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The Diagnostic Value of Transthoracic Echocardiography for Pulmonary Hypertension: A Systematic Review and Meta-Analysis

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Purpose

Pulmonary hypertension (PH) is an important cause of morbidity and mortality. A commonly proposed non-invasive method in the diagnosis and assessment of PH is Transthoracic Echocardiography (TTE). In this systematic review and meta-analysis, our aim was to assess the accuracy of echocardiography in the diagnosis of PH.

Methods

The search was done up to the 31st of January 2023 using MEDLINE, Scopus, CENTRAL, and Web of Sciences databases. The studies were included if they were randomized controlled trials or observational in design and evaluated the diagnostic performance of TTE in diagnosing PH in comparison to right-sided heart catheterization as a reference method. The diagnostic performance measures included sensitivity, specificity, Diagnostic Odds Ratio (DOR), Positive Likelihood Ratio (PLR), and Negative Likelihood Ratio (NLR).

Results

The total number of the included patients was 4,523 from 38 articles. The overall sensitivity and specificity of echocardiography in diagnosing pulmonary hypertension were 54.8% (95%CI: 45.7%-63.6%) and 52.1% (95%CI: 39.0%-64.9%), respectively. Moreover, the pooled DOR was 1.321 (95%CI: 0.695-2.51). The pooled PLR and NLR were 1.145 (95%CI: 0.830-1.579) and 0.867 (95%CI: 0.628-1.197), respectively. The highest diagnostic performance of TTE was among group 1 and 3 PH patients.

Conclusion

Our analysis revealed that TTE had low diagnostic sensitivity, specificity, and accuracy. Due to the overall poor diagnostic performance of TTE, the diagnosis of PH and the assessment of response to therapies require right-sided heart catheterization. Future prospective studies to improve the diagnostic performance of TTE in the diagnosis of PH are needed.

INTRODUCTION

The prevalence of Pulmonary Hypertension (PH) is around 1% in the general population, yet it is much higher among the elderly population (people>65 years), approaching 10%.¹ To improve the patient's outcomes, early detection and accurate assessment in follow ups are considered crucial.² The gold standard for the diagnosis of PH is right

sided heart catheterization.^{3,4} The superiority of catheterization over other methods stems from its ability to measure flow, gradients, and resistance which are considered major determinants of pulmonary hypertension prognosis.⁵ However, it is considered invasive and expensive, which may limit its frequent and repeated use.^{3,4} Additionally, right sided heart catheterization was associated with a rate of ad-

 a Corresponding Author: Ahmad A. Toubasi
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 Mobile: +962798035061 verse events of around 1.1% in the most experienced centers. $^{\rm 4}$

On the other hand, echocardiography is considered noninvasive and readily available.⁶ In addition, many echocardiographic parameters are closely related to pulmonary hemodynamics.⁶ These echocardiographic parameters that can be used to assess pulmonary hypertension include right heart cavities and cardiac dimensions, right ventricular diastolic dysfunction, right ventricular systolic dysfunction, and myocardial strain.⁶ To improve the assessment of parameters among patients with PH, multiple techniques were considered, one of which is exercise as studies showed that during exercise some parameters change among patients with PH compared to controls which enhances the ability of echocardiography to diagnose PH.⁶

Multiple systematic reviews were done to assess the diagnostic accuracy of transthoracic echocardiography between 2010-2019.⁷⁻¹⁰ However, these studies only included studies before 2019.⁷⁻¹⁰ In addition, they included a small number of studies, performed a simple diagnostic analysis and did not assess detailed subgroup analysis especially for World Health Organization (WHO) pulmonary hypertension groups.⁷⁻¹⁰ In the recent years multiple original studies were conducted.⁶ In the view of right sided heart catheterization drawbacks, limitations of the previously conducted meta-analyses, and the need to accommodate the rapidly growing literature, we decided to conduct this systematic review and meta-analysis to assess the accuracy of echocardiography in the diagnosis of PH.

METHODS

This review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number (CRD42023395408). We report this review in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

SEARCH STRATEGY

The search was done on the 31st of January 2023 independently by TNA and AAT using MEDLINE, Scopus, The Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Sciences databases. The search strategy combined terms about pulmonary hypertension and echocardiography, where we used the medical subject heading (MeSH) database to optimize keyword selection. The following terms were used in conducting the search: (Pulmonary Hypertension) AND (Echocardiography OR 2D Echocardiography OR Contrast Echocardiography OR Cross-Sectional Echocardiography OR Transthoracic Echocardiography OR M-Mode Echocardiography OR Two-Dimensional Echocardiography). No time or language restrictions were applied. Any discrepancy was resolved by a third senior researcher (DD).

STUDY SELECTION

The studies were included in this systematic review metaanalysis if they were:

- Observational studies that evaluated the diagnostic value of 2-dimensional TTE in diagnosing pulmonary hypertension compared to right sided heart catheter-ization as a reference (gold standard).
- Randomized Controlled Trials investigating the diagnostic value of 2-dimensional TTE in diagnosing pulmonary hypertension compared to right sided heart catheterization as a reference (gold standard).

