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Evaluation of screening tools for primary ciliary dyskinesia in Egypt: single center study

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ABSTRACT

Background: Primary ciliary dyskinesia (PCD) is a chronic respiratory illness that places significant strain on the healthcare system due to the complexity and expense of its diagnosis and treatment methods. The diagnostic process typically requires skilled technicians and an assortment of intricate, costly, and time-consuming approaches. Implementing screening tools can enhance efficiency by focusing the diagnostic process on those strongly suspected of having PCD. Tools such as the PCD Rule (PICADAR), North America Criteria Defined Clinical Features (NA-CDCF), the Clinical Index Score (CI), and the newly proposed CI_{new13} could potentially serve as useful screening tools. This study aims to examine the effectiveness of these tools individually, compare their performance against each other, and assess their results relative to prior research.

Methods: We conducted a diagnostic accuracy test on 83 Egyptian patients referred to Alexandria University Children's Hospital for potential PCD diagnosis between January 2015 and December 2022. The scores obtained from the screening tools were calculated and assessed.

Results: Of the initial group, 10 patients were ruled out because they fit other diagnostic parameters. Forty-three cases received a confirmed diagnosis, while 30 did not. Notably, the confirmed cases consistently scored higher on our screening tools than those that remained unconfirmed (p <.001, for all tested scores). We used receiver operating characteristic curves to assess and compare the effectiveness of each tool. The NA-CDCF had the smallest area under curve 0.736 (95% confiedence interval 0.619-0.832); in contrast, the CI score had the largest 0.898 (95% confidence interval 0.808-0.957).

Conclusion: All the tools tested were effective in identifying suitable patients for PCD testing at statistically significant levels. However, the PICADAR and NA-CDCF scores' performance did not significantly differ in the current study. The CI and CI_{new13} scores, on the other hand, outperformed both.

Key words: Primary ciliary dyskinesia, Diagnosis, Screening, Egypt

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Introduction

Primary Ciliary Dyskinesia (PCD) is a rare genetic disease with diverse symptoms that adversely impact health [1]. Typically affecting the respiratory system, PCD presents differently in every patient due to the disrupted motion of cilia [2-4]. Potential symptoms may include constant wet cough, persistent runny nose with or without blockages, middle ear complications that could impair hearing, defects in laterality, recurring chest infections, neonatal respiratory distress, and fertility problems during reproductive years [5].

Diagnosing PCD is a demanding, costly, and time-intensive process. The lack of a universally accepted diagnostic test, combined with the inability of a single test or combination of tests to conclusively rule out the condition, exacerbates the challenge [2, 3]. Various screening tools have been developed and validated to identify patients with a high likelihood of having PCD [6, 7]. These include the PICADAR questionnaire, the NA-CDCF score, and the CI score (Supplementary material Tables 1, 2, and 3) [8-10]. Numerous PCD centers employ these measures to target diagnostic efforts on those most likely to benefit from the rigorous diagnostic process [11]. CI_{new13} (Supplementary material Table 4) is a recently suggested screening tool, tested and proposed by Martinů et al. [7].

The current study aims to evaluate the performance of these tools within our study group, comparing their effectiveness with each other and with previous research.

Patients

This study comprised 83 patients from 75 distinct families, all evaluated for PCD between January 2015 and December 2022. These patients were suspected of PCD based on criteria from the European Respiratory Society (ERS) Task Force. The ERS suggests a PCD diagnosis when several symptoms, such as chronic moist coughing, persistent rhinorrhea, laterality defects, newborn respiratory distress, auditory issues, unexplained bronchiectasis, and congenital heart malformation, exist concurrently [2]. Patients diagnosed with conditions other than PCD were excluded from the study. Infants under one year of age were also excluded due to insufficient medical data for accurate clinical score assessment.

Methods

Study design

Diagnostic test accuracy study.

Study setting

Tertiary health care facility.

Recruiting location

Respiratory Department, Alexandria University Children's Hospital. We obtained permission from the Ethics Committee of Alexandria University before conducting the study (IRB number: 00012098).

Outcome measures

We collected information on age, sex, and history of parental consanguinity. We calculated primary outcomes using various screening tools, namely the PICADAR score, the NA-CDCF score, the CI score, and the newly proposed CI_{new13} score. Responses to these questionnaires and diagnostic test results were retrieved from medical records.

