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Research Articles

Markers of pediatric respiratory distress predictive of poor outcome in low- and middle-income countries: a systematic review

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Background

Lower respiratory tract diseases remain significant causes of pediatric mortality in low- and middle-income countries. In these settings, staff must quickly triage patients for timely initiation of treatment and potential transfer to higher levels of care. World Health Organization (WHO) guidelines focus on two physical exam findings – tachypnea and chest indrawing – without addressing the multitude of other respiratory assessment tools used by healthcare workers. This lack of additional validated markers makes triage of patients challenging. The aim of this study was to systematically review respiratory assessments in children under five years of age that have been associated with poor clinical outcomes in resource limited settings.

Methods

We conducted a systematic search for studies published between January 1, 2008 and January 21, 2018 using Ovid MEDLINE and Embase including patients five years of age and younger. Major categories of search terms were "respiratory distress", "respiratory symptoms", "low- and middle-income countries" and "clinical assessment". We extracted data relevant to study characteristics, respiratory assessments and clinical outcomes.

Findings

Out of 2317 identified publications, 63 full text articles fit inclusion criteria, 56 reported statistically significant associations and were included in analyses and these publications included 53 unique study populations. Publications were from: low-income countries (26%), lower middle-income countries (55%) and upper middle-income countries (19%). The most common respiratory assessments were hypoxia (50%), tachypnea (46%) and chest indrawing/retractions (38%). Death was the most frequently reported clinical outcome (54%), followed by hypoxia (23%). Hypoxia, chest indrawing/retractions and tachypnea were the most commonly reported risk factors for mortality.

Conclusions

Hypoxia, chest retractions and tachypnea are key risk factors for mortality form pediatric respiratory disease in resource limited settings. Death is the primary outcome of interest for research in this area. As pediatric respiratory interventions are deployed in these settings, better understanding of which respiratory assessments are predictive of poor clinical outcomes could guide management and transfer of care decisions.

Lower respiratory tract diseases remain significant causes of pediatric mortality globally, accounting for 16% of deaths under age five.[1–3] The burden of respiratory mortality is greatest in low- and middle-income countries (LMICs) where many health facilities lack sufficient pediatric acute care resources.[4,5] Staff in resource-limited facilities must quickly triage patients using available assessment techniques for timely initiation of treatment and potential transfer to higher levels of care. World Health Organization (WHO) guidelines for care of sick children focus on two physical exam findings- tachypnea and chest indrawing- without addressing the multitude of other respiratory assessment tools used by healthcare workers.[6,7] The lack of additional validated markers of respiratory distress linked to relevant clinical outcomes makes triage of these pediatric patients challenging.[8]

Treatment options for pediatric respiratory distress including oxygen, continuous positive airway pressure (CPAP)

and high flow nasal canula (HFNC) are increasingly available in LMICs; however, evidence-based treatment algorithms for initiation and use of these therapies are lacking.[9,10] Several studies have looked at the correlation of respiratory symptoms or composite scores to important single clinical markers which may indicate therapy is needed. A meta analysis of children with lower respiratory tract infections, however, did not find a single clinical sign or symptom that accurately and reliably identified hypoxemia.[11] Although scores of dyspnea are in use to guide management of asthma and bronchiolitis, they have undergone limited and inadequate validation for disease severity.[12,13] Additionally, many resource-limited settings (RLS) lack technology to perform advanced diagnostics used to guide therapy, such as blood gas analysis and pulmonary function tests. As pediatric respiratory interventions are deployed in RLS, understanding which respiratory assessments are predictive of poor clinical outcomes could guide management and transfer of care decisions.

The objective of this review is to determine which respiratory assessments in children under five years of age have been associated with poor clinical outcomes in RLS.

METHODS

We conducted a systematic review of the literature following the PRISMA checklist.[14] We conducted a search for studies published between January 1, 2008 and January 21, 2018 using Ovid MEDLINE (**Online Supplementary Document**, *Appendix S1*) and Embase.com. All results were limited to English, German or Spanish languages and ages 0-5. Major categories of search terms were "respiratory distress", "respiratory symptoms", "low- and middle-income countries (LMIC)" and "clinical assessment".

ELIGIBILITY CRITERIA

Publications that met the following criteria were included:

1. Took place in a low- or middle-income country as defined by the World Bank, July 2019.[15]
2. ⩾ 50% of subjects were under five years of age.
3. Evaluation of subjects occurred in a hospital, emergency department or outpatient clinic setting (not in a home).
4. Respiratory diagnostic assessment, including physical exam, vital sign, laboratory test and/or diagnostic/imaging study, was performed (no parent report symptoms) .
5. Association between a respiratory diagnostic assessment and a poor clinical outcome (including death, clinical course, transfer, monitoring or laboratory result and/or treatment requirement) was reported.

Publications that met the following criteria were excluded:

1. Not original research (comments, editorials, letters and/or notes).
2. Systematic reviews.
3. Case reports or case series with <30 patients.
4. Respiratory diagnostic assessment involved advanced equipment, such as respiratory viral PCR and/or pulmonary function testing.
5. Clinical outcome was a diagnosis, such as pneumonia and/or bronchiolitis.

