Title. Schistosomiasis-associated pulmonary arterial hypertension – a systematic review

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METHODS

Search strategy

This systematic review of the literature was registered on PROSPERO (CRD42018104066) and was performed according to PRISMA guidelines [1]. PubMed/MEDLINE, the Cochrane Library, SciELO, African Journals Online, and Google Scholar were searched in June 2018. Databases were searched with pre-specified search-terms including "schistosomiasis", "*Schistosoma*", pulmonary arterial hypertension, Sch-PAH, "Schistosomiasis-associated pulmonary arterial hypertension", "pathophysiology", "haemodynamics", "hemodynamics", "survival", "mortality" among others. The search terms for PubMed/MEDLINE are provided in the online supplement and were adapted for requirements of other databases. Only peer-reviewed, original literature published between January 1st 1990 and June 29th 2018 were included to ensure relevance and topicality. No restrictions on language were applied.

Population, inclusion and exclusion criteria, study design

This systematic review and meta-analysis aimed at adult, non-pregnant patients with Sch-PAH. Original research providing information on pathophysiologic mechanisms, hemodynamics and survival of Sch-PAH and iPAH patients were utilized.

Definitions of Sch-PAH and iPAH

Sch-PAH was defined as PAH, detected by right heart catheterization (mean pulmonary arterial pressure (mPAP) ≥25mmHg, mean pulmonary arterial wedge pressure (mPAWP) <15mmHg) associated with findings highly suggestive for schistosomiasis (primarily schistosomiasis mansoni), which included liver ultrasonographic findings highly likely to be associated with schistosomiasis (periportal fibrosis, left lobe enlargement), plus exposure to an endemic region of schistosomiasis, or presence of schistosomal eggs in microscopic examination of stool, urine, or rectal biopsy [2]. iPAH served as comparator to Sch-PAH [3, 4]. iPAH was defined as mPAP ≥25mmHg in the presence of a normal mPAWP <15mmHg and exclusion of CTEPH, PH due to lung disease and risk factors for other forms of PAH [5].

Outcomes – pathophysiologic mechanisms

Due to abundant data on pathophysiological mechanisms in iPAH, main pathophysiological patterns, as presented at the World Symposium on Pulmonary Hypertension (WSPH 2018), were considered (**Table 1**) and sought for similarities and analogies in Sch-PAH [6]. Basic science studies and animal studies were eligible for evaluation of the pathophysiologic mechanisms of Sch-PAH [7].

Outcomes – hemodynamics

Only data derived from national registries were sought for hemodynamics of iPAH due to abundance of these data. For hemodynamics in Sch-PAH, all peer-reviewed original studies assessing hemodynamics by right heart catheterization in human adults were included. Only hemodynamics from treatment naïve patients were considered in both iPAH and Sch-PAH. All studies assessing PAH by echocardiography were excluded from analysis.

Outcomes – survival

Survival data in iPAH were extracted from national registries. Survival data in Sch-PAH patients were derived from clinical registries, cross-sectional, and retrospective studies. Most studies assessed 3-year-survival and 5-year-survival. All studies assessed survival using Kaplan-Meier survival estimates based on all-cause mortality.

Study selection, data extraction and management

Two independent reviewers (DK and CG) assessed the studies for eligibility [8, 9]. In case of disagreement on inclusion or exclusion, controversies were settled by judgment of a third author (CK). Firstly, article titles and abstracts were screened, followed by assessment of full texts. In addition, references of the included articles were screened for further eligible studies. Studies were excluded on the following basis: no outcome measure reported, no variation in outcome measures, non-primary literature, conference posters or review articles, no variation in exposure, and non-human studies for

evaluation of hemodynamics and survival but not for pathophysiology. Disparities were resolved by consensus between DK and CG [9].

