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Prevalence of pulmonary hypertension in peritoneal dialysis patients: a meta-analysis

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Abstract

Purpose Recent epidemiological evidence indicates an association between peritoneal dialysis (PD) patients and pulmonary hypertension (PH). However, the true prevalence of PH associated with PD has not been well described. So we conducted a meta-analysis to summarize the point prevalence of PH in adults with PD.

Methods PubMed, EMBASE, the Cochrane Collaboration, and the reference lists of relevant articles were searched to identify eligible studies. We used a random-effect meta-analysis model to estimate the prevalence of PH. We also performed sensitivity analyses and assessments of publishing bias.

Results Fourteen observational studies ($n = 1483$ participants) were included in this meta-analysis. The result of analysis in random-effect model showed that the pooled prevalence was 21% (95% CI 16–28), with significant heterogeneity between these studies ($I^2 = 84\%$, $p < 0.01$). Sensitivity analysis further demonstrated the results to be robust. Besides, the Egger's test ($p = 0.287$) showed no significant publication bias.

Conclusions PH is highly prevalent in patients with PD. Further studies are encouraged to definitively clarify the relationship between PH and PD.

Keywords Pulmonary hypertension · Prevalence · Peritoneal dialysis · Meta-analysis

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Abbreviations

CKD	Chronic kidney disease
PD	Peritoneal dialysis
PH	Pulmonary hypertension
PASP	Pulmonary artery systolic pressure

Introduction

Chronic kidney disease (CKD) is defined as gradual loss of renal function over time, and it affects 10–16% of the adult population worldwide [1]. According to the KDIGO guidelines, end-stage renal disease (ESRD) is defined as a glomerular filtration rate less than 15 mL/min [2]. In the ESRD, renal replacement therapy such as dialysis or kidney transplantation becomes necessary to maintain life. It seems that by the year 2030, the number of CKD patients with ESRD requiring dialysis should be more than 2.2 million [3]. Hemodialysis (HD) and peritoneal dialysis (PD) are the two most common dialysis therapies. Pulmonary hypertension (PH) is frequently associated with CKD and ESRD, and is a hemodynamic and pathophysiological state defined as pulmonary artery systolic pressure (PASP) of at least

25 mmHg at rest, with a pulmonary capillary wedge pressure of 15 mmHg or less [4]. Epidemiological studies have indicated that a prevalence of PH ranges from 9% to 39% in ESRD patients without dialysis, between 18.8% and 68.8% in HD patients, and between 0% and 42% in PD patients [5]. However, the researchers primarily focused their attention about the disorder to CKD and HD patients in existing studies and the information available in the literature regarding PH in PD patients is limited. Therefore, we conducted the present meta-analysis to quantify the prevalence of PH in PD patients, which may provide clinical guidance in this area.

Methods

Our study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [6]. The protocol has been published in the PROSPERO International Prospective Register of systematic reviews, and the registration number is CRD42018089531.

Search strategy

PubMed, EMBASE, and Cochrane Library databases were searched for observational studies to March 11, 2018. A combination of terms(both as Medical Subject Headings search terms and key words) used was as follows: ("pulmonary hypertension" or "pulmonary arterial hypertension" or "pulmonary artery systolic pressure" or "pulmonary artery pressure") and ("dialysis" or "continuous ambulatory peritoneal dialysis" or "peritoneal dialysis") and ("risk" or "prevalence" or "epidemiology" or "morbidity"). Furthermore, we searched reference lists of all included studies for additional eligible studies. Two of the authors (YL and WS) independently screened titles and abstracts, analyzed full-text articles, and ascertained the final eligible records. Literature language were not restricted. Conflicting results were resolved by discussion. We merged retrieved citations using EndNote X7.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study design was an observational study; (2) studies had to provide point prevalence of PH in patients receiving PD or sufficient data to calculate it. Reviews, comments, letters, abstracts, case series, and animal studies were excluded.

Data extraction

For each included study, the following data were extracted by two authors (WS and YR) separately: first author's name, publication year, study design, country origin, sample size, proportion of men, mean age, PH criteria, PH diagnostic methods, and PH prevalence. When needed, we contacted the original author for clarification.

Quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used to assess the methodological quality of the included studies [7]. Two authors (LY and WS) performed the quality assessment independently. Disagreements were resolved through discussion.