DATA EXTRACTION

Citations were managed with Covidence (Copyright © 2019 The Cochrane Collaboration).[16] Five reviewers screened and discussed 100 abstracts to reach consensus on inclusion and exclusion criteria. Four reviewers screened an additional 30 abstracts, of which 60% were included/rejected unanimously with an inter-rater reliability of 0.57. Remaining abstracts were screened by one reviewer, and included abstracts underwent full text review. Two reviewers reviewed and reached consensus on inclusion of full text publications and categorization of bias. Disagreement on study inclusion/ exclusion, data selection and bias assessment were resolved by discussion between the two reviewers. If no concensus was found between two reviewers, discussions between all review authors was used to resolve the disagreement. Data was extracted into REDCap (8.11.9- ©2019 Vanderbilt University).[17]

ASSESSMENT OF BIAS

We used the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) score to objectively evaluate bias in six domains,[18] namely:

1. Selection of participants – Selection biases caused the inadequate selection of participants
2. Confounding variables – Selection biases caused by the inadequate confirmation and consideration of confounding variables.
3. Measurement of exposure – Performance biases caused by inadequate measurements of exposure.
4. Blinding of outcome assessments – Detection biases caused by the inadequate blinding of outcome assessments.
5. Incomplete outcome data – Attrition biases caused by the inadequate handling of incomplete outcome data.
6. Selective outcome reporting – Reporting biases caused by the selective reporting of outcomes.

For each domain, a study was determined to have "low risk," "high risk," or "unclear risk" of bias according to specific score criteria. Two reviewers performed bias assessment on each publication.

DATA SYNTHESIS

Given the heterogeneity of publications, a meta-analysis was not performed. In line with the review objective, we focused analysis on publications reporting a statistically significant association between an assessment and outcome for reporting results. The data were summarized descriptively, stratified by country income level.[15] When >1 publication described identical study populations (study location, age group, inclusion criteria, study dates), the study population was only included once in **Table 2** (summary characteristics). All other analyses report data from each in-

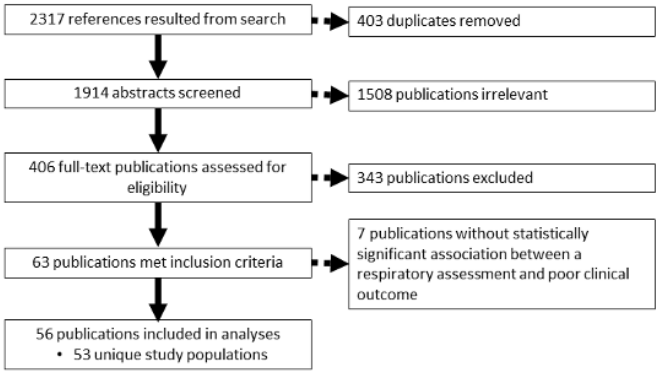

Figure 1: Flowchart of Study Evaluation

dividual publication regardless of population overlap. "Statistical significance" was determined by the authors of the manuscripts.

RESULTS

Of 2317 identified publications, 1914 abstracts were screened, and 406 underwent full text review. 343 publications were excluded after full text review because: they did not fit inclusion criteria (79%), no full texts were available (12%) or the content was not relevant (9%). 56 of 63 full text publications reported statistically significant associations and were included in analyses (**Figure 1**) – representing 53 unique study populations. Kuti[19–21] and Chisti[22,23] published multiple manuscripts using identical study populations. Two additional publications by Chisti described study populations enrolled during almost identical study periods at the same site and some patients may have been included in both publications.[24,25] We did not receive author confirmation about this question, so these populations were considered unique in this analysis. Relevant findings of each publication, stratified by country income level, are summarized in **Table 1** (plates A, B and C) with more details found in the **Online Supplementary Document**, *Appendix S2*.