Statistical analysis

The grand mean and its standard deviation (SD) were calculated based on means ±SD from individual studies [10]. In a sensitivity-analysis, the grand mean and SD were recalculated after removing single studies in a stepwise manner. In a further sensitivity-analysis, the grand mean and SD were recalculated after removing the study with the largest study population in order to determine the influence of large sample sizes on the grand mean [9].

Grand means±SD of hemodynamic variables and survival of Sch-PAH patients were compared with those of iPAH using the independent student's t-test [11].

Quality assessment and ethics approval

This systematic review and meta-analysis was performed according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) initiative [1]. Two independent reviewers evaluated all included studies on quality and risk of bias. An adapted version of the Newcastle-Ottawa scale was utilized to assess the quality and risk of bias of hemodynamic and survival studies on Sch-PAH (**Table E1**) [12]. The SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool was used to assess animal studies for methodological quality [13, 14]. Furthermore, a proposal of this systematic review was submitted to the Ethics Committee of the London School of Hygiene and Tropical Medicine under the reference number #14675. No ethics approval was required as this systematic review and meta-analysis was conducted of already published, peer-reviewed data. There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Search terms for PubMed/MEDLINE.

Pathophysiologic mechanisms

- “schistosomiasis” AND “pulmonary arterial hypertension” AND “pathophysiology”
- “schistosoma” AND “pulmonary arterial hypertension“ AND “pathophysiology”
- “Sch-PAH” AND “pathophysiology”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “TGF”
- “schistosoma” AND “pulmonary arterial hypertension” AND “TGF”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “interleukin”
- “schistosoma” AND “pulmonary arterial hypertension” AND “interleukin”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “IL”
- “schistosoma” AND “pulmonary arterial hypertension” AND “IL”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “BMPR”
- “schistosoma” AND “pulmonary arterial hypertension” AND “BMPR”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “HIF”
- “schistosoma” AND “pulmonary arterial hypertension” AND “HIF”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “ICAM”
- “schistosoma” AND “pulmonary arterial hypertension” AND “ICAM”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “nitric oxide”
- “schistosoma” AND “pulmonary arterial hypertension” AND “nitric oxide”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “prostacycline”
- “schistosoma” AND “pulmonary arterial hypertension” AND “prostacycline”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “endothelin”
- “schistosoma” AND “pulmonary arterial hypertension” AND “endothelin”

Outcomes – hemodynamic patterns in right heart catheterization

iPAH

- “pulmonary arterial hypertension” AND “registry” [title]
- “pulmonary hypertension” AND “registry” [title]

Sch-PAH

- “schistosomiasis” AND “pulmonary arterial hypertension”
- “schistosoma” AND “pulmonary arterial hypertension“
- “schistosoma” AND “PAH“
- “schistosomiasis” AND “PAH“
- “schistosomiasis” AND “pulmonary arterial hypertension” AND “hemodynamics”
- “schistosoma” AND “pulmonary arterial hypertension“ AND “hemodynamics”
- “schistosoma” AND “PAH“ AND “hemodynamics”
- “schistosomiasis” AND “PAH“ AND “hemodynamics”
- “Sch-PAH“ AND “hemodynamics”

Outcomes – survival

- “schistosomiasis” AND “pulmonary arterial hypertension” AND “survival”
- “schistosoma” AND “pulmonary arterial hypertension“ AND “survival”
- “Sch-PAH” AND “survival”
- “schistosomiasis” AND “pulmonary arterial hypertension” AND mortality
- “schistosoma” AND “pulmonary arterial hypertension“ AND mortality
- “Sch-PAH” AND “mortality”

Table E1. Quality of evidence from individual studies on Sch-PAH included in meta-analysis.

