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Original Research Article

A systematic review of clinical decision tools used for diagnosing pulmonary embolism in the pediatric population

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Abstract

Objective: This review aims to evaluate the diagnostic accuracy of existing, adult clinical decision tools for pulmonary embolism, in the pediatric population. As a secondary objective, this review aims to summarize the diagnostic use of pre-identified risk factors and clinical features of pulmonary embolism in the pediatric population.
Methods: A systematic search and screening of the Pubmed, Embase, CINAHL, and Cochrane databases was done in January 2018. Studies evaluating the diagnostic accuracy of clinical decision tools and/or risk factors and clinical features for pulmonary embolism in the pediatric population were included. The measures of diagnostic accuracy of clinical decision tools were calculated. The pooled sensitivity and specificity of risk factors were calculated using a bivariate random effects model. All included studies were assessed for quality using QUADAS-2.
Results: Six studies were included: three case-control and three retrospective cohort studies. We found that no standard clinical decision tool for pulmonary embolism has been evaluated in the pediatric population. As well, adult clinical decision tools have low diagnostic utility in pediatrics.
Conclusion: Adult clinical decision tools should not be used for pediatric patients. There was no single risk factor or clinical feature displaying reliable sensitivity; however, a central venous line, a recent surgery, or the finding of hemoptysis, all have a positive likelihood ratio greater than two, demonstrating their potential diagnostic utility. Large, prospective cohort studies are needed.

Keywords: pediatric, pulmonary embolism, clinical decision making, clinical decision rules, clinical decision tools

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Introduction

Pulmonary embolism has long been described and studied in the adult population because of the high mortality and morbidity rates; however, there is a lack of research addressing pulmonary embolism in pediatric patients. The incidence of pulmonary embolism in this younger population is steadily increasing as medical advances allow critically ill children with predisposing conditions, such as congestive heart disease and malignancy, to survive for longer (1-4).

Pulmonary embolism in the pediatric population, as in the adult population, is correlated with increased morbidity and a high mortality rate of around 10% (5). As emboli interrupt pulmonary blood flow, cardiac output is obstructed, and consequently hypotension and hypoxia occur(1,3,6,7). Additionally, recurrent thrombosis is a problem in the pediatric population (8). Using information from the Canadian Childhood Thrombophilia Registry, Monagle et. al, have found that over a mean follow up of 2.86 years, 8.1% of pediatric patients with pulmonary embolism had recurrent thrombosis (8).

Adding to the difficulty of pediatric pulmonary embolism diagnosis is the invasive and expensive nature of the current diagnostic gold standard, pulmonary angiography (9). Other available methods for diagnosing pulmonary embolism are ventilation perfusion scans and computed tomography pulmonary angiography. While ventilation perfusion scans offer a more accessible method, conditions like congenital heart disease, known to predispose pediatric patients to pulmonary embolism, can interfere with the interpretation of test results (10,11). On the other hand, computed tomography pulmonary angiography requires radiation exposure, which is accompanied by risks that are still undetermined in the pediatric population (12). This further necessitates valid and reliable clinical decision tools to aid physician decision making around when to clinically rule-out pulmonary embolism, and when to subject patients to more invasive and potentially harmful testing.

While numerous clinical decision tools for pulmonary embolism are validated in the adult population, such as the Wells criteria, Pulmonary Embolism Rule-out Criteria (PERC), and the revised Geneva score, there is a paucity of information available for the pediatric population (13-15). This can be partially attributed to the low incidence of pediatric pulmonary embolism, and as such, current medical practices for pediatric pulmonary embolism are based off of data from the adult population (1,7,9,16). There are, however, important differences in pulmonary embolism between the pediatric and adult populations. Pediatric pulmonary embolism is often clinically silent and exists primarily in patients with underlying medical conditions, such as congenital heart disease or infection, that mask the acute pulmonary embolism diagnosis (8,17). Thus, clinicians may have a low suspicion of pulmonary embolism in the pediatric population. This makes the acceptance of adult recommendations for the pediatric population less than ideal (1,18).

The aim of this systematic review is to synthesize the available literature that evaluates the diagnostic validity of clinical decision tools for pulmonary embolism in the pediatric population. As a secondary objective, this systematic review will summarize the diagnostic

validity of risk factors and clinical features for pulmonary embolism in the pediatric population, in order to aid in the development of a clinical decision tool specific to the pediatric population.

Methods

Search strategy

Electronic searches were conducted for Pubmed via Medline, Embase via OVID, CINAHL via EBSCO and the Cochrane Controlled Trials registry on January 26th, 2018. The following search terms were used for Medline and modified for each database: (pulmonary embolism[MeSH] OR pulmonary embolism) AND (diagnosis[MeSH] OR diagnosis* OR decision tree[MeSH] OR OR decision trees OR decision support techniques[MeSH] OR decision support techniques OR d-dimer OR clinical prediction OR clinical decision) AND (paediatric OR pediatric OR children OR child). Additionally, reference lists from retrieved publications were screened for missing articles. Publications were restricted to studies published after 2000 and written in English. The year 2000 was chosen as the cut-off point for the year of publication, as the first clinical decision tool for pulmonary embolism was published in 2001.

Study selection

Two members of the study team independently scrutinized titles and abstracts, and judged articles to be excluded or to undergo full-text article review. Studies were deemed acceptable for full-text review if the title and/or abstract indicated that the paper evaluated the diagnosis of venous thromboembolism or pulmonary embolism in the pediatric population, or if it did not present an age range in the abstract.

The full-text article was obtained if it was judged eligible by at least one reviewer. A full-text screening form was created and piloted. Cohen's Kappa was calculated to determine the interrater reliability prior to conducting the full-text review. These full-text articles were then judged to be included or excluded by two independent reviewers, and consensus for inclusion was reached by discussion mediated by a third reviewer.