Statistical analysis

We used the Statistical Package for Social Science (SPSS) program (ver 27) to collect and analyze data [12]. We performed diagnostic test accuracy analysis and generated the area under the receiver operator (ROC) characteristics curve (AUC) using MedCalc software (ver 20) [13]. The Kolmogorov-Smirnov test showed the distribution of variables to be normal, warranting the use of parametric statistics [14]. Accordingly, we conducted both parametric and non-parametric analyses [14, 15]. For sample size calculation, we accepted a beta error of up to 20%, setting the study's

power at 80%, resulting in a minimum sample size of 62 patients. We designated an alpha level of 5% and a significance level of 95%. Statistical significance was identified at a p of <0.05 [16].

Results

The study initially included 83 patients, but ten were excluded; five due to severe allergic rhinitis and asthma, four with cystic fibrosis, and one with an immune deficiency disorder. Thus, the study comprised 73 patients: 33 males (45.21%) and 40 females (54.79%). Their mean age was approximately 8.09 years, with a standard deviation of 4.34. Table 1 includes more demographic details of the group.

PCD was confirmed in 43 patients, referred to as "definite PCD", while the remaining 30 could not be definitively diagnosed and were labeled as "possible PCD or undefined". The confirmation of PCD was based on either a distinctive ciliary axonemal defect detected by transmission electron microscopy as per international consensus guidelines in two cases [14], bi-allelic pathologic mutations in a PCD-associated gene in 25 cases, or a combination of both in the remaining 16 cases.

Table 2 juxtaposes the PICADAR, NA-CDCF, CI, and CI_{new13} scores for confirmed and non-confirmed cases. In confirmed cases, the PICADAR, NA-CDCF, CI, and CI_{new13} had median values of 9, 3, 6, and 9, respectively. Whereas, the median values among non-confirmed cases for the PICADAR, NA-CDCF, CI, and CI_{new13} were 6, 2, 3, and 7, respectively. There was a statistically significant difference in the scores of confirmed cases compared to non-confirmed ones for each tested score (p <.001 for all scores).

The receiver operating characteristic curves for the various screening tools were compared, as depicted in Figure 1. The areas beneath these curves were calculated and are displayed in Table 3. The NA-CDCF had the smallest area (0.736, 95% CI 0.619-0.832); in contrast, the CI score had the largest (0.898, 95% CI 0.808-0.957). Based on the existing data, the cut-off value with the highest combined sensitivity and specificity was determined for each of the four tools tested; their performance is outlined in Table 3. These values were >7 for the PICADAR, >2 for the NA-CDCF, >4 for the CI score, and >7 for the CI_{new13}. These are

Table 1. Some demographic data for the study cohort.

		Confirmation for PCD		
	All children (n=73)	**Not confirmed (n=30)**	**Confirmed (n=43)**	**Test of significance p**
Age at enrollment (year)				
• Min-Max	1.17-16.00	2.00-15.00	1.17-16.00	
• Mean±SD	8.09±4.34	7.08±4.09	8.80±4.42	$t_{(df=71)}$ =1.686
• SE of Mean	0.51	0.75	0.67	p=.096 NS
• 95.0% CI of the mean	7.08-9.11	5.55-8.61	7.44-10.16	
• 25th Percentile – 75th Percentile	5.00-12.00	3.00-10.00	6.00-12.00	
Sex				
• Male	33 (45.21%)	15 (50.00%)	18 (41.86%)	χ^2(df=1)=0.473
• Female	40 (54.79%)	15 (50.00%)	25 (58.14%)	p=.492 NS
Consanguinity				
• No	19 (26.03%)	12 (40.00%)	7 (16.28%)	χ^2(df=1)=5.165, **p=.023***
• Yes$^{(R)}$	54 (73.97%)	18 (60.00%)	36 (83.72%)	Z=3.359, **p<.001*** **OR: 3.429** 95% CI: 1.152-10.202

n, number of patients; PCD, Primary Ciliary Dyskinesia; TEM, Transmission Electron Microscope; Min-Max, Minimum to Maximum; SD, Standard deviation; SE, Standard error; CI, Confidence interval; t, Independent Sample t test; χ^2, Pearson Chi-Square; df, degree of freedom; Z, Z score for absolute difference between groups (p for significance of 95% CI difference); OR, Odds Ratio; NS, Statistically not significant (p≥.05); *, Statistically significant (p<.05); R, Risk category.