The following study types were excluded: editorials, unstructured narrative review articles or other publications which did not report any primary data or did not present new analyses of existing data. In addition, studies which evaluated the diagnostic value of echocardiography in diagnosing pulmonary hypertension in comparison to methods other than right sided heart catheterization, or which used another method as an adjunct to echocardiography and compared it to right sided heart catheterization, were also excluded.

The study selection was performed using Rayyan (https://www.rayyan.ai/). The articles retrieved from the search were screened using title/abstract then the remaining studies were screened using their full-text form. The study selection was done by two independent investigators (TNA and AAT) and any disagreement was resolved by a third senior researcher (DD).

MAIN OUTCOMES

The topic of interest is the diagnostic value of 2-dimensional TTE in diagnosing PH compared to right sided heart catheterization (gold standard). The included diagnostic value measures are sensitivity, specificity, Diagnostic Odds Ratio (DOR), Positive Likelihood Ratio (PLR), and Negative Likelihood Ratio (NLR). In addition, we investigated these diagnostic values if the echocardiography was performed during exercise. PH was defined as pulmonary artery pressure higher than 25 mmHg while exercise PH was defined as pulmonary artery pressure higher than 30 mmHg during exercise.¹¹ The included studies measured pulmonary artery pressure through echocardiography using the Bernoulli equation by adding peak tricuspid regurgitation velocity to the estimate of right atrial pressure. Moreover, to evaluate the diagnostic value of the 2-dimensional echocardiography across the World Health Organization (WHO) PH groups, a sub-group analysis was done for each of the 5 WHO groups. Group 1 includes patients with idiopathic PH and PH due to connective tissue diseases, hereditary, drug induced and congenital heart disease while group 2 includes patients with PH due to left-sided heart disease. Groups 3, 4 and 5 include patients with pulmonary hypertension due to lung disease, chronic pulmonary thromboembolism, and miscellaneous causes, respectively.

DATA EXTRACTION AND QUALITY ASSESSMENT

We developed a spreadsheet for data extraction. The following variables were extracted; title, year of publication, study design, country of origin (defined as the country in which the study was located), sample size, number of patients with PH, WHO pulmonary hypertension groups that were included in the studies, primary outcome measure, type of 2-dimensional TTE (exercise vs resting), as well as True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) values. The data extraction was performed by the same two independent researchers (TNA and AAT) and any discrepancy was resolved by a senior researcher (DD). The risk of bias in the included studies was assessed using Newcastle-Ottawa Scale (NOS) for observational studies. NOS is composed of 3 components including selection, comparability, and outcome. The selection component includes sampling methods and representativeness while the comparability component includes adjustment for confounding variables. The outcome component involves the appropriateness of the outcome definition. The highest score which can be achieved in NOS is 9.

STATISTICAL ANALYSIS

For all the studies, we constructed 2 x 2 contingency table, then the sensitivity, specificity, DOR, PLR and NLR were calculated for each study. When more than one threshold was used by any of the included studies, the threshold with the largest Youden index was used in the analysis. The mentioned diagnostic parameters were pooled using the random effects model. In addition, the Summarized Receiver Operating Characteristic (SROC) curve was constructed using these diagnostic parameters. All the mentioned analysis except the SROC was conducted using Meta XL, version 5.3 (EpiGear International, Queensland, Australia). The SROC was generated using MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.01.¹²

RESULTS

The search yielded 1,553 articles, 75 of which were duplicates. The remaining 1,478 articles were screened using their title/abstract and 1,135 articles were excluded because they were reviews, case reports, editorials, laboratory studies and cadaveric studies. The rest of the articles (343 articles) were screened using their full-text form and 305 were excluded due to not using right sided heart catheterization as a reference (gold standard) for comparison, using other types of echocardiography (such as transesophageal echocardiography), combining another method with echocardiography, or not reporting the data regarding the diagnostic value of echocardiography. Finally, 38 articles were included in the analysis.¹³⁻⁴⁹ Supplementary figure 1 describes the study selection process.

THE DIAGNOSTIC VALUE OF ECHOCARDIOGRAPHY

Thirty eight studies were included in the analysis of investigating the diagnostic value of echocardiography (Figure 1). The overall sensitivity and specificity of echocardiography in diagnosing PH were 54.8% (95%CI: 45.7%-63.6%) and 52.1% (95%CI: 39.0%-64.9%), respectively. Moreover, the pooled DOR was 1.321 (95%CI: 0.695-2.51). The pooled PLR and NLR were 1.145 (95%CI: 0.830-1.579) and 0.867 (95%CI: 0.628-1.197), respectively. Supplementary table 2 summarizes the diagnostic value measures of echocardiography. The overall accuracy of echocardiography in establishing the diagnosis was 53.4%. Supplementary figure 2 demonstrates the SROC curve of echocardiography.