Eligibility criteria

Inclusion criteria

In order to be included, studies had to meet the following criteria:

1. The study included children 21 years or younger as per the American Academy of Pediatrics definition. The study must also have presented separate information for this age group.

2. Patients had a suspected diagnosis of pulmonary embolism.
3. Medical findings used in the clinical decision tool, including patient's risk factors and physical examination details were described in adequate detail.
4. A diagnosis of pulmonary embolism was confirmed by radiography such as computed topography pulmonary angiography or ventilation/perfusion scans.

Exclusion criteria

Studies with the following characteristics were excluded:

1. Case reports, case series, and systematic reviews.
2. All children in study were diagnosed with pulmonary embolism.
3. Insufficient detail reported on patient's risk factors and physical examination findings.

Assessment of study quality

Two reviewers blinded to the paper's author, journal, and institution independently assessed the risk of bias and applicability of these studies using QUADAS-2, a tool designed specifically for evaluating studies of diagnostic test accuracy (19).

Data Extraction

A data extraction form was created and piloted. Two reviewers independently extracted relevant data. The following data was collected from each study: date of publication, journal of publication, geographic location of study, study design, clinical setting (eg. hospital outpatient, hospital inpatient, or emergency department), type of reference standard applied (eg. ventilation- perfusion lung scan, helical computed tomography, computed tomography pulmonary angiography), demographic characteristics of sample (age range, mean age, sex), prevalence of pulmonary embolism in the study population, clinical decision tool evaluated and corresponding 2x2 tables, risk factors (eg. oral contraception use, central venous catheterization, malignancy, surgery, and dehydration) and clinical features (eg. heart rate, SpO_2) evaluated, and the outcome of patients with each risk factor and clinical feature. If key data was missing, article authors were contacted regarding missing information.

Statistical analysis

Primary Outcome Analysis

The primary outcome was the diagnostic accuracy of the clinical decision tools. This included the sensitivity, specificity, positive predictive values, negative predictive values, positive likelihood ratios, negative likelihood ratios, and their corresponding 95% confidence intervals. These were calculated using the *RcmdrPlugin.EZR* package in R (R Version 3.5.0) (20).

Secondary Outcome Analysis

As a secondary outcome, the diagnostic accuracy of each risk factor and clinical feature was calculated. For risk factors and clinical features evaluated in five or more studies, the bivariate random-effects model was used to summarize the sensitivity and specificity using the *mada* package in R (R Version 3.5.0) (20-22). The positive and negative likelihood ratios were not pooled, but calculated as point estimates from the pooled sensitivity and specificity values (23). Heterogeneity was also quantified using the I^2 value which estimated the percentage of total variation that is due to heterogeneity between the studies rather than chance and takes into account the number of included studies. I^2 scores range from 0% (no heterogeneity) to 100% (extreme heterogeneity).

For findings evaluated in less than five studies, sensitivities, specificities, positive and negative likelihood ratios were calculated using the *madad* function in the *mada* package in R (R Version 3.5.0) (20). These were presented along with their corresponding 95% confidence intervals.

Results

As shown in **Figure 1**, over 3000 titles and abstracts were screened, and 6 articles met the final inclusion and exclusion criterion. The characteristics of these six studies can be found in **Table 1**. The risk of bias and applicability of included studies assessed using the QUADAS-2 Tool are displayed in **Table 2** and **Table 3**, respectively.

Clinical Decision Tools

Out of the included studies, only two studies evaluated the accuracy of preexisting clinical decision tools (Pulmonary Embolism Rule Out Criteria and Wells Criteria); however, five out of six studies created clinical decision tools after data analysis. A brief description of the clinical decision tools and their diagnostic accuracies are displayed in **Table 4.**

Risk Factors and Clinical Features

Table 5 displays the pooled measures of sensitivity and specificity of risk factors and clinical features that were evaluated in five studies. No risk factors nor clinical features were evaluated by all six studies. The measures of heterogeneity, positive likelihood ratios, and negative likelihood ratios are also displayed. The appendices display the measures of diagnostic accuracy of risk factors and clinical features evaluated in four or fewer studies.