Table 2. Comparison between the values for the PICADAR, NA-CDCF, CI, and CI_{new13} scores between confirmed and non-confirmed cases.

		Confirmation		
	All children (n=73)	**Not confirmed (n=30)**	**Confirmed (n=43)**	**Test of significance *p***
PICADAR total score (out of 14)				
• Min-Max	2.00-14.00	2.00-14.00	4.00-14.00	Z(MW)=3.532 *p*<.001*
• Median	8.00	6.00	9.00	
• 95.0% CI of the Median	8.00-10.00	5.00-8.00	8.00-10.00	
• 25th Percentile – 75th Percentile	6.00-10.00	5.00-8.00	7.00-11.00	
NA-CDCF total score (out of 4)				
• Min-Max	1.00-4.00	1.00-4.00	2.00-4.00	Z(MW)=3.624 *p*<.001*
• Median	3.00	2.00	3.00	
• 95.0% CI of the Median	3.00-4.00	2.00-3.00	3.00-4.00	
• 25th Percentile – 75th Percentile	2.00-3.00	2.00-3.00	3.00-4.00	
CI total score (out of 7)				
• Min-Max	2.00-7.00	2.00-6.00	3.00-7.00	Z(MW)=5.877 *p*<.001*
• Median	5.00	3.00	6.00	
• 95.0% CI of the Median	5.00-6.00	3.00-4.00	6.00-7.00	
• 25th Percentile – 75th Percentile	4.00-6.00	3.00-4.00	5.00-6.00	
CI_{new13} total score (out of 13)				
• Min-Max	4.00-13.00	4.00-13.00	7.00-13.00	Z(MW)=5.071 *p*<.001*
• Median	9.00	7.00	9.00	
• 95.0% CI of the Median	9.00-10.00	7.00-9.00	9.00-10.00	
• 25th Percentile – 75th Percentile	7.00-10.00	6.00-8.00	9.00-11.00	

PICADAR, Primary ciliary dyskinesia rule; NA-CDCF, North America criteria defined clinical features; CI, Clinical index; CI_{new13}, Clinical $index_{new13}$; n, number of patients; Min-Max, Minimum to Maximum; CI, Confidence interval; $Z_{(MW)}$, Z of Mann-Whitney U test; *, Statistically significant (*p*<.05).

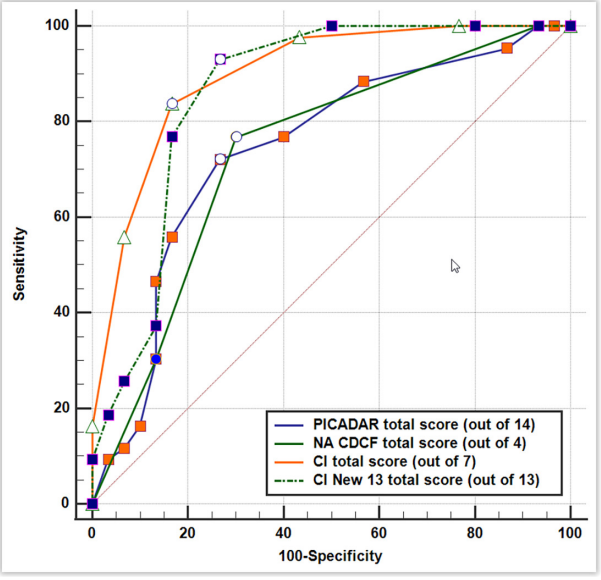

Figure 1. ROC curves for the PICADAR, NA-CDCF, CI, and CI_{new13} scores to discriminate between the confirmed and the non-confirmed cases.

suggested as the new threshold cut-offs for testing Egyptian patients suspected of PCD.