		Newcastle-Ottawa Assessment Scale			
Author	**Design**	**Selection max = 4***	**Comparability max = 2***	**Exposure/Outcome max = 3***	**Risk of Bias**
Alves et al. 2015 [15]	Prospective study	***	**	***	Low
Fernandes et al. 2010 [4]	Retrospective study	**	**	***	Medium
Fernandes et al. 2012 [3]	Retrospective study	*		**	High
Fernandes et al. 2018* [16]	Cross-sectional study	**	**	***	Medium
Hoette et al. 2015 [17]	Retrospective study	**	**	***	Medium
Japyassú et al. 2012 [18]	Retrospective study	**		***	Medium
Lapa et al. 2009 [19]	Prospective study	****	**	***	Low
Valois et al. 2014 [20]	Cross-sectional study	***	**	***	Low

Low ROB: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Medium ROB: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; High ROB: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Sch-PAH=schistosomiasis-associated pulmonary arterial hypertension

*indicating studies utilized for only hemodynamics

†indicating case reports excluded from further analyses

Table E2. Included peer-reviewed studies on pathophysiologic mechanisms of Sch-PAH.

Author	Study design	Pathway/pathophysiological mechanism	*Schistosoma* species
Araújo et al. 2010 [21]	Animal study	HIF-1α, VEGF	*S. mansoni*
Chabon et al. 2014 [22]	Animal study	VEGF	*S. mansoni*
Crosby et al. 2010 [23]	Animal study	Vascular remodeling, Th1 and Th2 response	*S. mansoni*
Crosby et al. 2011 [23]	Animal study	Vascular remodeling, Praziquantel	*S. mansoni*
Crosby et al. 2015 [24]	Animal study	BMPR-II	*S. mansoni*
Dos Santos Ferreira et al. 2014 [25]	Case-control study	TGFβ, IL13	*S. mansoni*
Freitas et al. 2007 [26]	Animal study	TGFβ	*S. mansoni*
Graham et al. 2010 [27]	Animal study	IL13	*S. mansoni*
Graham et al. 2011 [28]	Human necropsy and animal study	Presence of egg antigen in lungs	*S. mansoni*
Graham et al. 2013 [29]	Human necropsy and animal study	TGFβ	*S. mansoni*
Graham et al. 2013 [30]	Animal study	IL6	*S. mansoni*
Kumar et al. 2015 [31]	Animal study	IL4, IL13	*S. mansoni*
Kumar et al. 2017 [32]	Animal study	TGFβ, TSP-1	*S. mansoni*
Mauad et al. 2014 [33]	Case-control study	Vascular remodeling, T-cell and mast cell density	*S. mansoni*
Oliveira et al. 2011 [34]	Animal study	NO, caveolin 1	*S. mansoni*
Osman et al. 2004[35]	*In vitro* study	TGFβ, SmSmad4	*S. mansoni*
Osman et al. 2006 [36]	*In vitro* study	TGFβR2	*S. mansoni*

Sun et al. 2017 [37]	Database study	BMPR-II, IL4, Eng, SMAD9	*S. mansoni*
Lapa et al. 2014 [38]	Case-control study	E-Selectin, P-Selectin, PDGF	*S. mansoni*

Table E3. Peer-reviewed studies included in meta-analysis of hemodynamics and survival of Sch-PAH.

Author	Country	Study period	Study design	Study population	*Schistosoma* species	n
Alves et al. 2015 [15]	Brazil	01/2008–12/2013	Prospective registry	PAH patients diagnosed at 1 center	NA	35
de Amorim Correa et al 2010† [39]	Brazil	NA	Case report	NA	*S. mansoni*	1
Fernandes et al. 2010 [4]	Brazil	2004 – 2008	Retrospective study	Sch-PAH and iPAH patients diagnosed at 1 center	*S. mansoni*	54
Fernandes et al. 2012* [3]	Brazil	06/2003–06/2010	Retrospective study	Sch-PAH patients diagnosed at 1 center	*S. mansoni*	12
Fernandes et al. 2018 [16]	Brazil	NA	Cross-sectional study	Sch-PAH patients diagnosed at 1 center	S. mansoni	102
Gavilanes et al. 2018† [40]	Brazil	NA	Case report	NA	NA	1
Hoette et al. 2015* [17]	Brazil	NA	Retrospective study	Sch-PAH and iPAH patients diagnosed at 1 center	*S. mansoni*	22
Japyassú et al. 2012* [18]	Brazil	01/2005–09/2009	Retrospective study	Sch-PAH patients diagnosed at 1 center	NA	84
Lapa et al. 2009* [19]	Brazil	01/2006–08/2007	Prospective study	Hepatosplenic schistosomiasis diagnosed at 1 center	*S. mansoni*	12
Mendes et al. 2010† [41]	Brazil	NA	Case report	NA	NA	1
Valois et al. 2014* [20]	Brazil	2007–2010	Cross-sectional study	Sch-PAH and iPAH patients diagnosed at 1 center	*S. mansoni*	8