SUB-GROUP ANALYSIS

SUB-GROUP ANALYSIS FOR THE DIAGNOSTIC VALUE OF EXERCISE ECHOCARDIOGRAPHY

Four studies evaluated the diagnostic value of exercise echocardiography in diagnosing PH (Supplementary figure 3). The model that pooled these studies showed that the pooled sensitivity and specificity were 60.9% (95%CI: 39.4%-78.8%) and 32.8% (95%CI: 15.9%-55.8%), respectively. The false positive rate was 67.2% (95%CI: 44.2%-84.1%). Supplementary table 3 demonstrates the summary of diagnostic measures of exercise echocardiography in diagnosing PH. The overall accuracy of exercise echocardiography was 46.3%. Supplementary figure 4 shows the SROC curve of exercise echocardiography.

SUB-GROUP ANALYSIS FOR THE DIAGNOSTIC VALUE OF ECHOCARDIOGRAPHY AMONG PATIENTS WITH GROUP 1 PH

The model that evaluated the diagnostic value of echocardiography in diagnosing patients with group 1 PH included 8 studies (Supplementary figure 5). This model demonstrated that the pooled sensitivity and specificity were 68.5% (95%CI: 38.5%-88.4%) and 62.8% (95%CI: 24.8%-89.6%), respectively. The pooled diagnostic odds ratio was 3.684 (95%CI: 0.275-49.368). The pooled PLR and NLR were 1.844 (95%CI: 0.500-6.801) and 0.501 (95%CI: 0.134-1.872), respectively. Supplementary table 4 shows the summary measures of diagnostic value of echocardiography among patients with group 1 PH. The overall accuracy of echocardiography in diagnosing group 1 PH was 65.5%. Supplementary figure 6 demonstrates the SROC for echocardiography among patients with group 1 PH.