Figure 2 presents a Venn diagram, delineating the similarities and differences among four screening tools. The tools agreed on results for 52 patients when using the original, recommended cut-off points. Figure 3 displays box and whisker plots of the calculated scores for each tool, distinguishing between confirmed and not-confirmed cases. These plots are based on both the originally suggested cut-offs (red line) and the best-performing cut-offs from our study cohort (blue lines).

Discussion

Diagnosing PCD is particularly challenging in low and middle-income countries due to the costly and complex diagnostic tools [17]. In this study, we evaluated the effectiveness of various predictive tools

Table 3. Area under the ROC curves for the different screening tools and the best detected cut-off thersholds among the study cohort.

Index	AUC (%) (95% CI)	Z	Cut-off Value(YI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Overall Test Accuracy (%) (95% CI)
PICADAR[a,b]	0.743 (0.627-0.838)	3.957 (p=.0001*)	>7	72.09 (56.33-84.67)	73.33 (54.11-87.72)	79.49 (67.54-87.83)	64.71 (51.99-75.64)	72.60 (60.91-75.64)
NA-CDCF[a,b]	0.736 (0.619-0.832)	3.809 (p=.0001*)	>2	76.74 (61.37-88.24)	70.00 (50.60-85.27)	78.57 (67.45-86.65)	67.74 (53.76-79.14)	73.97 (62.38-83.55)
CI[c,d]	0.898 (0.808-0.957)	10.907 (p<0001*)	>4	83.72 (69.30-93.19)	83.33 (65.28-94.36)	87.80 (76.19-94.19)	78.12 (64.03-87.76)	83.56 (73.05-91.21)
CI_{new13}[c,d]	0.862 (0.761-0.932)	7.251 (p<0001*)	>7	93.02 (80.94-98.54)	73.33 (54.11-87.72)	83.33 (73.31-90.10)	88.00 (70.68-95.71)	84.93 (74.64-92.23)

Cut-off value (YI), the value at which the diagnostic test is able to discriminate the outcome i.e. for PICADAR; test (>7), total score of >7 (i.e. starting from 8 because the score has no decimal points) is able to discriminate Primary Ciliary Dyskinesia. YI, Youden index J. Different superscript letters indicate significant difference according to pairwise comparison of ROC curves [18].

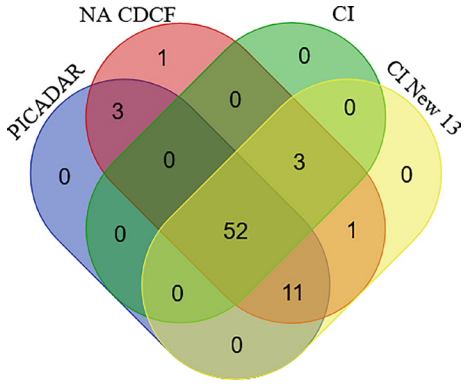

Figure 2. Venn diagram for the tested screening tools. When applying the originally proposed cut-offs, 52 PCD patients tested positive with the four screening tools, while 11 had positive results with the PICADAR, NA-CDCF, and CI_{new13} but not the CI score. Three patients had positive results with the NA-CDCF, CI, and CI_{new13} but not with PICADAR. Another 3 patients tested positive for PICADAR and NA-CDCF but neither CI nor CI_{new13}.

within our study group, comparing their performance with each other and with previously published data. This research could streamline the diagnostic process by identifying those who truly need to navigate the rigorous diagnostic pathway.

In the present study, median scores for the screening tools (PICADAR, NA-CDCF, CI, and the newly proposed CI_{new13}) were much higher in confirmed cases (9, 3, 6, and 9, respectively) than in non-confirmed ones (6, 2, 3, and 7, respectively); this was statistically relevant with p <.001 for all scores. This is in line with the original articles and subsequent validation studies [7-11]. However, we observed that the median value of each individual score was higher for both PCD and non-PCD patients compared to what was reported in the previous validation studies. This discrepancy could be due to the fact that our study cohort was younger than those in prior studies (range from 1.17 to 16.00 years with a median value of 8). This age range may have facilitated a more accurate recall of neonatal and infancy histories, key components of the screening scores, which may often be overlooked by adults. A recent external validation was carried out by Martinů et al. [7] on 1,834 patients, with ages ranging from 0 to 70.90 years and a median age of 6.1 years. In this validation, the median values for PCD patients were significantly higher than non-PCD patients (for PICADAR 7 vs.3, NA-CDCF 3 vs. 2, and the CI score of 5 vs. 3, p <.001 for the three scores).

