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.

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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, 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.

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.

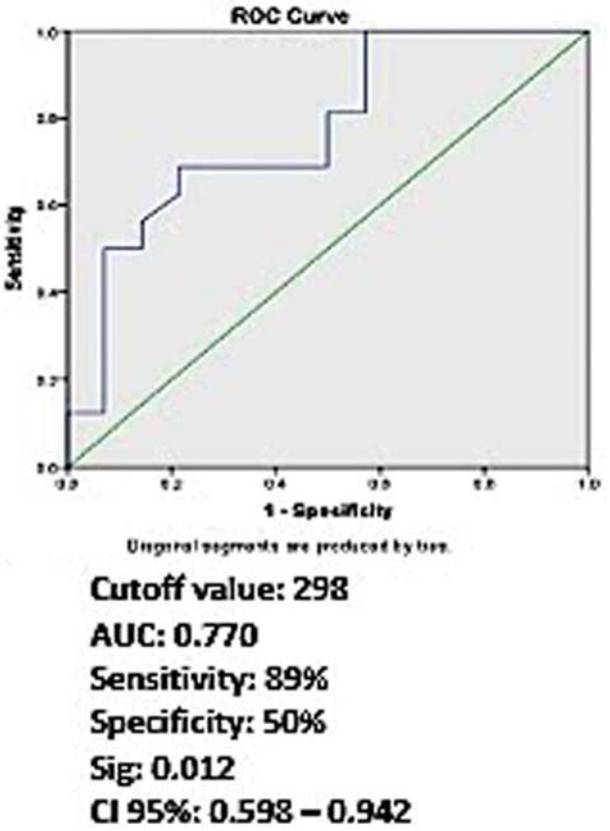
New predefined sensitivity cut-off of 89% (corresponding to >298 risk points) of step 1 total prediction score was established (Fig. 1); in addition, a predefined specificity cut-off of 50% (corresponding to >37.5 risk points) of step 2 total prediction score was also established (Fig. 2).

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).

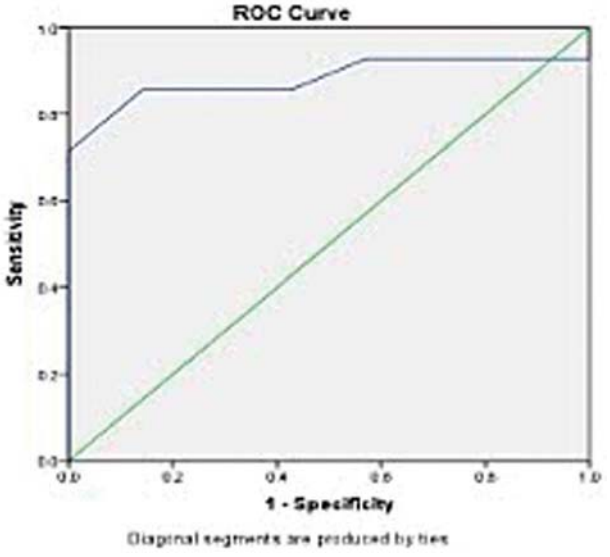
Step 1 showed no true positive cases and 20% specificity in diagnosis of PAH among patients with rheumatoid arthritis (RA) (Table 7), whereas step 2

Figure 1



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%.

However, in the DETECT study [4], the NPV was 96%.

Comparing the results of step 2 and confirmed diagnosis by RHC, our study revealed that of 21 patients evaluated by the algorithm, 13 patients were true PAH positive (sensitivity of 92.8%) and two patients were true PAH negative (specificity of 28.5%), whereas PPV was 72.2% and NPV was 66.7%.

These findings were partially in accordance with the DETECT study [4] findings in step 2 which revealed that of 267 patients included in step 2 algorithm, 69 patients were true PAH positive (sensitivity of 98.5%) and 68 true PAH negative (specificity of 34.5%), whereas PPV was 34.5% and NPV was 98.5%.

In the current study, the estimated overall sensitivity and specificity for the whole algorithm (step 1+step 2) were calculated among the study group and were found to be 80 and 64%, respectively.

However, in the DETECT study [4], high overall sensitivity (96%) and low overall specificity (48%), with PPV of 35% and NPV of 98%, were obtained, whereas in the study by Guillén-Del Castillo *et al.* [7], sensitivity, specificity, PPV, and NPV were 100, 42.9, 68.6, and 100%, respectively.

In our study, receiver operating characteristic (ROC) curve analysis was used to determine the discriminatory performance to distinguish between PAH and non-PH. The combined discriminatory ability of the variables in step 1 expressed as the area under the curve of the ROC curve was 0.77 (95% confidence interval: 59.8–94.2%) with new sensitivity cut-off value of 89% (corresponding to >298 risk score), whereas the DETECT study [4] illustrated 97% sensitivity cut-off value (corresponding to >300 risk score).

