratified subgroup analysis was also performed to reduce the heterogeneity. In the subgroup analyses for OS, the results were consistent with the overall data, suggesting that PH might not be a statistically significant prognostic factor for CF regardless of the follow-up period, PAP detection method, cutoff values, or sample size.

Physiologically, there is a potential explanation for this insignificant association between PH and OS of CF. The PAP elevation in patients with lung parenchymal diseases like CF is usually mild[30,31] compared with other forms of PH, and the studies to date may not include many subjects with moderate (mean PAP $>$ 35 mmHg) or severe (mean PAP $>$ 45 mmHg) PH that would be more likely to affect mortality. The shortage of cardiac output data in published studies is problematic, as PAP may decline when the right ventricle (RV) fails and is unable to maintain an appropriate cardiac output. In fact, CF patients who develop right heart failure often have poor prognosis. Belkin et al[32] reported that the presence of RV dysfunction was more common in CF patients who died (51%) compared with those awaiting lung transplantation (21%).

Nevertheless, some methodological limitations of current meta-analysis were inevitable and should be taken into consideration when interpreting the results. First of all, only published studies were included. The exclusion of unpublished papers, abstracts, and letters to the editor may lead to potential publication and reporting bias, because positive results are more likely to be acceptable by journals. Second, some survival outcomes were calculated from Kaplan–Meier curves, which may have introduced some imprecision. Notably, Fraser and colleagues' study[9] suggested a possible prognostic value of PH in CF survival. However, it was not included in our meta-analysis due to insufficient OS data. Third, lack of the original data of reviewed studies limited further analysis of the optimized cutoff value for PAP as a significant prognostic factor for CF survival. Tonelli et al[6] noted that patients with a mean PAP of at least 40 mmHg had a trend toward worse survival than those with a mean PAP below 40 mmHg. In the included studies, only Scarsini et al[17] reported that severe PH (mean PAP $\geq$ 35 mmHg) rather than mild degree of PH (mean PAP 25–35 mmHg) was significantly associated with mortality ($P = .028$). Thus, subgroup analysis based upon the severity of PH (e.g., mild, moderate, and severe) are needed in the future to assess the impact of PH severity on CF patient survival. Fourth, 6 of our included studies enrolled patients with advanced lung disease or waiting for lung transplantation. Whether the prognostic utility of PH differs between early-stage CF and late-stage CF remains unclear. Finally, although we tried to minimize the heterogeneity, our study was based on published literature, which limited our ability to correct for potential confounding factors if they were not reported.[33] Importantly, the data we analyzed did not include

data on lung transplant, and it may be possible that CF subjects with PH are more likely to receive lung transplant, thus confounding interpretations of this survival data. Thus, appropriate multivariate analysis will be important in future studies to examine whether PAP could be a prognostic factor for CF, independent of other known clinical factors such as age, sex, disease severity, genotype, and treatment.

In conclusion, our findings suggest that the presence of PH was strongly correlated with worse blood-gas parameters and worse lung function, but had no significant prognostic value on survival among patients with CF. However, further large-scale studies are needed to confirm these findings with attention to factors such as indices of right heart failure and systolic pulmonary artery pressures that predict outcome in other forms of PH.

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