Table 1A. Low income country publications included

Ref	Author, Year	Country	Primary setting‡	Age range	Assessment → Outcomes reported	Bias categories§					
						1	2	3	4	5	6
26	Acacio S, 2015	Mozambique	Outpatient	1 - 59m	Crepitations or rales/ fever/ wheeze or rhonchi → referral from peripheral health center to district hospital outpatient department† Crepitations or rales†/ Nasal flaring → referral to emergency department†	🟢	🟢	🟢	🟡	🟢	🟢
27	Basnet S, 2015	Nepal	Inpatient	1 - 59m	CXR finding/ Hypoxia --> increased time to recovery of illness†/ treatment failure†	🟢	🟢	🟢	🟢	🟢	🟢
28	Bassat Q, 2008	Mozambique	Inpatient	1 - 59m	Chest indrawing → death†	🟢	🟢	🟢	🟡	🟡	🟡
29	Bassat Q, 2016	Mozambique	Inpatient	0 - 59m	Hypoxia → prolonged admission/ death Chest indrawing/ CXR finding/ cyanosis†/ grunting/ nasal flaring/ tachypnoea†/ thoracoabdominal breathing† → hypoxia	🟢	🟢	🟢	🟢	🟢	🟢
30	Graham SM, 2011	Malawi	Inpatient	1m - 17y	Hypoxia → death	🟡	🔴	🟢	🟢	🟡	🟢
31	John BM, 2015	Nepal	NICU	Preterm - 1m	Downe's score/ hypoxia → death/ increased frequency of respiratory support at 72 hours of age/ mechanical ventilation	🟢	🔴	🟢	🟢	🟡	🟡
32	King C, 2016	Malawi	Outpatient	1 - 59m	Hypoxia → non-recovery at day 5†	🟡	🟡	🔴	🟡	🔴	🟢
19	Kuti BP, 2013	Gambia	Inpatient	1 - 59m	Cyanosis†/ grunting†/ head nodding → hypoxia	🟢	🟢	🟢	🟢	🟡	🟢
20	Kuti BP, 2013	Gambia	Inpatient	1 - 59m	Grunting/ hypoxia → death	🟢	🟢	🟢	🟢	🟡	🟢
21	Kuti BP, 2014	Gambia	Inpatient	1 - 59m	Grunting/ head nodding → prolonged hospital stay	🟢	🟢	🟢	🟡	🟡	🟢
33	McCollum ED, 2013	Malawi	Inpatient	0m - 17y	Chest indrawing/ nasal flaring/ tachypnoea → hypoxia	🟢	🟡	🟢	🟢	🟢	🟢
34	Nantanda R, 2008	Uganda	Inpatient	1 - 11m	Grunting/ hypoxia → death	🟢	🟢	🟢	🟢	🟢	🟢
35	Nantanda R, 2014	Uganda	Inpatient	1 - 59m	Hypoxia → death† / prolonged hospital stay	🟢	🟢	🟢	🟢	🟢	🟢
36	Ramakrishna B, 2012	Malawi	Inpatient	1m - 17y	Hypoxia → death	🟢	🟢	🟢	🟢	🟢	🟢
37	Sigauque B, 2009	Mozambique	Inpatient	0 - 59m	Crepitations → (decreased) death Wheezing/rhonchi → death	🟢	🟡	🟢	🟢	🟢	🟢
38	Wandeler G, 2015	Senegal	Inpatient	1 - 59m	Cyanosis†/ nasal flaring/ tachypnoea/ → hypoxia Chest-indrawing/ grunting → hypoxia*	🟢	🟢	🟢	🟢	🟢	🟢

🟢 = low risk of bias, 🟡 = unclear risk of bias, 🔴 = high risk of bias

† Association significant on multivariate analysis. ‡ Primary Setting: Inpatient = Inpatient general ward. PICU = Pediatric Intensive Care Unit. Emergency = Emergency Department. Outpatient = Outpatient clinic

§ Bias categories: 1.) Comparibility of participants 2.) Confounding variables 3.) Measurement of Exposure 4.) Blinding of outcome assessments 5.) Incomplete outcome data 6.) Selective outcome reporting