Figure 1. PRISMA Flow Diagram

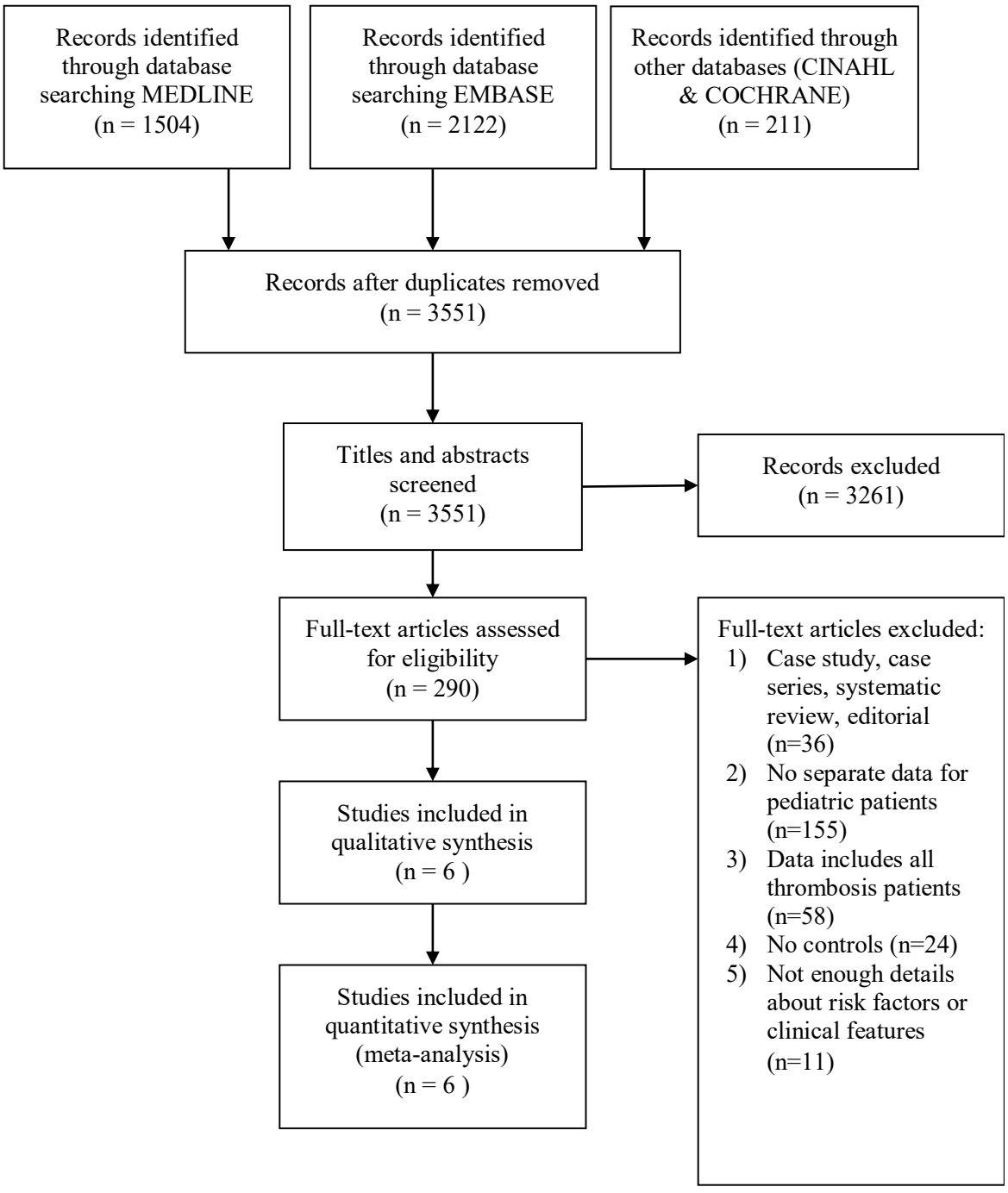

Table 1. Characteristics of Included Studies

Authors	Clinical setting[a]	Study design	Reference Standard[b]	Cases			Controls			Funding
				Median age (range)[c]	n	% Female	Median age (range)[c]	n	% Female	
Biss 2009 (24)	Non-specific hospital	Case-Control	VQ, CTPA, PA or ECHO	13 (0.003-17)	50	46%	12 (1-17)	25	44%	Baxter Bioscience Canada, Heart and Stroke Foundation of Canada
Hennelly 2016 (25)	ED	Retrospective Cohort	(VQ OR CTPA) AND treatment	15.2 (IQR: 13.9-20)	36	56%	16.9 (IQR: 15-20.8)	525	67%	Not specified
Lee 2011 (26)	ED, IP, and OP	Retrospective Cohort	CTPA	Mean 13.6 (SD: 5.4)	36	50%	Mean 14.1 (SD: 4.0)	191	54%	Not specified
Wang 2015 (27)	ED	Case-Control	VQ OR CTPA	15 (12-18)	11	91%	15 (3-18)	39	67%	No external funding
Kanis 2017 (28)	ED, IP and OP	Retrospective Cohort	VQ OR CTPA	15 (IQR: 13-16)	51	49%	15 (14-17)	492	68%	The Eli Lilly Foundation Physician Scientist Award
Victoria 2008 (29)	Non-specific hospital	Case-Control	VQ OR CTPA	Mean 17 (13-21; SD: 2.6)	13	70%	Mean 17 (13-21; SD: 2.4)	26	69%	Not specified

[a] ED = emergency department; IP = inpatient; OP = outpatient

[b] VQ = ventilation–perfusion scan; CTPA = computed tomography pulmonary angiography; PA = conventional pulmonary angiography; ECHO = echocardiogram.

[c] IQR = interquartile range; SD = standard deviation. IQR or SD was included if age range of included cases was unavailable.

Table 2. Assessment of risk of bias in included studies using the QUADAS-2 tool

	Biss 2009[24]	**Hennelly 2016[25]**	**Lee 2011[26]**	**Wang 2015[27]**	**Kanis 2017[28]**	**Victoria 2008[29]**
Patient Selection: Could the selection of patients have introduced bias?	High	Low	Low	High	High	High
Index Test: Could the conduct and interpretation of the index test have introduced bias?	High	Unclear	Unclear	Unclear	High	Unclear
Reference Standard: Could the reference standard, its conduct, or its interpretation have introduced bias?	High	Unclear	Low	Unclear	Unclear	Unclear
Flow and Timing – Could the patient flow have introduced bias?	High	High	Low	High	High	High

Table 3. Assessment of applicability in included studies using the QUADAS-2 tool

	Biss 2009[24]	**Hennelly 2016[25]**	**Lee 2011[26]**	**Wang 2015[27]**	**Kanis 2017[28]**	**Victoria 2008[29]**
Patient Selection: Are there concerns that the included patients do not match the review question?	Low	Low	Low	High	High	Low
Index Test: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	High	High	High	High	High	High
Reference Standard: Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	High	Low	Low	High	Low

Table 4. Diagnostic accuracy of clinical decision tools evaluated in primary studies