Action Control Contro Control Control	Study	тр	Total (TP+FN)		Sensitivity	95% CI
Rallids et al., 2021 19 39			(
Accmania et al., 2021 5 11	Rallidis et al., 2021	19	39		0.49	[0.32; 0.65]
Bourna et al. 2020 Frantavier al. 2019 Saveda et al. 2019 Control et al. 2019 Control et al. 2019 Control et al. 2017 Control et al. 2018 Control et al. 2019 Control et al. 2018 Control et al. 2019 Control et al. 2018 Control et al. 2018 Control et	Kooranifar et al., 2021	5	11		0.45	[0.17; 0.77]
E-Yalkuvi et al., 2019 E-Yalkuvi et al., 2019 Swada et al., 2019 E-Yalkuvi et al., 2019 E-Yalkuvi et al., 2017 E-Yalkuvi et al., 2018 E-Yalkuvi	Bournia et al., 2020	17	74		0.23	[0.14; 0.34]
Samada et al., 2015 47 57 47 57 Code (16, Frogment et al., 2017 27 27 468 664 671 Code (16, Frogment et al., 2017 27 27 468 664 671 Code (16, Frogment et al., 2013 3 150 468 1637 163 Lattle et al., 2013 49 101 468 1637 163 Lattle et al., 2013 19 21 468 1637 1637 Lange et al., 2013 19 21 468 1637 1637 Lange et al., 2017 19 22 4 464 1637 1637 Lange et al., 2016 16 225 4 051 1040 052 1041 058 1041 051 1040 052 1041 051 1041 058 1042 1051 051 1041 058 1042 1051 051 055 051 055 051 055 052 0450 051	El-Yatawi et al., 2019	39	/5		0.52	[0.40; 0.64]
Conversion Conversion <thconversion< th=""> Conversion Conversi</thconversion<>	Sawada et al., 2019	42	57		0.23	[0.17; 0.30]
Zubar et al. 2017 Corr 22 22 Corr	Broderick Foregrap et al. 2017	520	791		0.62	[0.70; 0.91]
Toodpayma arial, 2015 21 80	Zhao et al. 2017	27	27		1.00	[0.87:1.00]
Coduit of al. 2013 150	Boodpeyma et al. 2015	21	80		0.26	[0.17:0.37]
Lattice rata. 2013 Lange et al 2015 Sadauskas et al 2015 Lange et al 2015 Lattice et al 2015 Lattice et al 2015 Lattice et al 2016 Lattice et al 2017 Lattice et al 2016 Lattice et al 2017 Lattice et al 2	Codullo et al. 2013	3	150	-	0.02	[0.00.0.06]
Lange etal, 2013 Lange etal, 2013 Lange etal, 2013 Lange etal, 2013 Lange etal, 2017 Study St	Lafitte et al., 2013	69	101		0.68	[0.58: 0.77]
Kouzu et al. 2009 37 77	Lange et al., 2013	143	212		0.67	[0.61; 0.74]
Denton et al. 1997 Cale at al. 1990 Cale at al. 1989 Cale at al. 1989 Consuld Assumesser et al. 1987 Sadauskas et al. 2017 Sadauskas et al. 2015 Shino et al. 2015 Cale at al. 2016 Cale at al. 2015 Cale at al. 2016 Cale at al. 2016 Cale at al. 2016 Cale at al. 2017 Cale at al. 2018 Cale at al. 2019 Cale at al. 2018 Cale at al. 2017 Cale at al. 2018 Cale at al. 2018 Cal	Kouzu et al., 2009	37	77		0.48	[0.37; 0.60]
Cai et al., 1990 Cai et al., 1990 Bertoli et al., 1989 Cawald-Mammosser et al., 1987 Study Stud	Denton et al., 1997	19	29		0.66	[0.46; 0.82]
Berbi et al. 1989 26 59 0.44 [0.31:0.58] Cowald-Mammosser et al., 1987 45 88 0.58 [0.46:0.62] Shino et al., 2015 61 106 0.58 [0.46:0.62] Shino et al., 2015 61 106 0.58 [0.46:0.62] Shino et al., 2015 21 67 0.58 [0.46:0.62] Meng et al., 2016 39 187 0.58 [0.46:0.67] Nagel et al., 2015 21 67 0.58 [0.46:0.67] Neng et al., 2016 29 63 0.58 [0.46:0.80] Willens et al., 2020 29 63 0.58 [0.38:0.70] Degani-Cost et al., 2017 13 24 0.55 [0.38:0.70] Degani-Cost et al., 2018 15 50 17 0.58 [0.48:0.80] Willens et al., 2021 55 80 0.58 [0.48:0.48] Nowak et al., 2018 15 50 0.58 [0.48:0.48] Nowak et al., 2018 15 50 0.58 [0.48:0.48] Nowak et al., 2018 15 50 0.58 [0.48:0.48] Shipa et al., 2018 15 50	Cai et al., 1990	32	70		0.46	[0.34; 0.58]
Oswald Mammosser et al., 1987 32 39	Bertoli et al., 1989	26	59		0.44	[0.31; 0.58]
Jang et al., 2017 45 88 0.51 0.40:082 Shino et al., 2015 61 106 0.58 0.48:0.57 Nagel et al., 2015 21 67 0.31 0.21:0.43 Meng et al., 2015 21 67 0.31 0.21:0.43 Meng et al., 2016 29 63 0.56 0.38:0.70 Degani-Cost et al., 2021 62 88 0.56 0.38:0.70 Degani-Cost et al., 2021 62 88 0.56 0.38:0.70 Degani-Cost et al., 2021 62 88 0.56 0.38:0.70 Degani-Cost et al., 2016 50 80 0.56 0.38:0.70 Degani-Cost et al., 2016 50 80 0.56 0.38:0.70 Degani-Cost et al., 2017 7 0.51 0.42:0.68 Nowak et al., 2018 59 70 0.68 0.57:0.80 Nowak et al., 2018 59 70 0.56 0.38:0.70 Degani-Cost et al., 2016 59 0.56 0.28:0.77 Degani-Cost et al., 2016 59	Oswald-Mammosser et al., 1987	32	39		0.82	[0.66; 0.92]