The current study demonstrated that the PICADAR score achieved its maximum combined sensitivity and specificity at a cut-off point of >7 (meaning 8, as the score does not include decimal points). The sensitivity and specificity were 72.09% and 73.33%, respectively. Using this cut-off would result in 39 patients testing positive and being referred for PCD testing, with 31 of them receiving a confirmed diagnosis,

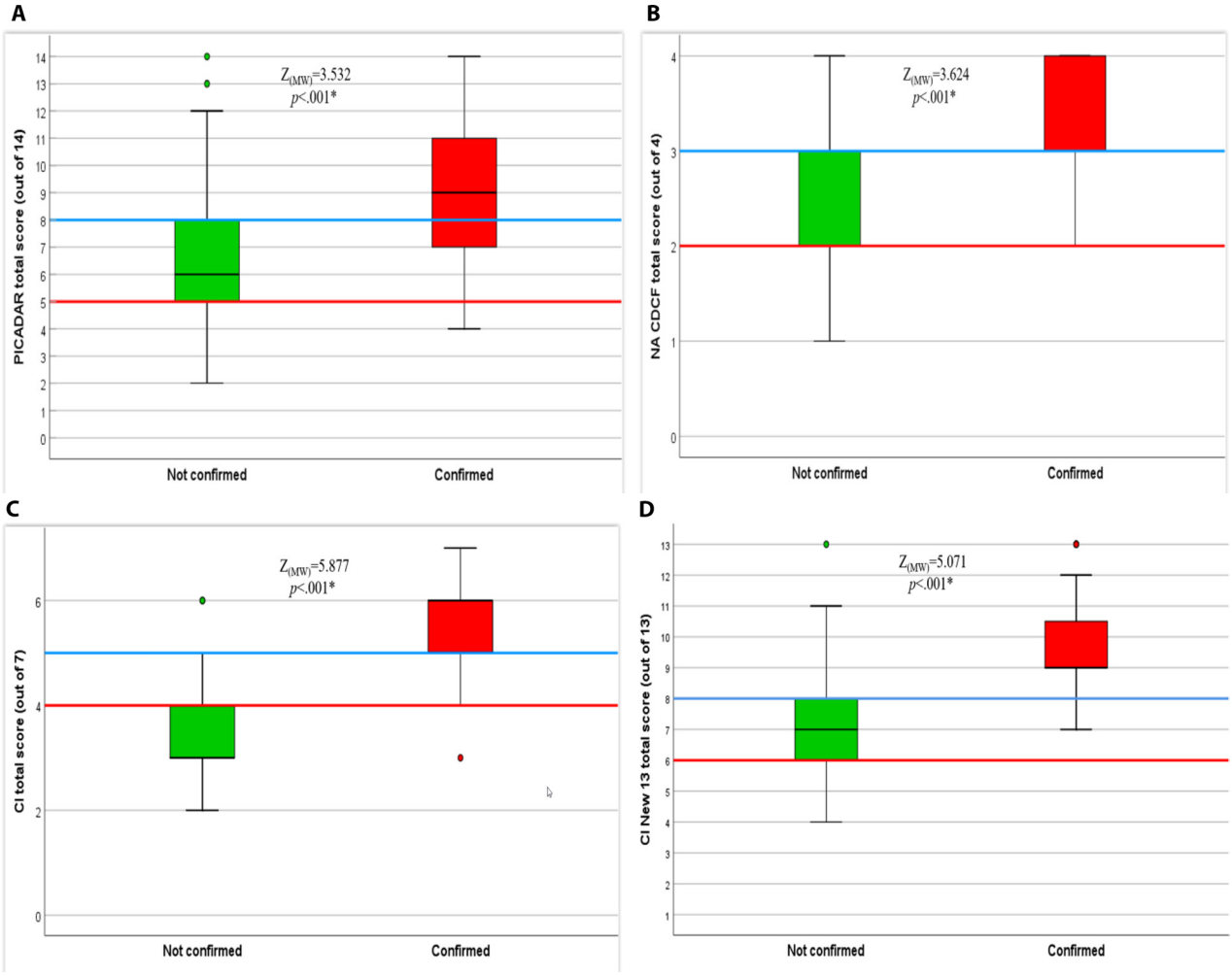

Figure 3. Box and whisker graph of the different screening tools (a: PICADAR, b: NA-CDCF, c: CI score, and d: CI_{new13}) in the studied group. The thick line in the middle of the box represents the median, the box represents the inter-quartile range (from 25th to 75th percentiles), and the whiskers represent the minimum and maximum after excluding outliers (circles). The horizontal red line represents the original cut-off value, while the horizontal blue line represents the cut-off with the best performance among the study cohort.

resulting in a positive predictive value (PPV) of 79.49%. A study conducted by Martinů et al. [7] demonstrated that the best predictive characteristics were achieved at a cut-off threshold of 6.

When we applied the cut-off threshold of 5, initially proposed by Behan et al. [10] to our patients, 67 tested positive and were referred for PCD evaluation. Of these, 41 were confirmed diagnoses. The sensitivity stood at 95.35%, surpassing the original article's 90% in its validation group. In contrast, the specificity was 13.33%, below the 75% reported in the original article's validation group [10].

In the present study, the greatest combined sensitivity and specificity for the NA-CDCF score were observed at a cut-off of >2 (effectively starting at 3, as the score does not include decimal points). This resulted in a sensitivity of 76.74% and a specificity of 70.0%. Using this value, 42 patients would test positive and be referred for PCD testing. Of these, 33 would receive a confirmed diagnosis, leading to a PPV of 78.57%. Similarily, Martinů et al. [7] found that a cut-off threshold of 3 yielded the most accurate predictive characteristics.

Applying the initial cut-off threshold value of 2, proposed by Leigh et al. [9] our study would yield positive

test results for 71 patients, 43 of whom would indeed be diagnosed with PCD. The sensitivity would be 100%, exceeding the 80% reported in Leigh's article. However, the specificity would drastically drop to 6.67%, significantly lower than the 72% reported in the initial study [9].