Clinical Decision Tool Evaluated	A priori or Post hoc	# of disease+	# of disease-	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive predictive value	Negative predictive value	LR+ (95% CI)	LR− (95% CI)
Biss 2009: Wells Simplified Probability Score[24]	A priori	50	25	0.720 (0.575 - 0.838)	0.600 (0.387 - 0.789)	0.783 (0.636 - 0.891)	0.517 (0.325 - 0.706)	1.800 (1.081 - 2.998)	0.467 (0.270 - 0.807)
Biss 2009: Wells Simplified Probability Score & D-Dimer[24]	A priori	27	12	0.593 (0.388 - 0.776)	0.667 (0.349 - 0.901)	0.800 (0.563 - 0.943)	0.421 (0.203 - 0.665)	1.778 (0.753 - 4.197)	0.611 (0.333 - 1.120)
Hennelly 2016: PERC (excluding age <50 years) [25]	A priori	36	525	1.000 (0.858 - 1.000)	0.240 (0.204 - 0.279)	0.083 (0.059 - 0.113)	1.000 (0.957 - 1.000)	1.316 (1.254 - 1.381)	0.000 (N/A)
Hennelly 2016: Wells (alternate diagnosis is less likely than PULMONARY EMBOLISM = 0) [25]	A priori	36	525	0.167 (0.064 - 0.328)	0.960 (0.940 - 0.975)	0.222 (0.086 - 0.423)	0.944 (0.921 - 0.962)	4.167 (1.795 - 9.672)	0.868 (0.749 - 1.006)
Hennelly 2016: Wells (alternate diagnosis is less likely than PULMONARY EMBOLISM = 3) [25]	A priori	36	525	0.861 (0.705 - 0.953)	0.579 (0.536 - 0.622)	0.123 (0.085 - 0.170)	0.984 (0.963 - 0.995)	2.046 (1.734 - 2.413)	0.240 (0.106 - 0.543)
Hennelly 2016: PULMONARY EMBOLISM Model One of: Use of OCPs. Age-specific tachycardia, Hypoxia (SPO2 < 95%)[25]	A priori	36	525	0.889 (0.739 - 0.969)	0.560 (0.516 - 0.603)	0.122 (0.085 - 0.167)	0.987 (0.966 - 0.996)	2.020 (1.738 - 2.348)	0.198 (0.079 - 0.501)
Lee 2011: PULMONARY EMBOLISM Model At least one of: Immobilization, hypercoagulable state, excess estrogen state (OCP), Indwelling CVL, Prior PULMONARY EMBOLISM and/or DVT.[26]	Post hoc	36	191	0.944 (0.813 - 0.993)	0.634 (0.561 - 0.702)	0.327 (0.238 - 0.426)	0.984 (0.942 - 0.998)	2.577 (2.104 - 3.156)	0.088 (0.023- 0.339)
Lee 2011: PULMONARY EMBOLISM Model At least two of: Immobilization, hypercoagulable state, excess estrogen state (OCP), Indwelling CVL, Prior PULMONARY EMBOLISM and/or DVT. [26]	Post hoc	36	191	0.889 (0.739 - 0.969)	0.942 (0.899 - 0.971)	0.744 (0.588 - 0.865)	0.978 (0.945 - 0.994)	15.434 (8.597 - 27.710)	0.118 (0.047 - 0.297)
Lee 2011: PULMONARY EMBOLISM Model Three or more of: Immobilization, hypercoagulable state, excess estrogen state (OCP), Indwelling CVL, Prior PULMONARY EMBOLISM and/or DVT. [26]	Post hoc	36	191	0.333 (0.186 - 0.510)	1.000 (0.971 - 1.000)	1.000 (0.640 - 1.000)	0.888 (0.838 - 0.927)	N/A	0.667 (0.529 - 0.840)
Wang 2015: PULMONARY EMBOLISM Model One of: family history of VTE, Obesity, Current or recent OCP use, recent surgery, immobilization, trauma or fracture, CVL, infection, or malignancy [27]	Post hoc	11	39	1.000 (0.615 - 1.000)	0.308 (0.170 - 0.476)	0.289 (0.154 - 0.459)	1.000 (0.640 - 1.000)	1.444 (1.172 - 1.781)	0.000 (N/A)
Wang 2015: PULMONARY EMBOLISM Model Two of: family history of VTE, Obesity, Current or recent OCP use, recent surgery, immobilization, trauma or fracture, CVL, infection, or malignancy [27]	Post hoc	11	39	0.818 (0.482 - 0.977)	0.538 (0.372 - 0.699)	0.333 (0.165 - 0.540)	0.913 (0.720 - 0.989)	1.773 (1.143 - 2.749)	0.338 (0.093 - 1.223)
Kanis 2017: PULMONARY EMBOLISM Exclusion Criteria All of: HR < 100bpm, respiratory rate < 22 breaths/min, SaO2% > 94%, no limb swelling, no recent surgery, no active cancer, no limb immobility, no CVL, and no prior VTE [28]	Post hoc	51	492	0.922 (0.811 - 0.978)	0.439 (0.395 - 0.484)	0.146 (0.109 - 0.189)	0.982 (0.954 - 0.995)	1.643 (1.469 - 1.837)	0.179 (0.069 - 0.460)

Table 5. Diagnostic validity of risk factors and clinical features evaluated in five studies

	Sensitivity	Specificity	I^2	LR+	LR-
Central Venous Line	0.225 (0.096 - 0.442)	0.920 (0.721 - 0.981)	92.0%	2.8125	0.8424
Congenital Cardiac Disease	0.133 (0.071 - 0.326)	0.920 (0.834 - 0.964)	75.9%	1.6625	0.9424
Malignancy	0.180 (0.128 - 0.247)	0.887 (0.733 - 0.957)	88.5%	1.5929	0.9245
Surgery	0.264 (0.165 - 0.394)	0.892 (0.872 - 0.910)	42.1%	2.4444	0.8251
Hemoptysis	0.067 (0.034 - 0.126)	0.970 (0.955 - 0.980)	1.0%	2.2333	0.9619
Tachycardia	0.591 (0.509 - 0.668)	0.627 (0.507 - 0.734)	84.5%	1.5845	0.6523

Discussion

Clinical decision tools

It is clear through this review, that there are only a small number of studies evaluating the diagnostic accuracy of clinical decision tools for pulmonary embolism in the pediatric population. All of these studies are retrospective cohort reviews or case-control studies, both of which have a high or unclear potential for risk of bias. From the limited number of studies we were able to review, it is clear that there is no standard clinical decision tool for pulmonary embolism for use in the pediatric population.