Table 1B. Lower middle income country publications included

Ref	Author, Year	Country	Primary setting‡	Age range	Assessment → Outcomes reported	Bias categories§ 1	2	3	4	5	6
39	Abdulkadir MB, 2015	Nigeria	Inpatient	1 - 59m	Hypoxia → death/ prolonged hospitalization	🟢	🟡	🟢	🟡	🟢	🟢
40	Addo-Yobo E, 2011	Bangladesh + 3	Outpatient	1 - 59m	Tachypnoea → treatment failure†	🟡	🟢	🟢	🟡	🟢	🟢
41	Agweyu A, 2014	Kenya	Inpatient	1 - 59m	Grunting → treatment failure	🟢	🟡	🟢	🟡	🟡	🟢
42	Agweyu A, 2018	Kenya	Inpatient	1 - 59m	Fever/ lower chest wall indrawing/ tachypnoea → death†	🟡	🟡	🟡	🟢	🟢	🟢
43	Asghar R, 2008	Bangladesh + 6	Inpatient	1 - 59m	Hypoxia → death/ treatment failure†	🟢	🟢	🟢	🟡	🟢	🟢
44	Ashraf H, 2012	Bangladesh	Outpatient	1 - 59m	Hypoxia/ tachypnoea → clinical failure	🟢	🔴	🟢	🟡	🟡	🟢
45	Awasthi S, 2008	India	Outpatient	1 - 59m	Tachypnoea → clinical failure†	🟢	🟢	🟢	🟢	🟢	🟢
46	Benet T, 2017	India + 3	Inpatient	1 - 59m	CXR finding/ cyanosis/ lower chest indrawing/ (lack of) rasping → hypoxia Hypoxia → death/ prolonged hospitalization	🟢	🟡	🟢	🟢	🟢	🟢
47	Bharti B, 2008	India	Inpatient	1m - 17y	CXR finding → length of stay	🟢	🟡	🟡	🟢	🟡	🟢
23	Chisti MJ, 2011	Bangladesh	Inpatient	1 - 59m	Hypoxia → death†	🟢	🟡	🟢	🟢	🟢	🟢
22	Chisti MJ, 2012	Bangladesh	Inpatient	1 - 59m	Lower chest indrawing/ nasal flaring → hypoxia†	🟢	🟡	🟢	🟢	🟢	🟢
24	Chisti MJ, 2013	Bangladesh	PICU	0 - 59m	Hypoxia → death†	🟢	🟢	🟢	🟢	🟢	🟢
25	Chisti MJ, 2013	Bangladesh	Inpatient	0 - 59m	Lower chest wall indrawing†/ tachypnoea → hypoxia	🟢	🟢	🟢	🟢	🟢	🟢
48	Chudasama RK, 2012	India	Inpatient	1 - 59m	Fever → death/intensive care unit admission	🟢	🟡	🟢	🟢	🟢	🟢
49	El Kholy AA, 2014	Egypt	Inpatient	1m - 17y	Cyanosis → prolonged length of hospital stay	🟢	🟡	🟡	🟢	🟡	🟢
50	Emukule GO, 2014	Kenya	Inpatient	0 - 59m	Tachypnoea → (decreased) death Chest wall indrawing†/ hypoxia/ nasal flaring/ wheezing → death	🟢	🟢	🟢	🟢	🟢	🟢
51	Gowraiah V, 2014	India	Inpatient	0 - 59m	Tachypnoea → death	🟢	🔴	🟢	🟡	🟡	🟡
52	Hazir T, 2011	Pakistan	Outpatient	1 - 59m	Wheezing → therapy failure	🟢	🟡	🟢	🟢	🟢	🟢
53	Ibraheem RM, 2014	Nigeria	Inpatient	1 - 59m	Hypoxia → difficult breathing Abnormal percussion note/ bronchial breath sounds/ cyanosis/ grunting/ intercostal retractions/ lower chest indrawing† → hypoxia	🟢	🟡	🟢	🟢	🟡	🟢
54	Jroundi I, 2014	Morocco	Inpatient	1 - 59m	CXR finding/ cyanosis†/ fever/ hypoxia/ tachypnoea/ wheezing → poor prognosis (death, intensive care or Respiratory Index Severity Children (RISC) score ≥3)	🟢	🟢	🟢	🟡	🟡	🟢
55	Mahajan V,	India	Emergency	1- 59m	Chest retractions/ fever/ grunting/ hypoxia/ tachypnoea → hospital admission†	🔴	🟢	🟢	🟡	🟢	🟢

	2016											
56	Morgan MC, 2017	Kenya	NICU	Preterm - 28d	Grunting/ nasal flaring/ retractions → **hypoxia†** Hypoxia/ nasal flaring → death†	🟢	🟢	🟢	🟢	🟢	🟢
57	Mwaniki MK, 2009	Kenya	Inpatient	0 - 59m	Hypoxia → death†	🟢	🟢	🟢	🟢	🟢	🟢
58	Naheed A, 2009	Bangladesh	Inpatient	0 - 59m	Tachypnoea → (decreased) death Chest indrawing → death	🟢	🟢	🟢	🟢	🟢	🟢
59	Orimadegun AE, 2013	Nigeria	Inpatient	0 - 17y	Chest retractions/ fast or difficult breathing/ grunting/ nasal flaring → hypoxia	🟢	🟡	🟢	🟢	🟢	🟢
60	Quiambao BP, 2009	Philippines	Inpatient	0 - 11m	Apnea/ CXR finding/ chest indrawing → death	🟢	🟢	🟢	🟢	🟢	🟢
61	Rao YK, 2012	India	Emergency	1 - 59m	Cyanosis/ grunting/ nasal flaring/ tachypnoea → hypoxia	🟡	🟡	🟢	🟢	🟢	🟢
62	Singla G, 2015	India	NICU	Preterm - 1m	Low respiratory rate/ hypoxia → death Abnormal respiratory rate/ hypoxia/ chest recessions/ respiratory distress → prolonged hospitalization Cyanosis → shortened hospitalization in surviving neonates	🟢	🔴	🟢	🟢	🔴	🟢
63	Webb C, 2012	Kenya	Inpatient	1 - 59m	Hypoxia → treatment failure	🟢	🟡	🟢	🟢	🟡	🟢
64	Wilson PT, 2017	Ghana	Inpatient	1 - 59m	Hypoxia/ tachypnoea → death†	🟢	🟡	🟢	🟢	🟢	🟢

🟢 = low risk of bias, 🟡 = unclear risk of bias, 🔴 = high risk of bias

† Association significant on multivariate analysis. ‡ Primary Setting: Inpatient = Inpatient general ward. PICU = Pediatric Intensive Care Unit. Emergency = Emergency Department. Outpatient = Outpatient clinic

§ Bias categories: 1.) Comparibility of participants 2.) Confounding variables 3.) Measurement of Exposure 4.) Blinding of outcome assessments 5.) Incomplete outcome data 6.) Selective outcome reporting