In this study, we found the optimal combined sensitivity and specificity score for the CI to be above 4 (due to the score not having decimal points, it started from 5). The sensitivity was 83.72%, and specificity was 83.33%. Applying this score would result in 41 patients testing positive and being referred for PCD testing. Out of these, 36 would receive a confirmed diagnosis, leading to an 87.80% PPV. On the other hand, Martinů et al. [7] showed that a cut-off value of 4 produced the best predictive characteristics.

Applying the original article's [8] suggested cut-off of 4 to our study would result in 55 patients being recommended for PCD testing, 42 of whom would receive a confirmed diagnosis. This cut-off provides a sensitivity of 97.67%, surpassing the 95.52% from the original article. However, its specificity, at 56.67%, falls short of the original's 72.49% [8].

Martinů et al. [7] proposed the CI_{new13} as a potential new predictive tool for PCD. When applied to the present cohort, this tool demonstrated the utmost combined sensitivity and specificity at a cut-off value greater than 7 (meaning it starts from 8 as the score does not accommodate decimal points). The sensitivity was measured at 93.02%, while the specificity came in at 73.33%. Previously, Martinů et al. [7] had reported that the CI_{new13} recorded its best performance at a cut-off value of 6, yielding an impressive 95.5% sensitivity alongside a 68.7% specificity.

The current study shows that while all four examined screening tools had adequate discriminative power for PCD, the CI and the newly proposed CI_{new13} tools outperformed both the PICADAR and NA-CDCF tools in terms of sensitivity and specificity. Despite this, the ease of use of the CI score makes it the preferred screening tool for PCD among suspected Egyptian patients. It only requires seven question-based clinical data and does not need further investigations. This is consistent with other research results [7]. Utilizing the CI score with a new suggested cut-off threshold greater than 4 (i.e., 5) will result in 13 patients being referred for unnecessary testing (false positives) while potentially missing one PCD patient (false negative) in the diagnostic process. The newly suggested CI_{new13} did not add significant benefit over the CI score and this goes with what was reported by Martinů et al. [7]. Moreover, this study, similar to the findings of Palmas et al. [11] shows no significant difference between the PICADAR and NA-CDCF scores, possibly due to overlapping parameters in both scores.