While we were able to assess two clinical decision rules validated in the adult population, neither was found to provide utility for decision making in children. This is true even when vital signs are adjusted to pediatric ranges. There may be many reasons for this lack of diagnostic accuracy. First of all, these studies are all retrospective, which intervenes with the ability to properly assess the "alternate diagnosis less likely than pulmonary embolism" condition in the Wells Criteria. Since this criterion is worth three points out of 12.5, its interpretation has huge implications on the accuracy of that decision tool. Additionally, pulmonary embolism in pediatric patients is often the result of underlying disease, which may in itself cause clinical features similar to pulmonary embolism.

Due to the of the lack of clinical decision tools available for use in the pediatric population, primary study often created clinical decision tools using the data they had collected. Out of these, one by Lee et al. shows favourable results. It proposes further imaging if a patient presents with at least two of the following: immobilization, hypercoagulable state, excess estrogen state, an indwelling central venous line, and/or prior history of pulmonary embolism and/or deep vein thrombosis.[26] This tool has a good balance between sensitivity at 88% and specificity at 94%. While this leaves 12% of pulmonary embolism patients with no further imaging, changing the rule threshold to only require one risk factor or clinical finding causes the specificity to fall to 63%. This would have to be balanced with the sensitivity increase to 94%, and further studied to confirm best use of this rule.. Another clinical decision tool created by Wang et al. has 100% sensitivity. It recommends further testing if a patient has one of: family history of venous thromboembolism, obesity, current or recent oral contraceptive use, recent surgery, immobilization, trauma or fracture, central venous line, infection, or malignancy.[27] Nevertheless, neither of these decision tools are studied prospectively, so further evaluation is needed before recommending either for clinical use.

Risk factors and clinical features

The included studies examined many different risk factors and clinical features of pediatric patients suspected to have pulmonary embolism; six of these features were examined across five studies. Not one single factor or combination of factors displayed a reliable sensitivity using the thresholds established in the primary literature; however, the presence of a central venous line, a history that includes recent surgery, or the finding of hemoptysis, all have a positive likelihood ratio greater than two, demonstrating the potential diagnostic utility of these risk factors and clinical features. It should be noted that there is a large heterogeneity when the studies evaluating the risk of central venous line are pooled. This may stem from the variability between the clinical settings, study designs, and reference standards used, but subgroup analysis could not be performed due to the small number of primary studies available. Regardless, the presence of a central venous line and/or recent surgery are both identified by the International Society of Thrombosis and Hemostasis Pediatric Pulmonary Embolism Working Group as frequent risk factors associated with pulmonary embolism.[30] While central venous lines are frequently used as life-saving interventions in critically ill patients, they provide a nidus for thrombus formation, resulting in increased risk of pulmonary embolism in both adults and children.[1,31] Similarly, surgery is known to be a provoking etiology for venous thromboembolism in both adults and children.[1,32] Lastly, hemoptysis in a patient with pulmonary embolism is due to pulmonary tissue infarction and the resulting ischemic pulmonary parenchymal necrosis.[33]

Limitations

The limitations of this systematic review include the small number of studies that met the inclusion criteria, and the fact that none of the studies were prospective in nature. Since many components, such as the completeness of data collection, cannot be controlled for in a retrospective design, the accuracy of the diagnostic validity of these clinical decision tools, as well as of the diagnostic use of risk factors and clinical features evaluated, may have been impacted. As well, the studies were all conducted in tertiary care hospitals, and patients presenting to these hospitals may be more acute and/or complex than those that would present to smaller hospitals. Additionally, previous studies have shown a bimodal distribution of pediatric pulmonary embolism incidence, with the first peak in infants less than one year of age and the second in adolescents.[1,17] The different risk factors present in the neonatal population, mean that they are likely to require a different clinical decision tool than older children.[2,4] None of the included studies reported separate data for the neonatal population, resulting in another limitation of this review and presenting an area for further investigation.

Through this review, it is evident that large scale prospective studies in varying hospital levels should be completed. We recognize that this is difficult given the low incidence of pulmonary embolism in the pediatric population. A prospective population-based study, in order to develop and validate a clinical decision tool for pulmonary embolism in the pediatric population would be valuable.

Conclusion

In summary, it is evident that the clinical decision rules used to evaluate the possibility of PE in the adult population are not recommended for pediatric patients, due to their low diagnostic accuracy. Given the increased susceptibility of pediatric patients to the radiation associated consequences of imaging techniques, such as computed tomography pulmonary angiography, the development of a clinical decision rule to assist in decision making around appropriate use of this imaging technology in necessary. Risk factors and clinical features found to increase the probability of PE in children are the presence of a central venous line, a history that includes recent surgery, and the finding of hemoptysis. Larger prospective studies are needed to assist in the creation of an appropriate clinical decision rule.