Table 1C. Upper middle income country publications included

Ref	Author, Year	Country	Primary setting‡	Age range	Assessment → Outcomes reported	Bias categories§					
						1	2	3	4	5	6
65	Araya S, 2016	Paraguay	Inpatient	1m - 17y	CXR finding/ (absence of) fever/ hypoxia/ tachypnoea → death	🟢	🟡	🟢	🟡	🟢	🟢
66	Coarasa A, 2010	Argentina	Emergency	1 - 24m	Argentinian respiratory distress scale/ Chilean respiratory distress scale --> hypoxia Chest indrawing --> hypoxia†	🟢	🟡	🟢	🟢	🟢	🟢
67	le Roux DM, 2015	South Africa	Outpatient	0 - 11m	Chest indrawing/ fever/ hypoxia /tachypnoea → inpatient admission	🟢	🟡	🟡	🔴	🟡	🟢
68	Lum LC, 2011	Malaysia	PICU	0 - 59m	Tachypnoea → mechanical ventilation	🟢	🟢	🟢	🔴	🟢	🟢
69	Mesquita M, 2009	Paraguay	Emergency	1 - 59m	Higher Respiratory Distress Assessment Instrument (RDAI) scores → hospital admission	🟢	🟢	🟢	🟡	🟢	🟢
70	Nathan AM, 2014	Malaysia	Inpatient	1m - 17y	Hypoxia → risk of life threatening disease†	🟢	🟡	🟢	🟢	🟢	🟢
71	Reed C, 2012	South Africa	Inpatient	1 - 59m	Hypoxia/ chest indrawing/ intercostal retractions/ wheezing/ tachypnoea → death†	🟢	🟢	🟢	🟢	🟢	🟢
72	Vidaurreta SM, 2011	Argentina	Inpatient	1 - 59m	Cyanosis/ retractions/ tachypnoea/ wheezing → hospital admission†	🟢	🔴	🟢	🟡	🟡	🟢
73	Vilas-Boas AL, 2014	Brazil	Inpatient	1 - 59m	Fever†/ chest retractions/ tachypnoea†/ wheezing† → treatment failure Crackles → (decreased) treatment failure†	🟢	🟢	🟢	🟢	🟢	🟢
74	Zhang Q, 2013	China	PICU	1 - 59m	Wheezing → (decreased) death/ (decreased) length of PICU stay/ (decreased) mechanical ventilation Head nodding → mechanical ventilation/ death Cyanosis/ grunting or groaning/ hypoxia/ tachypnoea → prolonged PICU stay/ mechanical ventilation/ death	🟢	🟡	🟢	🟡	🟢	🟢

🟢 = low risk of bias, 🟡 = unclear risk of bias, 🔴 = high risk of bias

† Association significant on multivariate analysis. ‡ Primary Setting: Inpatient = Inpatient general ward. PICU = Pediatric Intensive Care Unit. Emergency = Emergency Department. Outpatient = Outpatient clinic.

§ Bias categories: 1.) Comparibility of participants 2.) Confounding variables 3.) Measurement of Exposure 4.) Blinding of outcome assessments 5.) Incomplete outcome data 6.) Selective outcome reporting

Table 2: Description of studies

Category†	Count (n = 53)	(Percent)
Economic Category of Country‡		
Low Income	14	(26%)
Lower Middle Income	29	(55%)
Upper Middle Income	10	(19%)
Continent‡		
Africa	26	(49%)
Asia	22	(42%)
Europe	0	(0%)
North America	0	(0%)
South America	5	(9%)
Age of patients (may include more than one category)		
Premature infants (<37 weeks gestation)	3	(6%)
Neonates (0 - 28 days)	16	(30%)
Infants (29 days - <1 year)	50	(94%)
1 - <5 years	47	(89%)
5 - <18 years	8	(15%)
Primary Clinical Setting		
Outpatient	7	(13%)
Emergency Department	5	(9%)
Inpatient General Ward	35	(66%)
Pediatric Intensive Care Unit	3	(6%)
Neonatal Intensive Care Unit	3	(6%)
Type of Study		
Prospective (Cohort, case control, cross sectional)	37	(70%)
Retrospective Cohort	10	(19%)
Randomized Control Trial	6	(11%)
Type of Analysis		
Univariate	48	(91%)
Multivariate	31	(58%)

Multiple publications describing the same study[22,23] as well as these[19–21] were counted only once. †Most common category reported when >1 country in study. ‡World Bank.[15]

General characteristics of unique study populations are described in **Table 2**. Fifty-five percent of studies occurred in lower middle-income countries, and inpatient general wards was the most common clinical settings. Most studies included infants and/or children 1-4 years, with median patient age of 11 months (when reported). The number of study subjects aged less than 5 years ranged from 65 to 16,162, with a median of 420 (when reported). Bias distribution is shown in **Figure 2**. The confounding variables domain had the highest risk of bias, with 11% of publications having "high risk" and 39% having "unclear risk".