Sch-PAH=schistosomiasis-associated pulmonary arterial hypertension; iPAH=idiopathic pulmonary arterial hypertension

*indicating studies utilized for only hemodynamics

†indicating case reports excluded from further analyses

Table E4. Hemodynamics of Sch-PAH patients from case reports.

Author	n	CO – L/min	CI – L/min/m^2	mRAP – mmHg	mPAP – mmHg	mPAWP – mmHg	PVR – WU	PVRI – WU•m^2
de Amorim Correa et al 2010[39]	1	NA	3	NA	88	NA	23	NA
Gavilanes et al. 2018 [40]	1	6.9	NA	NA	33	10	3.3	NA
Mendes et al. 2010 [41]	1	NA	3.9	7	53	NA	8	NA

CI=cardiac index; CO=cardiac output; mPAP=mean pulmonary artery pressure; mPAWP=mean pulmonary arterial wedge pressure; mRAP=mean right atrial pressure; PVR=pulmonary vascular resistance; PVRI=pulmonary vascular resistance index; Sch-PAH=schistosomiasis-associated pulmonary arterial hypertension

*only hemodynamics of untreated patients considered

Table E5. Clinical registries eligible for meta-analysis of hemodynamics and survival of iPAH.

Author/registry name	Country	Study period	Study design	Study population	n
Alves et al. 2015 [15] Brazilian registry	Brazil	2008–2013	Prospective registry	PAH patients diagnosed at 1 center	51
Badesch et al. 2010*[42] REVEAL	USA	03/2006–09/2007	Prospective registry	PAH patients diagnosed at 54 centers in the US	1,166
Baptista et al. 2013*[43] Portuguese registry	Portugal	2008–2010	Prospective registry	PAH and CTEPH patients diagnosed at 5 centers	17
Rich et al. 1987*[44] NIH registry	USA	07/1981–12/1985	Prospective registry	iPAH patients diagnosed at 32 centers	187
Benza et al. 2010†[45] REVEAL	USA	03/2006–09/2007	Prospective registry	PAH patients diagnosed at 54 centers in the US	1,262
D'Alonzo et al. 1991†[46] NIH registry	USA	07/1981–12/1985	Prospective registry	iPAH patients diagnosed at 32 centers	194
Escribano-Subias et al. 2012[47] Spanish registry	Spain	07/2007–06/2008	Retrospective and prospective registry	PAH patients diagnosed at 31 centers	314
Fischler et al. 2008[48] Swiss registry	Swiss	1999–2004	Prospective registry	PH patients diagnosed at 9 centers	76