Statistical analyses

All of the statistical analyses were performed by the R3.4.3 Revised software. The Meta-prop function in the R software was used for the rate of merger. The prevalence reported in each study was logit transformed prior to computing the pooled prevalence [8]. Statistical heterogeneity was quantified using the Cochran's Q test and I^2 test. A high-level heterogeneity was considered if a high value of $I^2 > 75\%$ or a value of significance at $p < 0.10$. Owing to the high likelihood of heterogeneity between study variance, we used a random-effect model. Subgroup analysis and univariable random effects meta-regression were further conducted to explore the potential source of heterogeneity. Stratified analyses were conducted according to study design (cohort or cross-sectional), region (Asian or Non-Asian), sample size (< 100 or ≥ 100), year of publication (before 2012 or 2012–2017), and definition of PH based on PASP ≥ 35 mmHg (Yes or No). We conducted sensitivity analyses to estimate the influence of a study on the pooled prevalence by excluding one study at a time. Reporting bias was evaluated by the Egger's test [9]. $p < 0.05$ in 2-tailed test was considered statistically significant.

Results

Study selection, characteristics, and quality

As shown in Fig. 1, 692 results for relevant articles were retrieved via the above search strategy. Among them, 52 articles with full text were retrieved. Finally, 14 full texts were included in the meta-analysis [10–23]. The main