Respiratory assessments are reported in **Table 3**. Some trends by country income existed, for example, chest indrawing was most frequent in upper middle-income countries while low-income countries were most likely to report grunting and nasal flaring. Hypoxia, defined by most studies as oxygen saturation <90%, was the most common respiratory assessment and reported equally frequently among all income levels. Twenty publications reported increased mortality in hypoxic vs. non-hypoxic children with ranges of [(3.8%–29.0%) vs. (0%–7.1%) and odds ratios of (1.6–14.8)]. Nine publications reported prolonged admission or treatment failure in children with hypoxia.

Tachypnea was reported by twenty-six publications (**Table 3**). Tachypnea was defined by age-appropriate cutoffs in most publications but also as "fast breathing"[59] and "abnormal respiratory rate"[62] which included high and low rates. Upper middle-income country publications reported associations with tachypnea more often than other income categories and country income was associated with the outcome linked to tachypnea. All seven studies reporting an association between tachypnea and hypoxia were conducted

Table 3. Assessments of respiratory distress reported with statistically significant relationship to clinical outcome

	All Publications (n = 56)		Low Income (n = 16)		Lower Middle Income (n = 30)		Upper Middle income (n = 10)	
Assessment	**Count**	**(%)**	**Count**	**(%)**	**Count**	**(%)**	**Count**	**(%)**
Physical Exam Findings								
Chest Indrawing/ Retractions	21	(38%)	4	(25%)	12	(40%)	5	(50%)
Grunting	11	(20%)	5	(31%)	5	(17%)	1	(10%)
Cyanosis	10	(18%)	3	(19%)	5	(17%)	2	(20%)
Nasal Flaring	9	(16%)	4	(25%)	5	(17%)	0	(0%)
Wheezing	9	(16%)	2	(13%)	3	(10%)	4	(40%)
Head Bobbing	3	(5%)	2	(13%)	0	(0%)	1	(10%)
"Respiratory Distress"/ "Difficulty Breathing"	3	(5%)	0	(0%)	3	(10%)	0	(0%)
Crepitations, Rales, Crackles	5	(9%)	4	(25%)	0	(0%)	1	(10%)
Apnea	2	(4%)	0	(0%)	2	(7%)	0	(0%)
Other Exam Findings†	4	(7%)	1	(6%)	3	(10%)	0	(0%)
Vital Signs								
Hypoxia/Low Oxygen Saturation	28	(50%)	8	(50%)	15	(50%)	5	(50%)
Tachypnoea /Abnormal Respiratory Rate	26	(46%)	4	(25%)	14	(47%)	8	(80%)
Fever	9	(16%)	2	(13%)	4	(13%)	3	(30%)
Radiology								
Chest Xray Finding	8	(14%)	2	(13%)	5	(17%)	1	(10%)
Scores								
Respiratory Scores	4	(7%)	1	‡ (6%)	0	(0%)	3	§ (30%)

Publications may have included more than one of each category.
†Other exam findings: Thoracoabdominal breathing, abnormal percussion note, bronchial breath sounds, (lack of) rasping.
‡ Downe's Score. §Respiratory Distress Assessment Index (Lowell 1987), Argentinean Respiratory Distress Scale and Chilean Respiratory Distress Scale.

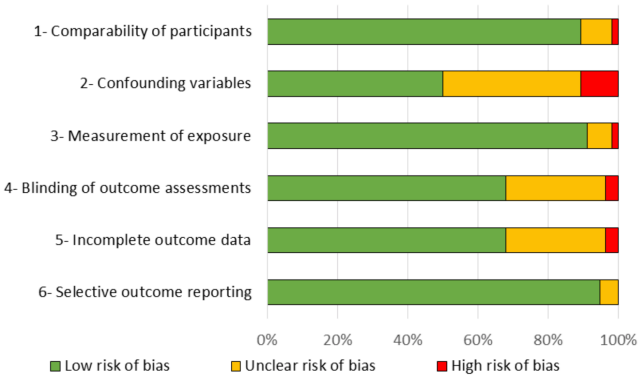

Figure 2: Distribution of types of bias assessments

* As defined by Kim et al.[18]

in low- or low middle-income countries.[29,33,38,55,59,61,75] Meanwhile the seven studies reporting increased mortality with tachypnea were conducted in low middle- or upper middle-income countries.[42,51,54,64,65,71,74] The mortality ranged from 1.7%-10.0% in tachypnoeic children vs. 0.7%-4.1% in non-tachypnoeic children. Two other publications instead reported decreased mortality in tachypnoeic children. Naheed (2009) evaluated 4155 Bangladeshi children 2- 59 months hospitalized with pneumonia and found that 95% of survivors, and 83% of non-survivors were

Table 4. Poor clinical outcomes reported with statistically significant relationship to respiratory assessment