Sadausas et al., 2010 Lee et al., 2015 Study Stu	Jiang et al., 2017	45	88		0.51	[0.40; 0.62]
Shimb et al., 2015 61 100	Sadauskas et al., 2010	116	225		0.52	[0.45; 0.58]
Lee et al., 2015 39 167 40.21 0.21	Shino et al., 2015	20	100		0.56	[0.46; 0.67]
Nage it al., 2015 2.0 0.7 0.30 0.27 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.60 0.57 0.58 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.58 0.57 0.55 0.57 0.55 0.57 0.55 0.57 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	Nagel et al. 2015	21	67		0.21	[0.15, 0.27]
Meng et al. 2021 52 88	Menn et al. 2018	50	72		0.69	[0.57:0.80]
rim et al. 2000 29 63	Meng et al. 2021	62	88	-181-	0.70	[0.60: 0.80]
Willens et al., 2008 23 42	Kim et al., 2000	29	63		0.46	[0.33; 0.59]
Degani-Costa et al. 2021 13 24	Willens et al., 2008	23	42		0.55	[0.39; 0.70]
Balici et al., 2016 50 80 0.62 (0.51 0.73) Nowak et al., 2013 59 107 0.55 (0.45 0.65) Nowak et al., 2018 77 1 - 0.66 (0.54 0.77) Hou et al., 2016 51 59 - 0.66 (0.57 0.76) Baliar et al., 2012 70 137 - 0.51 (0.42) 0.66 (0.57) Migures et al., 1990 46 57 0.4 0.6 0.8 1 Sensitivity Study TN (TN+FP) Specificity 95% CI Pallidis et al., 2021 5 8 - 0.49 (0.66 0.98 1) Sensitivity Study TN (TN+FP) Specificity 95% CI Pallidis et al., 2021 5 8 - 0.62 (0.24 0.91) Kooranifar et al., 2021 4 8 - 0.62 (0.24 0.91) Some at al., 2021 1 2 22 - 0.55 (0.30 0.98) Schneider et al., 2017 103 262 - 0.51 (0.30 0.98) Schneider et al., 2017 61 61 - 0.8 0.9 0.93 (0.83 0.03 0.98) Lafte et al., 2013 4 13 Lafte et al., 2015 7 15 Codule et al., 1990 7 20 Bertoli et al., 2015 6 12 Jang et al., 2016 104 109 Shine et al., 2017 8 19 Bertoli et al., 1990 7 20 Bertoli et al., 2016 104 109 Mag et al., 2018 4 5 Depanic Cast et al., 2013 4 13 Broderick Forseli et al., 1990 7 20 Bertoli et al., 1990 7 20 Bertoli et al., 1990 7 20 Bertoli et al., 2018 4 5 Depanic Cast et al., 2021 6 15 Mag et al., 2018 6 19 Mag et al., 2016 14 23 Mag et al., 2016	Degani-Costa et al., 2021	13	24		0.54	[0.33; 0.74]
Wang et al., 2013 59 107 0.55 0.45 0.65 Li et al., 2018 47 71 0.66 0.54 0.77 Hou et al., 2016 51 59 0.7 0.86 0.75 0.93 Shugara et al., 2016 62 67 0.81 0.023 0.83 0.25 0.51 0.42 0.20 0.43 0.25 0.53 Haddad et al., 1980 29 59 0.49 0.26 0.62 0.22 0.49 0.38 0.25 0.53 Haddad et al., 1981 19 50 0.49 0.26 0.62 0.24 0.49 0.49 0.25 0.55 0.32 0.75 0.55 0.32 0.75 0.55 0.32 0.76 0	Balci et al., 2016	50	80		0.62	[0.51; 0.73]
Nowak et al., 2018 19 56 0.34 (0.22, 0.48) Hou et al., 2016 51 59 0.66 (0.54, 0.77) Hou et al., 2016 51 59 0.81 (0.82, 0.63) Migures et al., 1990 46 57 0.81 (0.82, 0.63) Haddad et al., 1991 19 50 0.81 (0.82, 0.63) Haddad et al., 1981 19 50 0.81 (0.22, 0.76) Study TN Total 0.38 (0.22, 0.76) El-Yalawi et al., 2020 12 22 0.55 (0.32, 0.76) Schneider et al., 2017 51 6 0.33 (0.22, 0.76) Schneider et al., 2017 103 262 0.33 (0.22, 0.76) Schneider et al., 2013 1 8	Wang et al., 2013	59	107		0.55	[0.45; 0.65]
Li et al., 2016 47 71 - 0.66 [0.54; 0.77] Rajaram et al., 2016 51 59 - 0.68 [0.75; 0.94] Rajaram et al., 2018 62 67 - 0.81 [0.42; 0.60] Migures et al., 1980 46 57 - 0.81 [0.42; 0.63] Haddad et al., 1981 19 50 - 0.8 [0.25; 0.53] 0 0.2 0.4 0.6 0.8 1 Sensitivity 50 - 0.8 [0.25; 0.53] 0 0.2 0.4 0.6 0.8 1 Sensitivity 50 - 0.55 [0.42; 0.78] Ralificis et al., 2021 5 8 - 0.55 [0.42; 0.78] Ralificis et al., 2021 5 8 - 0.55 [0.42; 0.78] Radiad et al., 2019 2 3 Sawada et al., 2019 2 3 Sawada et al., 2019 50 54 - 0.33 [0.25; 0.26] Schneider et al., 2018 1 8 - 0.52 [0.24; 0.78] Erderick Forsgren et al., 2017 103 262 - 0.55 [0.32; 0.78] Lafite et al., 2013 3 20 - 0.55 [0.32; 0.78] Lafite et al., 2013 3 20 - 0.55 [0.32; 0.78] Lafite et al., 2013 3 20 - 0.55 [0.32; 0.78] Lafite et al., 2013 3 1 50 - 0.47 [0.21; 0.73] Codulo et al., 2013 3 1 50 - 0.47 [0.21; 0.73] Codulo et al., 2013 3 1 50 - 0.55 [0.55] Code compare at al., 2017 