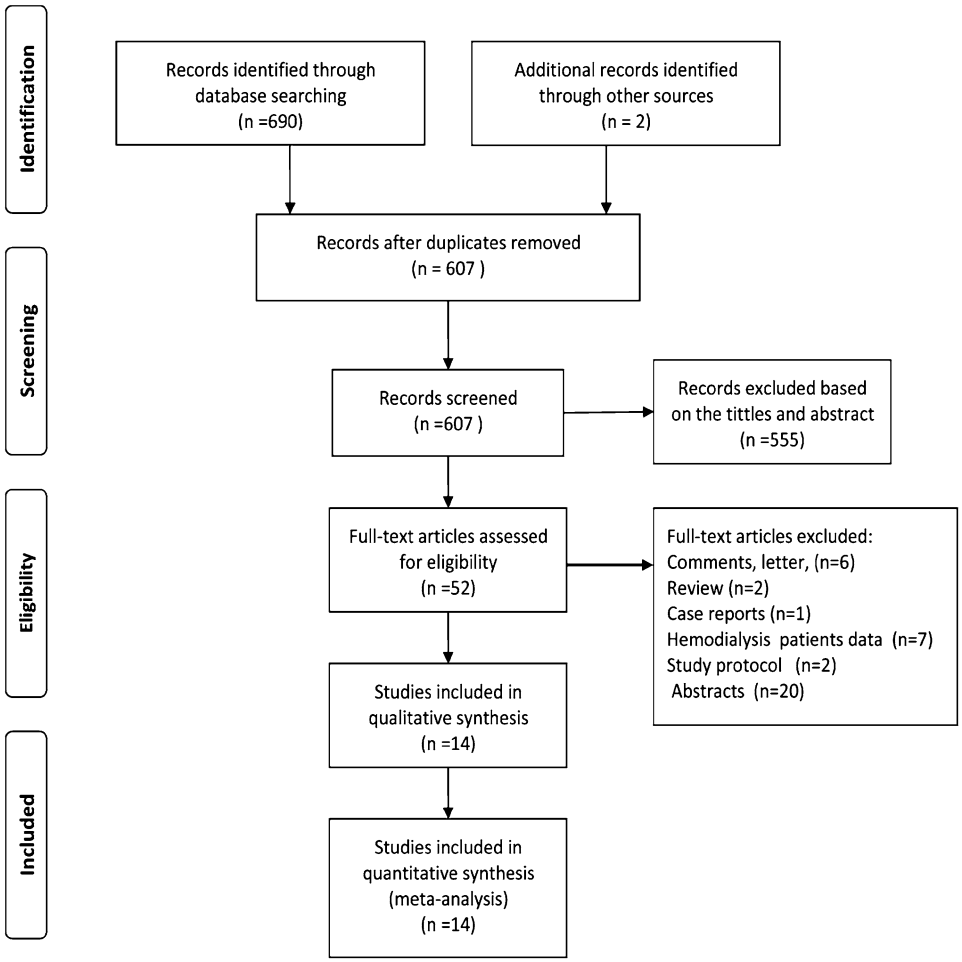

Fig. 1 Flow chart of study selection

Table 1 Characteristics of the included studies

Study	Design	Country	Sample size	Men (%)	Mean age	PH criteria	PH diagnostic methods	PH prevalence (%)
Yigla et al. [23]	Prospective	Israel	5	53.4 ($n=58$)	58.8 ($n=58$)	PASP ≥ 35	Echocardiography	0
Kumbar et al. [22]	Retrospective	USA	36	41.7	54.5	PASP ≥ 35	Echocardiography	42
Unal et al. [20]	Cross-sectional	Turkey	135	52.6	47.6	PASP > 35	Echocardiography	12.6
Bozbas et al. [21]	Retrospective	Turkey	68	73.4 ($n=500$)	31.6 ($n=500$)	PASP > 30	Echocardiography	5.9
Fabbian et al. [19]	Cross-sectional	Italy	27	62.7 ($n=56$)	60 ($n=56$)	PASP > 35	Echocardiography	18.5
Etemadi et al. [18]	Retrospective	Iran	32	45.4 ($n=$)	56.9 ($n=$)	PASP ≥ 35	Echocardiography	18.7
Oygar et al. [17]	Prospective	Cyprus	28	46.4	60	PASP ≥ 35	Echocardiography	35.7
Emara et al. [15]	Cross-sectional and retrospective	Saudi Arabia	12	58.3	46.1	PASP > 35	Echocardiography	16.7
Abedini et al. [16]	Cross-sectional	Iran	60	66.7	58.2	PASP ≥ 25	Echocardiography	8.3
Xu et al. [12]	Retrospective	China	618	57	50.5	PASP ≥ 35	Echocardiography	16
Alhamad et al. [14]	Prospective	Saudi Arabia	17	58.8	49.6	PASP ≥ 40	Echocardiography	23.5
Kim et al. [13]	Retrospective	Korea	88	47.7	54.8	PASP > 37	Echocardiography	22.7
Zeng et al. [11]	Prospective	China	180	68.9	56.4	PASP ≥ 35	Echocardiography	33.3
Zhang et al. [10]	Prospective	China	177	48	54.9	PASP ≥ 35	Echocardiography	36.5

PH pulmonary hypertension, *PASP* pulmonary artery systolic pressure.

characteristic of the studies included is presented in Table 1. Included studies were published during 2003–2016. These articles included 5 prospective, 5 retrospective, and 4 cross-sectional studies. Of these studies, three were conducted in China, two in Saudi Arabia, two in Turkey, two in Iran, one in Israel, one in United States, one in Italy, and one in Cyprus. Sample sizes of the included studies ranged from 5 to 618 patients and the mean age ranged from 41.7 to 73.4 years. According to the STROBE, 8 studies were deemed of high quality, and 6 of medium quality (Table S1).

PH prevalence

As shown in Fig. 2, the prevalence of PH in PD patients within the 14 individual study populations ranged between 0% and 42%, with an overall prevalence of 21% (95% CI 16–28). Significant heterogeneity was observed ($I^2 = 84\%$, $p < 0.01$). In addition, there were 9 studies reporting the prevalence of PH in HD patients, and the estimated prevalence of PH is 36% (95% CI 27–48) (Fig. 3).

Subgroup analyses and meta-regression

In most cases, high heterogeneity was still present in stratified analyses except for cross-sectional studies ($I^2 = 0\%$). In subgroup analyses, the increased prevalence was more significant in patients within cohort studies, non-Asian populations, large sample size, year of publication in 2012–2017, and definition of PH based on PASP ≥ 35 mmHg. We used meta-regression to explore the sources of heterogeneity and found that region, sample size, and year of publication may be potential sources of heterogeneity (Table 2).

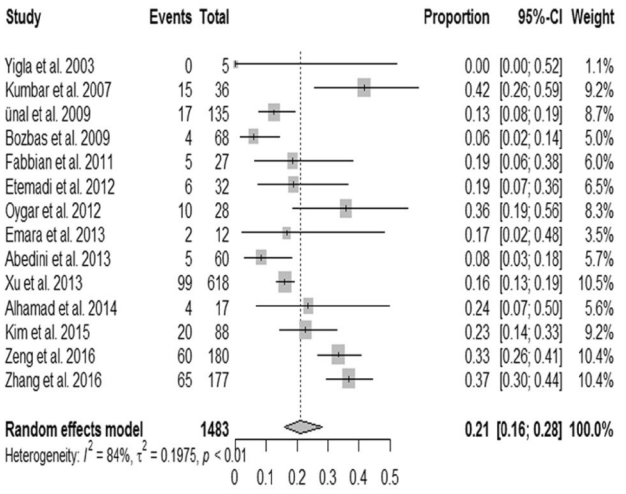

Fig. 2 Forest plot for prevalence of PH in PD

Sensitivity analyses and reporting bias

Sensitivity analyses were performed by excluding one study at a time (Fig. S1). And the results indicated that the omission of any studies led to changes in estimates between 20% (95% CI 14–27) and 23% (95% CI 17–30). The changes were not significant. The Egger's test ($p = 0.287$) showed no significant publication bias.