	All Publications (n = 56)		Low Income (n = 16)		Lower Middle Income (n = 30)		Upper Middle Income (n = 10)	
Outcome	**Count**	**(%)**	**Count**	**(%)**	**Count**	**(%)**	**Count**	**(%)**
Clinical Course								
Death	30	(54%)	9	(56%)	17	(57%)	4	(40%)
General Ward Admission	4	(7%)	0	(0%)	1	(3%)	3	(30%)
ICU Admission	3	(5%)	0	(0%)	2	(7%)	1	(10%)
Referral to Higher Level of Care	1	(2%)	1	(6%)	0	(0%)	0	(0%)
Poor Prognosis	1	(2%)	0	(0%)	1	(3%)	0	(0%)
Treatment Course								
Length of Hospitalization	9	(16%)	3	(19%)	5	(17%)	1	(10%)
Treatment Failure	7	(13%)	1	(6%)	5	(17%)	1	(10%)
Prolonged Recovery	3	(5%)	2	(13%)	1	(3%)	0	(0%)
Treatment Requirement								
Hypoxia	13	(23%)	4	(25%)	8	(27%)	1	(10%)
Mechanical Ventilation	3	(5%)	1	(6%)	0	(0%)	2	(20%)
Continous Positive Airway Pressure	1	(2%)		(0%)	0	(0%)	1	(10%)
Respiratory Support at 72 hours	1	(2%)	1	(6%)	0	(0%)	0	(0%)

Publications may have included more than one of each category.

tachypnoeic (P<0.001).[58] Non-survivors were more likely to have severe pneumonia, but analyses were not adjusted for severity of illness. Emukule (2014) evaluated 3581 Kenyan children less than 5 years hospitalized with respiratory illness. Sixty-four percent of survivors had tachypnea versus 56% of non-survivors (odds ratio, OR=0.7, 95% confidence interval, CI=0.5-0.9); however, this association was not significant in multivariate analysis.[50]

Clinical outcomes are reported in **Table 4**. The most commonly reported clinical outcome was death (54%), followed by hypoxia (23%), length of hospitalization (16%) and treatment failure (13%). Hypoxia was the most commonly reported risk factor associated with mortality (77%), followed by chest indrawing/retractions, (27%) and tachypnea (23%). No trends by income level existed for death, length of hospitalization nor treatment failure. Upper middle-income countries were more likely to report outcomes of general ward admission or need for mechanical ventilation.

Three authors reported risk factors for hypoxia and increased mortality in hypoxemic patients in the same study population. Bassat (2016) evaluated 825 children less than five years of age hospitalized with respiratory distress in Mozambique and found that tachypnea, cyanosis and thoracoabdominal breathing were independently associated with hypoxia, and these hypoxemic children had increased mortality (20% vs. 7%).[29] Kuti used a population of 420 Gambian children to report risk factors for hypoxia, including head nodding (35% vs 16%), grunting (61% vs 23%), and cyanosis (20% vs <1%)[19] and increased mortality in hypoxic vs. non hypoxic children (40% vs 18%).[20] Benet (2017)'s multicenter study of 405 hospitalized children (2 - 60 months old) reported risk factors for hypoxemia including: lower chest indrawing (90% vs. 77%), cyanosis (14% vs. 5%), lack of "rasping" (17% vs 6%), and generalized opacification on chest X-ray (CXR) (44% vs. 28%) as well as higher mortality in hypoxemic children (9% vs 2%).[46]

DISCUSSION

To our knowledge, this is the first systematic review of markers of pediatric respiratory distress associated with poor clinical outcomes in LMICs. Our findings underscore substantial heterogeneity in the literature related to this topic and this precluded meta-analysis.

This study demonstrates the following key findings: i) hypoxia, chest indrawing/retractions, and tachypnea are the most commonly reported risk factors for child mortality from respiratory disease in RLS; ii) studies in RLS most frequently report death as the primary outcome of pediatric respiratory illness; iii) hypoxia is a key respiratory assessment and outcome of interest in RLS; and iv) few trends exist related to reporting of respiratory assessments or outcomes based upon country income level.

The results of this review serve several purposes for clinicians and researchers caring for children in RLS: With increasing availability of advanced respiratory support (HFNC and CPAP), clinicians need validated criteria for identifying children likely to benefit from this support and/or in need of transfer to higher levels of care.[7] It can also help re-

searchers to develop and implement respiratory scores, choosing predictors based upon available resources and patient population.