Hoeper et al. 2013[49] COMPERA	Germany, Ireland, Italy, the Netherlands, UK	06/2007–11/2011	Prospective registry	PH patients diagnosed at 28 centers in 6 European countries	838
Humbert et al. 2006*[50] FPHN registry	France	10/2002–10/2003	Prospective registry	PAH patients diagnosed at 17 centers	264
Humbert et al. 2010†[51] FPHN registry	France	10/2002–10/2003	Prospective registry	PAH patients diagnosed at 17 centers	153
Jansa et al. 2014†[52] Czech registry	Czech Republic	2000–2007	Retrospective and prospective registry	PAH patients diagnosed at 4 centers	156
Ling et al. 2012[53] UK registry	UK, Ireland	2001–2009	Prospective registry	PAH patients diagnosed at 8 centers	448
Thenappan et al. 2007*[54] PHC	USA	1982–2006	Retrospective and prospective registry	PAH patients diagnosed at 3 centers	254
Thenappan et al. 2010†[55] PHC	USA	1982–2007	Retrospective and prospective registry	PAH patients diagnosed at 3 centers	239
Zhang et al. 2011[56] Chinese Registry	China	2007–2009	Retrospective registry	PAH patients diagnosed at 5 centers	173

COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN=French pulmonary hypertension network; iPAH=idiopathic pulmonary arterial hypertension; NIH=national institute of health; PHC=pulmonary hypertension connection; REVEAL=Registry to Evaluate Early And Long-term PAH Disease Management

*indicating publications utilized for only hemodynamics; † indicating publications utilized for only survival

Table E6. Hemodynamics of Sch-PAH patients. Mean hemodynamic parameters of Sch-PAH patients with calculated grand means.

Author	**n**	**CO – L/min**	**CI – L/min/m²**	**mRAP – mmHg**	**mPAP – mmHg**	**mPAWP – mmHg**	**PVR – WU**	**PVRI – WU•m²**
Alves et al. 2015 [15]	35	4.7 1.5	NA	10±5	44±14	11±4	9±5	NA
Fernandes et al. 2010 [4]	54	4.6±1.5	NA	10±5	57±19	11±3	11±6	NA
Fernandes et al. 2012 [3]	12	NA	2.7±0.6	11±6	64±19	12±3	12±7	NA
Fernandes et al. 2018* [16]	50	4.6±1.6	NA	10±5	52±17	12±4	10±7	NA
Hoette et al. 2015 [17]	22	3.8±1.2	NA	9±4	56±23	15±7	10±6	NA
Japyassú et al. 2012 [18]	84	NA	2.7±0.9	12±7	59±15	NA	12±6	NA
Lapa et al. 2009 [19]	12	4.8±1.1	NA	11±4	41±10	13±7	7±6	NA
Valois et al. 2014 [20]	8	4.0±0.6	2.4±0.5	12±5	58±19	13±3	12±6	NA
Grand mean	**277**	**4.4±1.3**	**2.6±0.7**	**11±5**	**54±17**	**12±4**	**10±6**	**NA**

CI=cardiac index; CO=cardiac output; mPAP=mean pulmonary artery pressure; mPAWP=mean pulmonary arterial wedge pressure; mRAP=mean right atrial pressure; NA=not applicable; PVR=pulmonary vascular resistance; PVRI=pulmonary vascular resistance index; Sch-PAH=schistosomiasis-associated pulmonary arterial hypertension; *only hemodynamics of untreated patients considered

Table E7. Hemodynamics of iPAH patients in clinical registries. Mean hemodynamic parameters of iPAH patients with calculated grand means.

Author/registry name	n	CO – L/min	CI – L/min/m^2	mRAP – mmHg	mPAP – mmHg	mPAWP – mmHg	PVR – WU	PVRI – WU•m^2
Rich et al. 1987 [44]	187	NA	2.3±0.9	10±6	60±18	8±4	NA	26±14
NIH registry								
Humbert et al. 2006 [50]	259	NA	2.3±0.7	9±5	56±14	8±3	NA	23±10
FPHN registry								
Thenappan et al. 2007 [54]	254	NA	2.0±0.7	11±7	56±13	10±4	14±7	NA
PHC								
Fischler et al. 2008 [48]	76	4.1±1.3	NA	9±7	49±17	NA	NA	NA
Swiss registry								
Badesch et al. 2010 [42]	1,166	NA	2.2±0.8	10±6	52±13	9±4	NA	23±11
REVEAL								
Escribano-Subias et al. 2012 [47]	314	NA	2.4±0.7	8±5	55±15	NA	12±6	NA
Spanish registry								
Ling et al. 2012 [53]	448	NA	2.1±0.7	10±6	54±14	9±4	NA	23±10
UK registry								
Baptista et al. 2013 [43]	17	4.2±1.5	NA	11±6	53±15	11±3	12±6	NA
Portuguese registry								