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Appendix

Appendix 1. Diagnostic validity of individual risk factors

	Immobilization (n = 895)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.560 (0.423 - 0.688)	0.480 (0.300 - 0.665)	1.077 (0.687 - 1.688)	0.917 (0.548 - 1.533)
Lee 2011	0.750 (0.589 - 0.862)	0.948 (0.906 - 0.971)	14.325 (7.613 - 26.954)	0.264 (0.150 - 0.465)
Wang 2015	0.273 (0.097 - 0.566)	0.846 (0.703 - 0.928)	1.773 (0.527 - 5.967)	0.860 (0.584 - 1.264)
Kanis 2017	0.333 (0.220 - 0.470)	0.937 (0.912 - 0.955)	5.290 (3.156 - 8.867)	0.711 (0.585 - 0.865)
	Injury or Trauma (n = 1192)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.139 (0.061 - 0.287)	0.907 (0.879 - 0.929)	1.488 (0.632 - 3.502)	0.950 (0.831 - 1.086)
Wang 2015	0.042 (0.004 - 0.301)	0.888 (0.754 - 0.953)	0.370 (0.021 - 6.401)	1.080 (0.919 - 1.269)
Kanis 2017	0.078 (0.031 - 0.185)	0.967 (0.948 - 0.980)	2.412 (0.838 – 6.941)	0.953 (0.878 - 1.034)
Victoria 2008	0.077 (0.014 - 0.333)	0.920 (0.750 - 0.978)	0.962 (0.096 – 9.639)	1.003 (0.826 - 1.219)
	Oral contraceptive pill (n = 863)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.306 (0.180 - 0.469)	0.853 (0.821 - 0.881)	2.083 (1.221 - 3.553)	0.814 (0.653 - 1.014)
Lee 2011	0.222 (0.117 - 0.381)	0.937 (0.893 - 0.964)	3.537 (1.557 - 8.036)	0.830 (0.694 - 0.992)
Wang 2015	0.727 (0.434 - 0.903)	0.846 (0.703 - 0.928)	4.727 (2.082 - 10.735)	0.322 (0.122 - 0.854)
Victoria 2008	0.350 (0.137 - 0.646)	0.971 (0.771 - 0.997)	11.900 (0.683 - 207.457)	0.670 (0.422 - 1.063)
	Previous DVT and/or PE (n = 1406)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.360 (0.241 - 0.499)	0.600 (0.407 - 0.766)	0.900 (0.491 - 1.650)	1.067 (0.728 - 1.562)
Hennelly 2016	0.250 (0.138 - 0.411)	0.943 (0.920 - 0.960)	4.375 (2.252 - 8.498)	0.795 (0.658 - 0.962)
Lee 2011	0.444 (0.295 - 0.604)	0.885 (0.832 - 0.923)	3.859 (2.256 - 6.599)	0.628 (0.467 - 0.845)
Kanis 2017	0.490 (0.359 - 0.623)	0.970 (0.950 - 0.981)	16.078 (9.079 - 28.474)	0.526 (0.402 - 0.689)
	Thrombophilic condition and/or coagulation disorder (n = 822)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.056 (0.015 - 0.181)	0.981 (0.965 - 0.990)	2.917 (0.664 - 12.815)	0.963 (0.889 - 1.043)
Lee 2011	0.222 (0.117 - 0.381)	0.932 (0.887 - 0.960)	3.265 (1.459 - 7.307)	0.835 (0.698 - 0.998)
Victoria 2008	0.444 (0.189 - 0.733)	0.960 (0.805 - 0.993)	11.111 (1.424 - 86.707)	0.579 (0.321 - 1.044)
	Collagen vascular disease and/or connective tissue disease (n = 581)			
	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.118 (0.055 - 0.234)	0.945 (0.921 - 0.962)	2.144 (0.929 - 4.947)	0.934 (0.843 - 1.034)
Victoria 2008	0.036 (0.004 - 0.268)	0.942 (0.784 - 0.987)	0.619 (0.027 - 14.216)	1.023 (0.891 - 1.175)
	Renal disease (n = 1104)			

	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.028 (0.005 - 0.142)	0.975 (0.958 - 0.985)	1.122 (0.151 - 8.337)	0.997 (0.942 - 1.055)
Kanis 2017	0.020 (0.003 - 0.103)	0.988 (0.974 - 0.994)	1.608 (0.197 - 13.094)	0.992 (0.954 - 1.033)
	Family history of PE/DVT (n = 593)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.273 (0.097 - 0.566)	0.897 (0.764 - 0.959)	2.659 (0.697 - 10.146)	0.810 (0.556 - 1.182)
Kanis 2017	0.039 (0.011 - 0.132)	0.963 (0.943 - 0.977)	1.072 (0.256 - 4.489)	0.997 (0.941 - 1.057)
	Infection (n = 88)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.273 (0.097 - 0.566)	0.974 (0.868 - 0.995)	10.636 (1.224 - 92.414)	0.746 (0.518 - 1.076)
Victoria 2008	0.231 (0.082 - 0.503)	0.760 (0.566 - 0.885)	0.962 (0.286 - 3.234)	1.012 (0.699 - 1.466)
	Asthma (n = 543)			
	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.078 (0.031 - 0.185)	0.764 (0.725 - 0.800)	0.333 (0.128 - 0.864)	1.206 (1.098 - 1.325)
	Diabetes mellitus (n = 543)			
	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.01 (0.001 - 0.086)	0.989 (0.975 - 0.995)	0.862 (0.048 - 15. 368)	1.002 (0.974 - 1.030)
	Neuromuscular disease (n = 38)			
	Sensitivity	Specificity	LR+	LR-
Victoria 2008	0.231 (0.082 - 0.503)	0.760 (0.566 - 0.885)	0.962 (0.286 - 3.234)	1.012 (0.699 - 1.466)
	Immobilization or surgery (n = 561)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.194 (0.098 - 0.350)	0.874 (0.843 - 0.900)	1.547 (0.766 - 3.121)	0.921 (0.782 - 1.085)
	Neoplasm (n = 38)			
	Sensitivity	Specificity	LR+	LR-
Victoria 2008	0.385 (0.177 - 0.645)	0.840 (0.653 - 0.936)	2.404 (0.776 - 7.450)	0.733 (0.461 - 1.163)
	Obesity (n = 50)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.364 (0.152 - 0.646)	0.821 (0.673 - 0.910)	2.026 (0.723 - 5.676)	0.776 (0.485 - 1.241)
	Post-partum (n = 543)			
	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.020 (0.003 - 0.103)	0.974 (0.955 - 0.984)	0.742 (0.099 - 5.557)	1.007 (0.966 - 1.050)
	Pregnancy (n = 543)			