This study's notable achievement is being the first to evaluate the effectiveness of PCD screening tools in Egyptian pediatric patients. However, our work has been somewhat constrained by the relatively small sample size (73 patients) from a single-center in comparison to 1,834, and 211 patients in Martinů et al. [7] and Palmas et al. [11] external validations, respectively. Hence, we strongly recommend additional studies with larger populations and multiple centers across Egypt.

Conclusion

The PICADAR, NA-CDCF, CI, and the recently proposed CI_{new13} scores may significantly predict which patients are suitable for PCD examination. In this study, the performance of PICADAR and NA-CDCF did not show any significant differences, but the CI and CI_{new13} scores were superior. Although PICADAR and NA-CDCF are commonly used, employing the CI score could reduce unneeded testing, while using the NA-CDCF might decrease the chance of undetected cases.

Abbreviations:

AUC: Area under curve
CI: Clinical index
ERS: European Respiratory society
NA-CDCF: North America criteria defined clinical features
PCD: Primary ciliary dyskinesia
PICADAR: Primary ciliary dyskinesia rule
PPV: Positive predictive value
ROC: Receiver operating characteristic curve

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Appendix

Supplementary files

Table S1. PICADAR.

Does the patient have a daily wet cough that started in early childhood?	Yes – complete PICADAR No – STOP. PICADAR is not designed for patients without a wet cough	
Was the patient born full term or preterm?	Term	2
Did the patient experience chest symptoms in the neonatal period (e.g. tachypnea, cough, Pneumonia)?	Yes	2
Was the patient admitted to a neonatal unit?	Yes	2
Does the patient have a situs abnormality (Situs Inversus or Heterotaxy)?	Yes	4
Does the patient have a congenital heart defect?	Yes	2
Does the patient have persistent perennial rhinitis?	Yes	1
Does the patient experience chronic ear or hearing symptoms (e.g. glue ear, serous otitis media, hearing loss, and ear perforation)?	Yes	1
Total score		**14**

Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J 2016; 47(4):1103-12.

Table S2. NA-CDCF score

Features
Unexplained neonatal respiratory distress in a full-term newborn with need for supplemental oxygen for ≥ 1 day and no meconium aspiration
Early-onset (before 6 months), year-round wet cough
Early-onset (before 6 months), year-round nasal congestion
Laterality defect

Leigh MW, Ferkol TW, Davis SD, Lee HS, Rosenfeld M, Dell SD, et al. Clinical Features and Associated Likelihood of Primary Ciliary Dyskinesia in Children and Adolescents. Ann Am Thorac Soc 2016; 13(8):1305-13.

Table S3. CI score

Clinical Index 7-Item Questionnaire (Each YES = 1 Point)
Did the child manifest with significant respiratory difficulties with breathing after birth?
Did the child have rhinitis or excessive mucus production in the first 2 months of life?
Did the child suffer from pneumonia?
Did the child present with 3 or more episodes of bronchitis?
Was the child treated for chronic secretory otitis or suffered from >3 episodes of acute otitis?
Does the child have a year-round nasal discharge or nasal obstruction?
Was the child treated with antibiotics for acute upper respiratory tract infection >3 times?

Djakow J, Rozehnalova E, Havlisova M, Svobodova T, Pohunek P. Clinical index to evaluate the risk of primary ciliary dyskinesia in children. Eur Respiratory Soc 2012; 40:2844.

Table S4. CI_{new13}.

Is the child full term?
Neonatal respiratory symptoms
Unexplained neonatal respiratory distress
Admission to a neonatal intensive care unit
Early-onset year-round wet cough
Rhinitis or nasal congestion in the first 2 months of life
Pneumonia in childhood
3 or more bronchitis episodes in childhood
Laterality defect
Congenital heart defect
Antibiotic therapy for rhinosinusitis > 3 times
Persistent year-round rhinitis
Chronic ear or hearing symptoms

Martinů V, Bořek-Dohalská L, Varényiová Ž, Uhlík J, Čapek V, Pohunek P, et al. Evaluation of a Clinical Index as a Predictive Tool for Primary Ciliary Dyskinesia. Diagnostics (Basel) 2021; 11(6):1088.