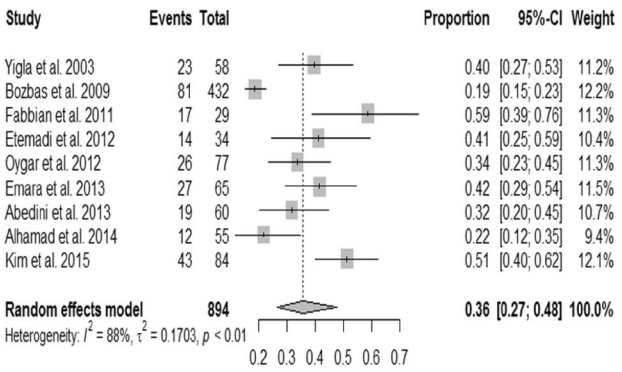

Fig. 3 Forest plot for prevalence of PH in HD

Table 2 Prevalence of PH in patients with PD

Subgroup	Prevalence	95% CI	I^2 (%)	p^a	p^b
Study design					
Cohort	0.25	0.18–0.34	86	< 0.01	0.0739
Cross-sectional	0.13	0.09–0.18	0	0.57	
Region					
Asian	0.20	0.14–0.27	85	< 0.01	0.0001
Non-Asian	0.30	0.14–0.65	69	0.07	
Sample size					
< 100	0.20	0.14–0.29	66	< 0.01	0.0002
≥ 100	0.23	0.14–0.37	95	< 0.01	
Year of publication					
Before 2012	0.16	0.07–0.34	84	< 0.01	0.0003
2012–2017	0.23	0.17–0.32	86	< 0.01	
Definition of PH based on PASP ≥ 35 mmHg					
Yes	0.24	0.18–0.34	86	< 0.01	0.0532
No	0.14	0.07–0.27	71	0.02	

[a] p value for heterogeneity among studies assessed with Cochran's Q test

[b] p value for interaction evaluated by meta-regression models

Discussion

To the best of our knowledge, this study is the first meta-analysis to present PH prevalence in PD patients. We confirmed PH is prevalent in PD patients. The prevalence of PH remained pronounced in all subgroups.

As with other published meta-analyses of this type [24, 25], our study has a high level of heterogeneity. We performed subgroup analyses and meta-regression analyses to explore sources of heterogeneity. In subgroup analyses, the prevalence of PH remained approximately 21% in all subgroups. Meta-regression analysis showed that region, sample size, and year of publication may be potential sources of heterogeneity. PH prevalence in PD patients is further increased and becomes statistically significant when we limit analysis to studies in non-Asians, and it is possible that the differences in information size (the Asian population of 1420 in our analysis was far larger than the non-Asian population of 63) may explain this finding. The prevalence of most studies published after 2012 was higher than that of published before 2012, suggesting that with the progress of medicine, the diagnostic methods and therapeutic levels of PD and PH are continuously improved.

Our study found that the prevalence of PH was lower in PD patients than in HD patients. This finding is in agreement with some studies [13, 15, 16, 18, 19, 21, 23]. However, Oygar et al.'s and Alhamad et al.'s studies showed the opposite results [14, 17]. A recent meta-analysis demonstrates that the prevalence of PH in CKD with stages 1, 2, 3, 4, and 5 was 10%, 13%, 28%, 30%, 30%, respectively [24]. Due to the limited data on PH in HD patients, for patients with ESRD requiring dialysis, further studies are needed in order to confirm the effect of different types of dialysis on PH.

Although investigators have yet to find the precise pathogenic mechanism of PH in ESRD populations, it is proposed that PH in ESRD is caused by diastolic dysfunction, left ventricular disorders, volume overload, endothelial dysfunction, sleep-disordered breathing, and vascular calcification [10, 26]. Nevertheless, few studies examined the risk factors promoting PH in PD patients. PH in PD patients may be induced by several risk factors such as serum albumin level, hypervolemia, NT-proBNP, C-reactive protein levels, and ejection fraction [10, 11, 20].

Several limitations of this meta-analysis must be considered. First, significant heterogeneity was detected in PD patients and PH, the differences in region, sample size, and year of publication were responsible for this between-study variation. Second, PASP was measured by echocardiography in PD patients rather than by cardiac catheterization, which may carry a risk for bias. Third, the sample sizes included studies were relatively small, which may have been under powered to detect certain differences. Fourth, most of the included studies did not provide a World Health Organization classification of PH. Therefore, we could not evaluate the association between different types of PH and PD. Finally, all of the included studies were observational studies in nature, residual confusion cannot be eliminated.

Conclusions

Our study demonstrates that about one-fifth of PD patients suffer from PH. However, because of significant heterogeneity and our small number of patients, the conclusion should be drawn cautiously. Further studies are necessary to confirm our findings and elucidate the precise mechanisms of development of PH in PD patients.

Author contributions JD and WS conceived and designed the study. YL, WS, BZ, and YR screened the abstract and full text, extracted data, assessed studies and drafted the manuscript. YL, WS, QL, and YS performed statistical analyses. YL, WS, and JD revised the manuscript. All authors read the manuscript and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Research involving human and animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

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