7 15 - 0.47 [0.21; 0.73] Codulo et al., 2013 3 1 50 - 0.55 [0.56] Code compare at al., 2017 7 15 - 0.57 [0.66] 0.61 [0.30; 0.88] Lafite et al., 2013 3 1 50 - 0.55 [0.56] 0.56 [0.24; 0.76] Kouzu et al., 2013 3 1 50 - 0.55 [0.56] 0.56 [0.56] Code compare at al., 2017 7 10 - 0.55 [0.02; 0.78] Codulo et al., 2013 3 1 50 - 0.55 [0.56] 0.56 [0.56] Code compare at al., 2017 7 8 19 - 0.55 [0.02; 0.78] Nagel et al., 2017 7 8 19 - 0.55 [0.02; 0.78] Nagel et al., 2016 12 - 0.79] Nagel et al., 2017 6 1 61 - 0.55 [0.26] 0.57 [0.59] Nagel et al., 2016 12 - 0.55 [0.27] 0.50 [0.27] Magner et al., 2016 12 - 0.55 [0.27] 0.50 [0.27] 0.50 [0.26] Neng et al., 2017 6 1 12 - 0.55 [0.27] 0.50 [0.27] 0.5	Nowak et al., 2018	19	56		0.34	[0.22; 0.48]
Hou et al., 2016 51 59 - 0.68 [0.75; 0.34] Rajarane et al., 2012 70 137 - 0.51 [0.42; 0.60] Shujaat et al., 2018 62 67 - 0.81 [0.68; 0.90] Ge et al., 1989 29 59 - 0.49 [0.36; 0.63] Haddad et al., 1981 19 50 - 0.8 1 Sensitivity Total Study TN (TN+FP) Specificity 95% CI Rallidis et al., 2021 5 8 - 0.62 [0.24; 0.91] Kooranifar et al., 2021 4 4 - 0.06 0.8 1 Sensitivity 55 [0.32; 0.76] Sawada et al., 2019 2 3 - 0.55 [0.32; 0.76] Schneider et al., 2019 50 54 - 0.33 [0.82; 0.98] Schneider et al., 2017 103 262 - 0.55 [0.32; 0.76] Codulo et al., 2013 3 20 - 0.12 [0.00; 0.53] Broderick-Forsgren et al., 2017 7 15 - 0.47 [0.00; 0.54] Codulo et al., 2013 3 1 50 - 0.55 [0.32; 0.76] Large et al., 2013 3 1 50 - 0.55 [0.32; 0.76] Large et al., 2017 8 19 - 0.55 [0.30; 0.38] Large et al., 2017 7 10 - 0.25 [0.30; 0.38] Codie let al., 2019 7 2 - 0.55 [0.30; 0.38] Large et al., 2017 8 19 - 0.42 [0.20; 0.33] Large et al., 2017 8 19 - 0.42 [0.20; 0.35] Broderick-Forsgren et al., 2017 7 103 262 - 0.55 [0.30; 0.38] Large et al., 2013 3 1 50 - 0.47 [0.72; 0.73] Codulo et al., 2013 3 1 50 - 0.47 [0.72; 0.73] Codulo et al., 2013 3 1 50 - 0.47 [0.72; 0.73] Codulo et al., 2013 3 1 50 - 0.47 [0.72; 0.73] Codulo et al., 2019 7 2 4 - 0.55 [0.30; 0.38] Large et al., 2016 7 10 - 0.42 [0.20; 0.67] SadadMamnosser et al., 1987 2 - 0.05 [0.07; 0.93] Benoli et al., 2016 7 1 - 0.71 [0.44; 0.90] Magel et al., 2016 104 109 - 0.35 [0.15; 0.59] Benoli et al., 2018 2 5 - 0.40 [0.16; 0.61] Sadauskas et al., 2016 104 109 - 0.35 [0.30; 0.38] Lee et al., 2018 2 5 - 0.40 [0.16; 0.61] Magel et al., 2018 4 5 - 0.40 [0.16; 0.61] Milens et al., 2018 4 5 - 0.40 [0.16; 0.61] Nowak et al., 2018 4 5 - 0.40 [0.16; 0.68] Kim et al., 2018 6 19 - 0.42 [0.20; 0.67] Balci et al., 2018 6 19 - 0.42 [0.20; 0.67] Balci et al., 2018 6 19 - 0.42 [0.20; 0.67] Balci et al., 2018 6 19 - 0.42 [0.20; 0.67] Balci et al., 2018 7 - 0.71 [0.44; 0.99] Do 2.2 0.4 0.6 0.8 1 Specificity	Li et al., 2018	47	71	- <u></u>	0.66	[0.54; 0.77]
Hajara et al., 2012 70 137 0.51 0.42;0.60 Migures et al., 1990 46 57 0.83 10.86;0.63 Haddad et al., 1981 19 50 0 0.22 0.4 0.6 0.88 10.86;0.63 Haddad et al., 1981 19 50 0 0.22 0.4 0.6 0.8 1 Study Total Total Specificity 95% CI Bournia et al., 2021 4 4 0.62 (0.24;0.91) Kooranifar et al., 2020 12 22 0.55 0.32(0.76) El-Yafawi et al., 2019 2 0.57 0.32(0.76) Schneider et al., 2017 61 61 0.12 0.000:033 Codulo et al., 2017 7 15 0.47 102;0:073 Codulo et al., 2013 4 13 0.47 102;0:073 Codulo et al., 2017 7 15 0.47 102;0:073 Codulo et al., 2013 4 0.55 <	Hou et al., 2016	51	59		0.86	[0.75; 0.94]
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Migures et al., 1990 40 57	Shujaat et al., 2018	62	67		0.93	[0.83; 0.98]
Constraint Constraint <td>Gootal 1990</td> <td>20</td> <td>50</td> <td></td> <td>0.01</td> <td>[0.66; 0.90]</td>	Gootal 1990	20	50		0.01	[0.66; 0.90]
National of al., 1501 13 30 13 30 13 30 13 30 13 13 13 13 13 13 13 13 13 13 13 13 13 13 13 13 100 <td>Haddad et al 1981</td> <td>10</td> <td>50</td> <td></td> <td>0.49</td> <td>[0.36, 0.63]</td>	Haddad et al 1981	10	50		0.49	[0.36, 0.63]
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Figure 1. Meta-analysis for studies that were included in the Main Analysis.

