Study of connective tissue disease-associated pulmonary hypertension

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Background Screening for pulmonary arterial hypertension (PAH), a leading cause of death in systemic sclerosis, facilitates earlier treatment. The aim of this work was to study connective tissue disease (CTD)-associated PAH guided by 'DETECT' algorithm.

Patients and methods This study was a prospective cross-sectional study conducted on 30 patients with CTDs, including 16 cases with systemic sclerosis, nine cases with systemic lupus erythromatosis, and five cases with rheumatoid arthritis.

Results According to right heart catheterization finding, estimated total sensitivity and specificity of step 1 and step 2 in diagnosis of PAH among all cases were 80 and 64%, respectively.

Conclusion The novel, evidence-based DETECT algorithm for PAH detection in CTDs is a sensitive, noninvasive tool and addresses resource usage.

Introduction

Pulmonary hypertension (PH) is a substantial global health issue in which all age groups are affected, with rapidly growing importance in elderly people [1].

Precise diagnostic classification of PH is essential, not least for reasons of treatment and prognosis, because treatment options that are efficacious in some forms of PH may be ineffective or even disadvantageous in other forms [2].

Pulmonary arterial hypertension (PAH) affects 0.5–15% of patients with connective tissue diseases (CTDs) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed CTD. Despite increasing recognition of PAH in CTDs, the diagnosis is often delayed, which may lead to unfavorable outcomes in these patients [3].

A two-step composite score has been proposed in the DETECT study to select patients who should have right heart catheterization (RHC) [4].

RHC is required to confirm the diagnosis of PAH to assess the severity of hemodynamic impairment and rule out left-sided heart disease. When performed at expert centers, these procedures have low morbidity (1.1%) and mortality (0.055%) rates [5].

The aim of the work was to study CTD-associated PAH guided by the novel 'DETECT' algorithm.

Patients and methods

This cross-sectional study was conducted on 30 patients with CTDs, including SSc, systemic lupus erythromatosis, and rheumatoid arthritis.

All patients (cross sectional) included in the study were recruited from the outpatient clinic and department of chest at specialized hospital Kobry Elkobba Armed Forces.

The study was undertaken in the period between December 2015 and December 2017. The study was approved by institutional ethical committee, and consent was obtained from all patients.

The following patients were excluded from the study: patients having PH confirmed by RHC before enrollment, patients receiving advanced PAH-specific target therapy, patients having forced vital capacity (FVC) less than 40% of predicted (to enrich for a higher likelihood of PAH), and pregnant patients.

All patients included in this study were subjected to the following: full history taking as well as thorough clinical examination. A two-step composite score

proposed in evidence-based 'DETECT' algorithm to select patients who should have RHC [4] is as follows: the first step included functional and laboratory tests to calculate a risk prediction score to exclude low-risk group of having PH and determined transition to step 2 variables for the other patients such as spirometry and DLco to calculate FVC% predicted/DLco% predicted, serum anticentromere antibody, and serum N-terminal pro-brain natriuretic peptide (NT-ProBNP), serum urate (mg/100 ml), as well as ECG for right axis deviation.

The NT-ProBNP was not done to all patients in the current study and was assigned as 50 risk points instead. Patients with total risk points from step 1 greater than 300 were referred to echocardiography. In the second step, the risk score from step 1 was added to total score of step 2 to produce the final PAH score to determine if RHC should be performed for definitive diagnosis. If total risk points from step 2 were greater than 35, patients were referred to RHC at chest specialized hospital Kobry El Kobba Armed Forces.

All variables had contributed risk points irrespective of the measured value.

If one variable from step 1 was not available, 50 risk points should be assigned instead, with the exception of current/past telangiectasias, which should be assigned 65 points. If one variable of step 2 was unavailable, it should be assigned ten points.

All patients included in the study underwent RHC according to ESC/ERS 2015 guidelines [5] to determine the diagnostic performance of the algorithm.