	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.039 (0.011 - 0.132)	0.976 (0.958 - 0.986)	1.608 (0.370 - 6.985)	0.985 (0.930 - 1.043)

Appendix 2. Diagnostic validity of individual clinical features

	D-Dimer (n = 213)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.852 (0.675 - 0.941)	0.250 (0.089 - 0.532)	1.136 (0.790 - 1.632)	0.593 (0.156 - 2.249)
Lee 2011	0.880 (0.700 - 0.958)	0.131 (0.080 - 0.208)	1.012 (0.861 - 1.191)	0.917 (0.285 - 2.951)
Wang 2015	0.929 (0.561 - 0.992)	0.528 (0.313 - 0.732)	1.966 (1.158 - 3.340)	0.135 (0.009 - 2.027)
Victoria 2008	0.944(0.629 - 0.994)	0.375 (0.165 - 0.646)	1.511 (0.948 - 2.408)	0.148 (0.009 - 2.414)
	Fever (n = 1170)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.222 (0.117 - 0.381)	0.870 (0.839 - 0.897)	1.716 (0.896 - 3.287)	0.894 (0.748 - 1.067)
Wang 2015	0.050 (0.005 - 0.345)	0.921 (0.719 - 0.982)	0.633 (0.028 - 14.167)	1.031 (0.850 - 1.252)
Kanis 2017	0.137 (0.068 - 0.257)	0.900 (0.871 - 0.924)	1.378 (0.659 - 2.882)	0.958 (0.855 - 1.073)
Victoria 2008	0.077 (0.014 - 0.333)	0.846 (0.665 - 0.938)	0.500 (0.062 - 4.033)	1.091 (0.869 - 1.369)
	Shortness of breath/dyspnoea (n = 1381)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.528 (0.370 - 0.680)	0.493 (0.451 - 0.536)	1.042 (0.756 - 1.435)	0.957 (0.670 - 1.367)
Lee 2011	0.472 (0.320 - 0.630)	0.497 (0.427 - 0.568)	0.940 (0.647 - 1.364)	1.061 (0.755 - 1.491)
Wang 2015	0.818 (0.523 - 0.949)	0.436 (0.293 - 0.590)	1.450 (0.980 - 2.147)	0.417 (0.113 - 1.536)
Kanis 2017	0.686 (0.550 - 0.797)	0.354 (0.313 - 0.397)	1.062 (0.872 - 1.293)	0.887 (0.581 - 1.354)
	Chest pain pleuritic (n = 352)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.320 (0.208 - 0.458)	0.760 (0.566 - 0.885)	1.333 (0.595 - 2.986)	0.895 (0.669 - 1.197)
Lee 2011	0.417 (0.271 - 0.578)	0.455 (0.386 - 0.526)	0.765 (0.509 - 1.150)	1.281 (0.933 - 1.758)
Wang 2015	0.727 (0.434 - 0.903)	0.385 (0.249 - 0.541)	1.182 (0.762 - 1.833)	0.709 (0.250 - 2.013)
	Cough (n = 1154)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.222 (0.117 - 0.381)	0.771 (0.734 - 0.805)	0.972 (0.517 - 1.827)	1.008 (0.842 - 1.208)
Wang 2015	0.545 (0.280 - 0.787)	0.769 (0.617 - 0.874)	2.364 (1.076 - 5.192)	0.591 (0.302 - 1.155)
Kanis 2017	0.118 (0.055 - 0.234)	0.829 (0.793 - 0.860)	0.689 (0.317 - 1.498)	1.064 (0.955 - 1.185)
	Hypoxia (n = 863)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.360 (0.241 - 0.499)	0.520 (0.335 - 0.700)	0.750 (0.432 - 1.301)	1.231 (0.800 - 1.892)
Hennelly 2016	0.250 (0.138 - 0.411)	0.968 (0.949 - 0.980)	7.721 (3.706 - 16.085)	0.775 (0.641 - 0.937)
Lee 2011	0.250 (0.138 - 0.411)	0.749 (0.683 - 0.805)	0.995 (0.537 - 1.843)	1.002 (0.815 - 1.231)
	S&S of DVT: limb swelling/pain (n = 650)			