SUB-GROUP ANALYSIS FOR THE DIAGNOSTIC VALUE OF ECHOCARDIOGRAPHY AMONG PATIENTS WITH GROUP **2** PH

Three studies evaluated the diagnostic value of echocardiography of group 2 PH (Supplementary figure 7). The model that pooled these studies revealed that the pooled sensitivity and specificity were 43.4% (95%CI: 3.4%-94.4%) and 53.0% (95%CI: 16.9%-86.2%). Furthermore, the pooled PLR and NLR were 0.924 (95%CI: 0.068-12.585) and 1.068 (95%CI: 0.129-8.82). Supplementary table 5 demonstrates the summary measures of the diagnostic value of echocardiography among patients with group 2 PH. The overall accuracy was 48.4%. Supplementary figure 8 shows the SROC curve of echocardiography in diagnosing patients with group 2 PH.

SUB-GROUP ANALYSIS FOR THE DIAGNOSTIC VALUE OF ECHOCARDIOGRAPHY AMONG PATIENTS WITH GROUP **3** PH

Eight studies investigated the diagnostic value of echocardiography of group 3 PH (Supplementary figure 9). The model that pooled these studies showed that the pooled specificity sensitivity and were 47.1% (95%CI: 35.3%-59.1%) and 65.3% (95%CI: 44.8%-81.3%), respectively. The overall DOR was 1.672 (95%CI: 0.906-3.086). The PLR and NLR were 1.356 (95%CI: 0.897-2.05) and 0.811 (95%CI: 0.656-1.002), respectively. Supplementary table 6 presents the summary measures of the diagnostic values of echocardiography in diagnosing group 3 PH. The pooled accuracy of echocardiography in diagnosing group 3 PH was 56.5%. Supplementary figure 10 demonstrates the SROC curve of echocardiography among patients with group 3 PH.

SUB-GROUP ANALYSIS FOR THE DIAGNOSTIC VALUE OF ECHOCARDIOGRAPHY AMONG PATIENTS WITH GROUP 4 PH

The model that evaluated the diagnostic value of echocardiography in diagnosing group 4 PH included 4 studies (Supplementary figure 11). This model showed that the pooled sensitivity and specificity were 55.4% (95%CI: 23.1%-83.7%) and 44.5% (95%CI: 4.8%-92.8%), respectively. The pooled PLR and NLR of echocardiography among patients with group 4 PH were 0.998 (95%CI: 0.478-2.081) and 1.003 (95%CI: 0.400-2.514) (Supplementary table 7). The overall accuracy of echocardiography in diagnosing patients with group 4 PH was 49.8% (Supplementary figure 12).

CHARACTERISTICS OF THE INCLUDED STUDIES

The total number of the included patients was 4,523 from 38 articles. The prevalence of PH in the included patients was 48.2% (2,181/4,523). The majority of the studies in-

vestigated the diagnostic value of resting echocardiography (89.5%) while 10.5% (4/38) evaluated the diagnostic value of exercise echocardiography. Moreover, 21.1% of the studies included patients with group 1 PH while 7.9%, 21.1%, and 7.9% of the studies included patients with group 2, group 3, and group 4 pulmonary hypertension, respectively. Supplementary table 1 shows the characteristics of the included studies.

QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The majority of the included studies (76.3%) had a good score in the NOS (>5). The highest score (9/9) was achieved by 18.4% of the included studies (7/38). On the other hand, 7.9% of the included studies had the lowest score (4/9). The detailed results of NOS assessment of the included studies are described in Supplementary table 1.

DISCUSSION

The aim of this study was to evaluate the sensitivity, specificity, PLR, NLR, DOR, and accuracy of TTE in comparison to right heart catheterization (reference). The overall sensitivity and specificity of echocardiography in diagnosing PH were 54.8% and 52.1%, respectively. The pooled DOR was 1.321 while the pooled PLR and NLR were 1.145 and 0.867, respectively. The overall accuracy of echocardiography in establishing the diagnosis of PH was 53.4%. Exercise echocardiography increased sensitivity to 60.9% but specificity decreased to 32.8%. The overall accuracy of exercise echocardiography was also lower than resting echocardiography (46.3%).

Previous meta-analyses showed that the sensitivity and specificity of TTE was around 80% and 70%, respectively.³, ^{10,50,51} In addition, these studies showed that the overall accuracy was higher than 70% in the main analysis. These findings contradict the results of our analysis models that demonstrated lower sensitivity, specificity, and accuracy. These contradictions can be explained by the fact that these meta-analyses included lower number of studies and patients which might have resulted in an overestimation of the diagnostic measures of echocardiography. The most recent meta-analysis conducted by the Cochrane collaboration only included 17 studies with total sample size of 3,656 patients⁵² while the largest meta-analysis of the aforementioned ones included 27 studies.⁴⁸ In comparison, our study searched databases up to the end of January 2023 and included larger number of studies (38 studies) and sample size (4,523 patients). Thus, our results are considered more reliable and precise with lower confidence intervals.