Results

This study was conducted on 30 patients with CTDs, including 16 (53.3%) with SSc, nine (30%) with systemic lupus erythromatosis, and five (16.7%) with rheumatoid arthritis. The mean age of the patients was 53.8 years, and most were females (83%). Most of them were SSc.

The following results were obtained from the current study: 21 patients had positive score (>300 risk points) by step 1 non-echocardiographic variables and were eligible for step 2 evaluation, whereas 18 patients had positive score (>35 risk points) by step 2 echocardiographic variables, and were eligible for RHC. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of step 1 of the algorithm to detect PAH were 87.5, 50,

Table 1 Comparison between step 1 result and confirmed diagnosis with right heart catheterization

	Final diagnosis with RHC (30 patients) [n (%)]		P value
	Positive	Negative	
Step 1 (30 patients)			
Positive	14 (46.6)	7 (6.6)	0.046 (S)
Negative	2 (23.3)	7 (23.3)	

RHC, right heart catheterization; S, statistically significant difference.

Table 2 Comparison between step 2 result and confirmed diagnosis with right heart catheterization

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
Step 2 (21 patients)			
Positive	13 (61.9)	5 (4.7)	0.247 (NS)
Negative	1 (23.8)	2 (9.5)	

RHC, right heart catheterization.

66.7, and 77.7%, respectively (Table 1); on the contrary, sensitivity, specificity, PPV, and NPV of step 2 of the algorithm to detect PAH were 92.8, 28.5, 72.2, and 66.7%, respectively (Table 2). Estimated total sensitivity and specificity of step 1 and step 2 in diagnosis of PAH among all cases were 80 and 64%, respectively.

New predefined sensitivity cut-off of 89% (corresponding to >298 risk points) of step 1 total prediction score was established (Fig. 1); in addition, a predefined specificity cut-off of 50% (corresponding to >37.5 risk points) of step 2 total prediction score was also established (Fig. 2).

Step 1 had 80% and 83.3% sensitivity and specificity, respectively, in the diagnosis of PAH among patients with SSc. PPV was 88.8% whereas NPV was 71.4% (Table 3). However, Step 2 had 100% sensitivity and did not show true negative or false negative cases (Table 4).

Step 1 had 100% and 33.3% sensitivity and specificity, respectively, in the diagnosis of PAH among patients with systemic lupus erythematosus (SLE). PPV was 75%, whereas NPV was 100% (Table 5). On the contrary, step 2 had 83.3% and 50% sensitivity and specificity, respectively, in diagnosis of PAH among patients with SLE, with PPV of 83.3% and NPV of 50% (Table 6).
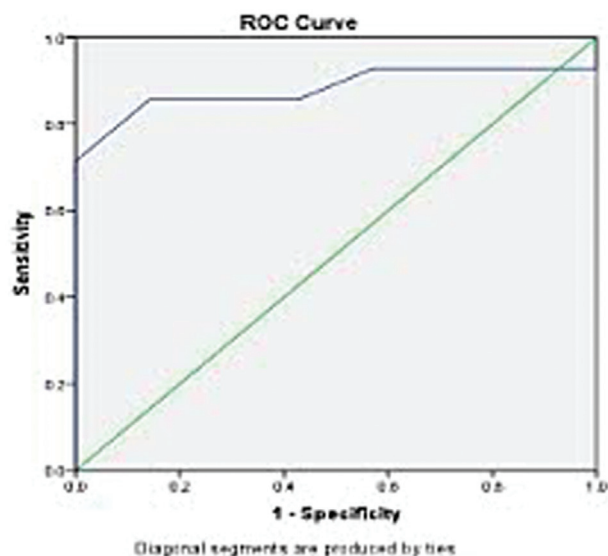
Step 1 showed no true positive cases and 20% specificity in diagnosis of PAH among patients with rheumatoid arthritis (RA) (Table 7), whereas step 2