Hypoxia, chest indrawing/retractions, and tachypnea were the assessments most commonly associated with mortality in this review. This is a reflection likely of a true physiologic association as well as the frequency with which these assessments are performed and studied in these populations. These assessments are in line with World Health Organization guidelines using tachypnea and chest indrawing as indications for antibiotic therapy and for categorization of pneumonia severity.[7] A recent meta-analysis from predominantly LMICs found that the strongest predictors of a pneumonia diagnosis in children under 5 years were tachypnea (likelihood ratio, LR=1.9), chest indrawing (LR=1.8) as well as grunting (LR=1.8) and nasal flaring (LR=1.8).[76] While evidence-based diagnosis is important for medication treatment including antibiotics and bronchodilators, determining severity of disease is more essential to guide respiratory treatments and transfer decisions. The heterogeneity of poor clinical outcomes in this review has limited the ability to do a meta-analysis, however some systematic reviews have reported associations with specific clinical outcomes. A recent systematic review in infants less than 60 days in RLS found that the strongest predictors of hospital admission were tachypnea (OR=1.5-3.1), grunting (OR=1.5 –2.9), severe chest indrawing (OR=1.5–8.9), and cyanosis (OR=1.5–25.8).[77]Several of these same exam findings have been previously reported to increase the likelihood of hypoxia: cyanosis (LR=10.4), grunting (LR=2.6), nasal flaring (LR=2.2) and chest retraction (LR=2.6); however authors concluded that "neither single nor combined symptoms and signs have satisfactory performance in predicting hypoxia among young children with acute respiratory infection".[10] Although our findings emphasize the importance of these common respiratory assessments, the heterogeneity in studies makes identifying optimal predictors for variably resourced clinical settings challenging.

Death was the most commonly reported outcome for respiratory disease in this review. Given that over 800,000 children under five died from lower respiratory diseases in 2017, it is not surprising that reducing mortality remains the focus.[2] Ongoing inequities in access to respiratory care, such as oxygen and CPAP, contribute to this discrepancy in mortality.[78–80] We did not find a trend toward reporting non-mortality outcomes as income level increased, in contrast to high-income countries that have transitioned to reporting predominantly non-mortality outcomes.[81–83] This could reflect high mortality rates in upper middle income countries, making death still the most relevant outcome. Alternatively, it may reflect differences in facility-level resources and mortality risk independent of country income level, given known differences in within-country resource availability and access to care. As more regional estimates of disease burden are reported through the local burden of disease project, we may gain understanding of how within country allocation of resources influences outcomes and potential respiratory assessments.[84,85]

The heterogeneity of reported risk factors and outcomes in this review is not unique to markers of respiratory distress or to RLS. Inconsistencies in measurement and reporting of outcomes are widespread and make it challenging to draw conclusions from many systematic reviews. Many researchers advocate for the development of core outcome sets, which contain a standardized collection of outcomes that should be measured and reported for a particular disease entity.[86] Development of a core outcome set for pediatric respiratory disease in RLS would need to involve stakeholders across the resource spectrum to ensure that the agreed upon collection of outcomes are relevant to their settings, similar to approaches used by inFACT, a network of investigator - led clinical research consortia that aims to promote international collaboration in critical care research and address barriers in undertaking trials.[87] A core outcome set could reduce study heterogeneity and improve the ability to use existing data to answer important clinical questions.

This review has a number of limitations. By focusing on publications reporting statistically significant associations with clinical outcomes, we introduced selection bias in addition to existing publication bias favouring significant associations. We minimized this bias by including studies reporting only univariate associations although likely many univariate associations would be not remain significant after multivariate analysis. We used LMICs as a proxy for RLS and categorized studies by country income, which may not equate to comparable resource availability in individual study sites. There was inadequate information about study location (urban vs. rural, national vs. district hospital) or available resources to develop a better stratification schema. We excluded multiple assessments of respiratory illness a priori, including more expensive laboratory or diagnostic tests (PCRs, PFTs), elements of patient history (ie cough) and non-specific danger signs (inability to drink, persistent vomiting, convulsions, lethargy, severe malnutrition) to focus on items most pertinent to respiratory disease in RLS. Only three publications evaluating composite scores were included in this review, which may relate to our search strategy or a paucity of validation of scores in RLS. We excluded specific diagnoses, such as pneumonia or asthma, as valid outcomes because these can be subjective or based on diagnostic criteria that include our assessments of interest (ex. tachypnea for pneumonia). Given the broad nature of the research question, our search strategy identified a large number of abstracts that could only be screened by one reviewer, increasing selection bias. For two publications we were unable to determine if they referred to the same study population, which could affect data in **Table 2**.

CONCLUSIONS

In conclusion, this review emphasizes the importance of hypoxia, chest retractions, and tachypnea as risk factors for mortality while highlighting death as the primary outcome of interest for pediatric respiratory disease in RLS. Given wide variability in clinical settings in LMIC, we were unable to determine consistent, validated markers of pediatric respiratory distress that correlate to poor clinical outcomes. Clinicians and researchers throughout LMIC would benefit from development of a core outcomes set to standardize methodology in future studies. More uniform measurement

of outcomes across RLS should allow for more thorough review with meta-analysis to be performed. An analysis like this has the potential to aid clinicians and researchers in identifying which markers of respiratory distress best identify children at highest risk of clinical deterioration and mortality.

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Competing interests: Author AH is an author of two abstracts in the search. She did not review these abstracts for inclusion. The authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author), and declare no other conflicts of interest.

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SUPPLEMENTARY MATERIALS

Appendix 1

Download: https://www.joghr.org/article/14136-markers-of-pediatric-respiratory-distress-predictive-of-poor-outcome-in-low-and-middle-income-countries-a-systematic-review/attachment/39268.docx

Appendix 2

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