The DOR is one of the indicators of test accuracy⁵³ which pools data from sensitivity and specificity into a single measure. Higher values of DOR indicate better discriminatory test performance. A DOR of 1 suggests that the test does not discriminate between patients with and those without the disease.⁵³ In our study, the pooled TTE DOR was low indicating low overall accuracy of the test. Although SROC and DOR are very important measures for diagnostic tools, they are not easily integrated into clinical practice.54 Thus, we also presented PLR and NLR as diagnostic measures. Our analysis showed that the PLR was 1.145, indicating that patients with PH have a mere 1.15 fold higher likelihood of having a positive TTE compared to controls, which is considered a very low probability to confirm the diagnosis of PH. On the other hand, NLR was found to be 0.867 indicating that if the TTE result for any individual is negative, the probability that this individual has PH is higher than 85%. This can be explained by the fact that the population included in the studies comprised of a group of high-risk patients for having PH which indicates that TTE has low diagnostic performance among this group. Future studies are recommended to study the correlation between TTE and right sided heart catheterization among low-risk patients to study the performance of echocardiography among the population with a low probability of having PH.

TTE had the highest sensitivity, specificity, DOR and PLR as well as the lowest NLR among patients with group 1 PH, who were mainly patients with connective tissue diseases. The overall accuracy in this group of patients was 65.5% indicating that TTE is a relatively accurate method in diagnosing PH among this group. TTE had lower sensitivity but higher specificity in diagnosing group 3 PH patients. The pooled accuracy among this group of patients was 56.5%, which is still higher than the cut off point of 50% for evaluating the accuracy of diagnostic tools. On the other hand, the accuracy of TTE among group 2 and group 4 PH patients was very low (below 50%). Also, the NLR among these groups of patients was higher than the PLR. These findings were similar to previous studies that indicated that the accuracy of echocardiography in diagnosing PH among patients with lung diseases is low.^{10,50} The plausible explanation behind these findings is that changes associated with chronic pulmonary diseases, including a marked increase in intrathoracic gas, consolidation of lung tissue, expansion of the thoracic cage and alteration in the position of the heart might decrease the imaging quality and the parameters measurement of TTE.⁵¹ Consequently, the use of TTE to measure pulmonary pressure among this group of patients might not be a valid method. However, it is important to highlight that a lower number of studies included patients with group 2 and 4 PH compared to group 1 and 3 which emphasize the need for conducting further studies among patients in these two groups of PH. Previous metaanalyses did not perform subgroup analysis according to the PH WHO grouping.

Several limitations are present in our study. First, a systematic review and meta-analysis is a secondary research method based on original studies. Although the majority of the included studies had a good quality score according to NOS, the low quality of some of the included studies might impact our results. Second, echocardiography relies heavily on the operator's ability, experience, and operational discipline which might differ between the included studies. Another limitation is that we did not perform sensitivity analysis for parameters used to diagnose PH, yet a previous meta-analysis showed that using different parameters did not affect the performance of echocardiography.¹⁰ Furthermore, despite conducting subgroup analyses on the level of PH groups, some of the included studies did not describe the basic disease and PH type in detail among the included patients. In addition, due to lack of data in the included studies, we were not able to conduct subgroup analyses according to pulmonary hypertension severity grading. Lastly, the low sensitivity and specificity found with TTE might be attributed to it being an operator dependent tool. The included studies did not investigate the inter-rater reliability; thus, we were not able to consider such factor in our analysis. Future studies are recommended to investigate this limitation of TTE in diagnosing pulmonary hypertension.

In conclusion, this is the largest and most updated systematic review and meta-analysis to evaluate the diagnostic performance of TTE in diagnosing pulmonary hypertension compared to right sided heart catheterization as a reference method. Our analysis revealed that TTE had low diagnostic sensitivity, specificity, and accuracy. The highest diagnostic measures for TTE were among WHO group 1 and group 3 PH patients as the accuracy was higher than 50%. On the other hand, TTE had a poor diagnostic performance among WHO groups 2 and 4 PH patients, indicating that using it among these groups of patients may not be reliable or valid. Considering the limitations, echocardiography might be a useful and non-invasive modality for measuring pulmonary artery pressure among group 1 and 3 PH patients. Also, it may be useful for first line surveillance in patients with a low risk of PH. However, the diagnosis of PH and the assessment of response to therapies require right sided heart catheterization due to the overall poor diagnostic performance of TTE. Future prospective large scale wellconducted studies that aim to improve the diagnostic performance of TTE in the diagnosis of PH are needed.

CONTRIBUTION

TNA and DJD were involved in Conceptualization; AAT and TNA were involved in Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, and Writing the original draft; JPV and DJD was involved in Supervision and Reviewing & Editing the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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SUPPLEMENTARY MATERIALS

Supplementary Material

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