Figure 1

Cutoff value: 298
AUC: 0.770
Sensitivity: 89%
Specificity: 50%
Sig: 0.012
CI 95%: 0.598 – 0.942
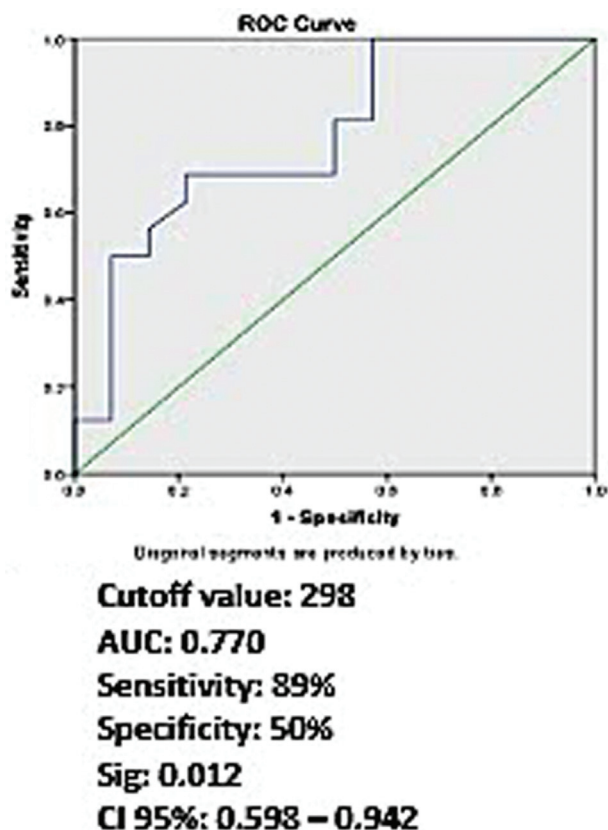
Receiver operating characteristic curve for detecting cut-off value for step 1.

Figure 2

Receiver operating characteristic curve for detecting cut-off value for step 2.

shows no true positive cases or false positive cases (Table 8).

There was a significant positive statistical correlation between mean pulmonary artery pressure (m PAP) and

Table 3 Diagnostic performance of step 1 for diagnosis of pulmonary arterial hypertension among patients with systemic sclerosis

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
SSc (16 patients)			
Positive	8 (50)	1 (6.2)	0.035s
Negative	2 (12.5)	5 (31)	

RHC, right heart catheterization; SSc, systemic sclerosis.

Table 4 Diagnostic performance of step 2 for diagnosis of pulmonary arterial hypertension among patients with systemic sclerosis

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
SSc (9 patients)			
Positive	8 (50)	1 (6.2)	–
Negative	0 (0)	0 (0)	

RHC, right heart catheterization; SSc, systemic sclerosis.

Table 5 Diagnostic performance of step 1 for diagnosis of pulmonary arterial hypertension among patients with systemic lupus erythematosus

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
SLE (9 patients)			
Positive	6 (66.6)	2 (22.2)	0.333 (NS)
Negative	0 (0)	1 (11.1)	

RHC, right heart catheterization; SLE, systemic lupus erythromatosis.

Table 6 Diagnostic performance of step 2 for diagnosis of pulmonary arterial hypertension among patients with systemic lupus erythematosus

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
SLE (8 patients)			
Positive	5 (66.6)	1 (22.2)	0.464 (NS)
Negative	1 (0)	1 (11.1)	

RHC, right heart catheterization; SLE, systemic lupus erythromatosis.

Table 7 Diagnostic performance of Step 1 for diagnosis of pulmonary arterial hypertension among rheumatoid arthritis

	Final diagnosis with RHC [n (%)]		P value
	Positive	Negative	
RA (5 patients)			
Positive	0 (0)	4 (80)	0.046 (S)
Negative	0 (0)	1 (20)	

RA, rheumatoid arthritis; RHC, right heart catheterization.