Hoeper et al. 2013 [49]	587	NA	2.2±0.7	8±5	44±12	10±3	10±6	NA
COMPERA								
Alves et al. 2015 [15]	51	4.1±1.3	NA	11±5	61±20	11±4	14±6	NA
Brazilian registry								
Zhang et al. 2011 [56]	173	NA	2.5±0.9	12±6	63±18	13±5	17±10	NA
Chinese Registry								
Grand mean	**3532**	**4.1±1.4**	**2.3±0.8**	**10±6**	**55±15**	**10±4**	**13±7**	**24±11**

CI=cardiac index; CO=cardiac output; COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN=French pulmonary hypertension network; iPAH=idiopathic pulmonary arterial hypertension; NIH=national institute of health; mPAP=mean pulmonary artery pressure; mPAWP=mean pulmonary arterial wedge pressure; mRAP=mean right atrial pressure; NA=not applicable; PHC=pulmonary hypertension connection; PVR=pulmonary vascular resistance; PVRI=pulmonary vascular resistance index; REVEAL=Registry to Evaluate Early And Long-term PAH Disease Management

Table E8. Survival rates of Sch-PAH patients in clinical registries. Mean survival of Sch-PAH patients with calculated grand means and standard deviation of all included studies.

Author	n	1-year survival – %	2-year survival – %	3-year survival – %	5-year survival – %
Alves et al. 2015 [15]	35	77	54	34	NA
Fernandes et al. 2010 [4]	54	95	95	86	NA
Fernandes et al. 2018 [16]	102	Treated: 100 Untreated: 92	Treated: 100 Untreated: 88	Treated: 94 Untreated: 78	Treated: 89 Untreated: 69
Grand mean	**191**	**91±9.9**	**84.3±20.8**	**73±26.8**	**79±14.1**
Excluding untreated arm		**90.7±12.1**	**83±25.2**	**71.3±32.6**	**-**
Excluding treated arm		**88±9.6**	**79±21.9**	**66±28**	**-**

Table E9. Survival rates of iPAH patients in clinical registries. Mean survival of iPAH patients with calculated grand means and standard deviation of all included studies.

Author/registry name	n	1-year survival – %	2-year survival – %	3-year survival – %	5-year survival – %
D'Alonzo et al. 1991 [46]	194	68	NA	48	34
NIH registry					
Humbert et al. 2010 [51]	153	83	67	58	NA
FPHN registry					
Thenappan et al. 2010 [55]	239	92	NA	75	66
PHC					
Fischler et al. 2008 [48]	76	89	78	73	NA
Swiss registry					
Benza et al. 2010 [45]	1,262	91	NA	74	65
REVEAL					
Escribano-Subias et al. 2012 [47]	314	89	NA	77	68
Spanish registry					
Ling et al. 2012 [53]	448	93	84	73	61
UK registry					
Hoeper et al. 2013 [49]	587	92	83	74	NA
COMPERA					

Jansa et al. 2014 [52] Czech registry	156	85	70	62	NA
Alves et al. 2015 [15] Brazilian registry	51	97	91	87	NA
Zhang et al. 2011 [56] Chinese Registry	173	68	57	39	21
Grand mean	**3653**	**86.1±9.7**	**75.7±11.7**	**67.3±14.1**	**52.5±19.9**

COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN=French pulmonary hypertension network; iPAH=idiopathic pulmonary arterial hypertension; NIH=national institute of health; PHC=pulmonary hypertension connection; REVEAL=Registry to Evaluate Early And Long-term PAH Disease Management

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