	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.222 (0.117 - 0.381)	0.933 (0.909 - 0.952)	3.333 (1.672 - 6.645)	0.833 (0.699 - 0.994)
Wang 2015	0.182 (0.051 - 0.477)	0.795 (0.645 - 0.892)	0.886 (0.219 - 3.586)	1.029 (0.747 - 1.419)
Victoria 2008	0.462 (0.232 - 0.709)	0.808 (0.621 - 0.915)	2.400 (0.899 - 6.411)	0.667 (0.390 - 1.141)
	Tachycardia age-adjusted (n = 683)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.540 (0.404 - 0.670)	0.640 (0.445 - 0.798)	1.500 (0.838 - 2.684)	0.719 (0.472 - 1.094)
Hennelly 2016	0.611 (0.449 - 0.752)	0.676 (0.635 - 0.715)	1.887 (1.414 - 2.518)	0.575 (0.380 - 0.870)
Wang 2015	0.778 (0.453 - 0.937)	0.737 (0.580 - 0.850)	2.956 (1.564 - 5.585)	0.302 (0.088 - 1.039)
	Chest pain (n = 611)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.694 (0.531 - 0.820)	0.198 (0.166 - 0.234)	0.866 (0.694 - 1.080)	1.542 (0.916 - 2.599)
Wang 2015	0.958 (0.699 - 0.996)	0.312 (0.191 - 0.467)	1.394 (1.097 - 1.772)	0.133 (0.009 - 2.090)
	DVT detected by lower limb Doppler Ultrasound (n = 66)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.200 (0.057 - 0.510)	0.833 (0.436 - 0.970)	1.200 (0.136 - 10.580)	0.960 (0.598 - 1.541)
Victoria 2008	0.727 (0.434 - 0.903)	0.744 (0.589 - 0.854)	2.836 (1.487 - 5.409)	0.367 (0.137 - 0.980)
	Syncope (n = 593)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.091 (0.016 - 0.377)	0.923 (0.797 - 0.973)	1.182 (0.136 - 10.268)	0.985 (0.800 - 1.212)
Kanis 2017	0.020 (0.003 - 0.103)	0.929 (0.903 - 0.948)	0.276 (0.039 - 1.970)	1.055 (1.008 - 1.105)
	S&S of DVT: lower limb - calf swelling (n = 1104)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.056 (0.015 - 0.181)	0.975 (0.958 - 0.985)	2.244 (0.526 - 9.564)	0.968 (0.894 - 1.049)
Kanis 2017	0.157 (0.082 - 0.280)	0.965 (0.945 - 0.978)	4.540 (2.062 - 9.996)	0.873 (0.775 - 0.984)
	S&S of DVT: upper limb (n = 636)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.049 (0.015 - 0.146)	0.981 (0.840 - 0.998)	2.549 (0.127 - 51.168)	0.970 (0.893 - 1.053)
Hennelly 2016	0.139 (0.061 - 0.287)	0.950 (0.928 - 0.966)	2.804 (1.145 - 6.867)	0.906 (0.793 - 1.034)
	S&S of DVT: lower limb - calf pain (n = 561)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.194 (0.098 - 0.350)	0.947 (0.924 - 0.963)	3.646 (1.711 - 7.767)	0.851 (0.724 - 1.00)
	S&S of DVT: lower limb (n = 75)			
	Sensitivity	Specificity	LR+	LR-
Biss 2009	0.220 (0.128 - 0.352)	0.920 (0.750 - 0.978)	2.750 (0.659 - 11.470)	0.848 (0.703 - 1.022)

	Abnormal chest X-ray (n = 42)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.222 (0.063 - 0.547)	0.909 (0.764 - 0.969)	2.444 (0.479 - 12.480)	0.856 (0.594 - 1.233)
	Cardiac symptoms (n = 39)			
	Sensitivity	Specificity	LR+	LR-
Victoria 2008	0.077 (0.014 - 0.333)	0.615 (0.425 - 0.776)	0.200 (0.029 - 1.398)	1.500 (1.066 - 2.112)
	Chest pain/shortness of breath (n = 39)			
	Sensitivity	Specificity	LR+	LR-
Victoria 2008	0.692 (0.424 - 0.873)	0.038 (0.007 - 0.189)	0.720 (0.497 - 1.043)	8.000 (0.992 - 64.532)
	Crackles/rales (n = 50)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.042 (0.004 - 0.301)	0.888 (0.754 - 0.953)	0.370 (0.021 - 6.401)	1.080 (0.919 - 1.269)
	Elevated C-reaction protein (n = 20)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.857 (0.487 - 0.974)	0.385 (0.177 - 0.645)	1.393 (0.824 - 2.356)	0.371 (0.053 - 2.586)
	Hypotension (n = 29)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.071 (0.008 - 0.439)	0.979 (0.828 - 0.998)	3.429 (0.075 - 157.683)	0.948 (0.766 - 1.174)
	Increased respiratory effort (n = 50)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.273 (0.097 - 0.566)	0.897 (0.764 - 0.959)	2.659 (0.697 - 10.146)	0.810 (0.556 - 1.182)
	Increased white cell count (n = 43)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.364 (0.152 - 0.646)	0.719 (0.546 - 0.844)	1.293 (0.496 - 3.370)	0.885 (0.539 - 1.455)
	Palpitations (n = 561)			
	Sensitivity	Specificity	LR+	LR-
Hennelly 2016	0.014 (0.001 - 0.117)	0.889 (0.859 - 0.913)	0.122 (0.008 - 1.927)	1.110 (1.058 - 1.165)
	Pulmonary hypertension (n = 227)			
	Sensitivity	Specificity	LR+	LR-
Lee 2011	0.194 (0.098 - 0.350)	0.963 (0.926 - 0.982)	5.306 (1.981 - 14.211)	0.836 (0.711 - 0.984)
	S1Q3T3 pattern on ECG (n = 29)			
	Sensitivity	Specificity	LR+	LR-

Wang 2015	0.500 (0.188 - 0.812)	0.783 (0.581 - 0.903)	2.300 (0.755 - 7.009)	0.639 (0.279 - 1.463)
	Seizure (n = 543)			
	Sensitivity	Specificity	LR+	LR-
Kanis 2017	0.020 (0.003 - 0.103)	0.990 (0.976 - 0.996)	1.929 (0.230 - 16.197)	0.990 (0.952 - 1.031)
	Shock index >1 (n = 28)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.500 (0.188 - 0.812)	0.864 (0.667 - 0.953)	3.667 (0.978 - 13.745)	0.579 (0.256 - 1.311)
	Sinus tachycardia: HR > 100 bpm on ECG (n = 29)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.500 (0.188 - 0.812)	0.783 (0.581 - 0.903)	2.300 (0.755 - 7.009)	0.639 (0.279 - 1.463)
	Tachypnoea >20 breaths per minute (n = 45)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.444 (0.189 - 0.733)	0.667 (0.503 - 0.798)	1.333 (0.562 - 3.164)	0.833 (0.445 - 1.562)
	Tachypnoea age-adjusted (n = 45)			
	Sensitivity	Specificity	LR+	LR-
Wang 2015	0.444 (0.189 - 0.733)	0.806 (0.650 - 0.902)	2.286 (0.851 - 6.137)	0.690 (0.376 - 1.264)