Table 8 Diagnostic performance of step 2 for diagnosis of pulmonary arterial hypertension among patients with rheumatoid arthritis

| | Final diagnosis with RHC [*n* (%)] | | *P* value |
	Positive	Negative	
RA (4 patients)			
Positive	0 (0)	3 (80)	–
Negative	0 (0)	1 (20)	

RA, rheumatoid arthritis; RHC, right heart catheterization.

Table 9 Correlation between mPAP and FVC%/DLco% predicted and DLco% predicted

| | mPAP | |
	r	*P* value
FVC%/DLco% predicted	0.625	0.000
DLco% predicted	−0.547	0.002

DLco, diffusion lung capacity of carbon monoxide; FVC, forced vital capacity; *r*, correlation.

FVC% predicted/DLco% predicted among the study group. On the contrary, there was significant negative statistical correlation between mean PAP and DLco% predicted (Table 9).

Discussion

Screening for PAH in SSc allows for earlier detection and treatment that prolongs survival and improves symptoms, but it is important that clinicians who follow patients with SSc screen and act upon the results, such as referring suspected PAH for RHC and treatment at an expert center [6].

For these reasons, the aim of this study was to study CTD-associated PAH guided by evidence-based 'DETECT' algorithm.

The study was conducted on 30 patients with CTD, including SSc, SLE, and RA.

A two-step composite score proposed in the 'evidence-based DETECT algorithm' [4] was applied to the included patients.

All patients included in the study underwent RHC to determine the diagnostic performance of the two steps and the corresponding risk point cutoffs.

The mean age for the study group was found to be 53.8 ±5.57 years. This finding partially copes with Coghlan *et al.* (The DETECT study) [4] who enrolled 408 patients with SSc and found that mean age was 57.9 years and also partially matches with the study by Guillén-Del Castillo *et al.* [7] who applied the

DETECT algorithm on 63 patients with SSc and found that the mean age was 62.4 years.

In this study, most cases were females (25 cases, 83.3%), whereas five (16.7%) cases were males. This finding was in accordance with the study by Guillén-Del Castillo *et al.* [7] who registered that 93% of his study group were females.

DETECT study [4] and the study by Guillén-Del Castillo *et al.* [7]) applied DETECT algorithm on patients with SSc only. Unfortunately, there are no available studies applying the DETECT algorithm on patients with CTDs other than SSc.

In our study, of 30 patients included in step 1 risk prediction score and evaluated by non-echocardiographic variables, 21 (70%) patients had positive score (>300 risk points) and were eligible for step 2 evaluation; however, NT-proBNP was missing and assigned 50 risk points instead.

Comparing this finding with the DETECT study [4], it was found that of 356 patients enrolled in step 1 of the algorithm, 304 (85%) patients had positive score (>300 risk points) and were eligible for step 2 evaluation.

Regarding step 2 evaluation by addition of total risk points of step 1 algorithm to two echocardiographic variables (TR velocity and RA area), 18 (85.7%) of 21 patients had positive score (>35 risk points) and were eligible for RHC.

On the contrary, the DETECT study [4] illustrated that 198 (74%) of 267 patients included in step 2 had positive score and were eligible for RHC.

In the study by Guillén-Del Castillo *et al.* [7], all cases (35 cases) included in step 2 had positive score and were eligible for RHC.

In the present study, all patients included underwent RHC, which revealed 16 (53.3%) patients with PAH versus 14 (46.7%) without PH.

On the contrary, in the DETECT study [4] 408 patients underwent RHC, which revealed 87 (19%) cases with PAH versus 321 (69%) without PAH.

In the current study, of 30 patients evaluated by step 1 algorithm and confirmed by RHC, 14 patients were true PAH positive (sensitivity of 87.5%) and seven patients were true PAH negative (specificity of 50%), whereas the PPV was 66.7% and NPV was 77.7%.