In the present study, the area under the curve (ROC curve) for the total risk points from step 1 plus step 2 variables was 0.888 (95% confidence interval: 73.9–100%) with new specificity cut-off of 50% (corresponding to >37.5 risk score) compared with 35% specificity cut-off (corresponding to >35 risk score) in the DETECT study [4].

In the current study, on comparing the two groups, there were no statistical differences between PAH group and non-PH group regarding serum urate level, positivity of anticentromere antibodies, and right axis deviation by ECG.

There was disagreement with the DETECT study [4] and the study by Guillén-Del Castillo *et al.* [7] which showed statistical differences between PAH group and non-PH group in the aforementioned variables.

Regarding the respiratory parameters, the PAH group had higher FVC% predicted/DLco% predicted than non-PH group (1.5±0.44 vs. 1.2±0.26, P=0.021).

This finding was in agreement with the DETECT study [6] in which FVC % predicted / DLco % predicted was 2.2 in PAH group whereas in non-PH group was 1.8.

Similarly, this finding also was in accordance with Guillén-Del Castillo *et al.* [7] with 2.0±0.7 in PAH group versus 1.5±0.4 in non-PH group (P<0.01).In the current study, there was a significant positive correlation between mean PAP and FVC % predicted/DLco % predicted among the study group. On the contrary, there was a significant negative correlation between mean PAP and DLco% predicted.

This finding matches with Riad *et al.* [8] in which 30 scleroderma diagnosed patients were subjected to spirometry and DLco and found significant differences in the values of FVC% and DLco% predicted, which was significantly lower in patients with suspected PAH, and FVC%/DLco% predicted was significantly higher in those patients. The best cut-off value of FVC /DLco for predicting suspected PH among the studied cases was a value greater than 1.91, with a sensitivity of 87.5% and a specificity of 100%.

Regarding the echocardiographic selected parameters, PAH group presented with higher TR velocity than non-PH group (3.4±0.59 vs. 2.8±0.37, P=0.028), and this finding matches with the DETECT study [4] and the study by Guillén-Del Castillo *et al.* [7].

Regarding RHC finding, PAH group was characterized by higher mean PAP (46±13.5 vs. 21 ±3.9, P=0.0); however, there was no statistical difference in mean PCWP between the two groups, and this finding was similar to the study by Guillén-Del Castillo *et al.* [7].

In the present study, of the enrolled 16 patients with SSc, 10 cases had PAH confirmed by RHC, such that step 1 showed eight true positive cases and five true negative cases with 80 and 83.3% sensitivity and specificity, respectively. Moreover, PPV was 88.8%, whereas NPV was 71.4%. On the contrary, step 2 had 100% sensitivity and did not show true negative or false

negative cases. This diagnostic performance was in accordance with that of the DETECT study [4].

Moreover, in our study, of the included nine patients with SLE, six cases had PAH confirmed by RHC, such that step 1 showed 6 true positive cases and only one true negative case confirmed by RHC with 100 and 33.3% sensitivity and specificity, respectively. PPV was 75% whereas NPV was 100%. Furthermore, Step 2 showed five true positive cases and only one true negative case with 83 and 50% sensitivity and specificity, respectively. PPV was 83.3%, whereas NPV was 50%.

In the current study, step 1 and step 2 had no true positive cases for PAH among patients with RA with 20% specificity. This may be because of a small and incomparable sample size.

Conclusion

The evidence-based DETECT algorithm for PAH detection in SSc is a sensitive, noninvasive tool and minimizes missed diagnoses and addresses resource usage. PAH detection in SLE using DETECT algorithm is a sensitive and noninvasive tool; however, the diagnostic performance should not be globalized until further studies are done on a large number of unselected patients. Application of DETECT algorithm for PAH detection in RA has low diagnostic performance. RHC remains a gold standard in diagnosis of PH, though being an invasive procedure.

Recommendation

It is worth mentioning that the application of DETECT algorithm for screening and early detection of PAH should be integrated in the management of patients with SSc and SLE before referral for RHC, as it is sensitive and noninvasive tool. Further research studies on larger groups of patients with comparable numbers of different diagnoses in multicenters over prolonged period should be performed for better analysis of diagnostic performance.

Limitation

The current study had the following limitations: first is the small sample of the studied population, which led to misrepresentation of the entire variables (e.g. telangiectasias were negative in all of the included patients); second, not all CTDs were represented in the current study; and lastly, NT-ProBNP variable of step one was missing in all patients, and fixed risk points were assigned instead.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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