APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

External validation of the PEN-FAST clinical decision rule in children with reported penicillin allergy: A pediatric cohort study

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Abstract

Background: Although penicillin allergy is frequently reported, the majority of labeled patients do not have confirmed hypersensitivity upon formal evaluation. The PEN-FAST clinical decision rule was developed to identify adults at low risk of true penicillin allergy; however, evidence supporting its performance in children remains limited.

Objective: To evaluate the diagnostic performance of the PEN-FAST score in a pediatric population with reported penicillin allergy.

Methods: We performed a retrospective cohort study including children younger than 18 years with a documented penicillin allergy label who underwent allergy evaluation at a tertiary referral center between January 2012 and February 2023. Children with suspected severe cutaneous adverse reactions (SCARs) or insufficient information to calculate the PEN-FAST score were excluded. Diagnostic evaluation included skin testing and/or drug provocation testing (DPT). Diagnostic performance of the PEN-FAST score was assessed by calculating sensitivity, specificity, predictive values, and the area under the receiver operating characteristic curve (AUC).

Results: Among 267 children included in the analysis, 19 (7.1%) had confirmed penicillin allergy. Using the original PEN-FAST cutoff of ≥ 3, the AUC was 0.62 (95%CI, 0.51–0.73), with sensitivity of 68.4%, specificity of 55.7%, positive predictive value of 10.6%, and negative predictive value of 95.8%. Exploratory analyses using alternative PEN-FAST score representations showed only minimal differences in discrimination.

Conclusion: In this pediatric cohort, the PEN-FAST score demonstrated limited accuracy in distinguishing true penicillin allergy. These findings suggest that the adult-derived decision rule may require further refinement before routine application in children.

Key words: Penicillin allergy, PEN-FAST score, Pediatric, Drug provocation test, Diagnosis

Citation:
Yuenyongviwat, A., Wedchakama, K., Sangsupawanich, P., Koosakulchai, V. (0000). External validation of the PEN-FAST clinical decision rule in children with reported penicillin allergy: A pediatric cohort study. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-210226-2237

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Introduction

Penicillin antibiotics remain a cornerstone of antimicrobial therapy worldwide and are recommended as first-line treatment for many common infections.[1] Their favorable safety profile, narrow antimicrobial spectrum, and cost-effectiveness make them central to antimicrobial stewardship initiatives.[1] However, formal allergy evaluation consistently demonstrates that the vast majority of individuals labeled as penicillin allergic do not have reproducible hypersensitivity upon confirmatory testing. Studies in both adult and pediatric populations have shown that more than 90% of such labels are inaccurate.[2,3] This discrepancy between reported and confirmed allergy has important clinical implications.

Inaccurate penicillin allergy labeling is associated with the use of broader-spectrum or second-line antibiotics, which may increase healthcare costs, prolong hospitalization, and contribute to antimicrobial resistance.[4] In children, early labeling may influence prescribing patterns for years, potentially affecting infection management throughout childhood and adolescence.[5] Therefore, identification of low-risk patients and implementation of structured delabeling strategies represent important priorities in pediatric allergy practice and antimicrobial stewardship programs.[6]

Drug provocation testing (DPT) remains the reference standard for confirming or excluding penicillin allergy.[7-9] Although skin prick testing (SPT) and intradermal testing (IDT) are widely incorporated into diagnostic algorithms, these procedures require trained personnel and specialized settings.[7-9] Increasing evidence supports the safety and diagnostic utility of direct drug provocation testing in selected low-risk pediatric patients, reducing the need for preliminary skin testing in appropriate cases.[10] A recent systematic review and meta-analysis reported a pooled confirmed hypersensitivity prevalence of 5.23% in children undergoing direct DPT for suspected non-severe beta-lactam hypersensitivity, with severe reactions being very uncommon.[11]

To facilitate clinical risk stratification, Trubiano and colleagues developed the PEN-FAST clinical decision rule to identify adults at low risk of true penicillin allergy.[12] The model incorporates key historical features and demonstrated good discrimination in adult validation cohorts. However, application of adult-derived clinical decision tools to pediatric populations may be limited by age-specific differences in immune responses, clinical presentation, infection epidemiology, and reliance on caregiver-reported histories.[13,14]

Several pediatric studies have evaluated PEN-FAST with variable results. In a multicenter pediatric cohort, Copaescu et al. reported lower discriminatory performance than in adults, particularly in younger children, suggesting that the adult-derived score may not be directly transferable across all pediatric age groups.[13] More recent studies by Güvenir et al. and Yağmur et al. also support the potential utility of PEN-FAST as a rule-out tool in selected pediatric settings, although performance appears to vary by clinical context.[15,16]

Collectively, these findings suggest that PEN-FAST performance in children is heterogeneous and may depend on age, reaction phenotype, diagnostic strategy, and referral setting. Despite these emerging data, pediatric evidence from Southeast and East Asia remains limited. Therefore, we aimed to externally validate the PEN-FAST score in children with reported penicillin allergy at a tertiary pediatric allergy center in southern Thailand.

Methods

Study design and setting

We conducted a retrospective observational cohort study at the Pediatric Allergy Clinic of Songklanagarind Hospital, a tertiary referral center in southern Thailand. The study period extended from January 2012 to February 2023.

Study population

Children younger than 18 years with a documented history of hypersensitivity to penicillin-class antibiotics, including amoxicillin, amoxicillin-clavulanate, penicillin, cloxacillin, or dicloxacillin, were eligible for inclusion. Patients with a history suggestive of severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or acute generalized exanthematous pustulosis, were excluded. Patients were also excluded if essential clinical information required to calculate the PEN-FAST score was unavailable.

Diagnostic protocol during the study period

Children with suspected hypersensitivity to penicillin-class antibiotics referred to the Pediatric Allergy Clinic underwent evaluation using a structured, standardized diagnostic approach. Since January 2012, the same institutional diagnostic pathway has been applied throughout the study period. Before testing, all patients underwent physician-led assessment using a detailed drug allergy history. Clinical information recorded included the suspected culprit antibiotic, demographic characteristics, manifestations of the index reaction, timing of symptom onset in relation to the last administered dose, prior allergy history, treatment received for the reaction, and the interval between the index event and formal allergy evaluation.

The diagnostic pathway was determined according to the timing and clinical phenotype of the index reaction, as follows. Children with non-severe delayed reactions were generally considered eligible for direct DPT without prior skin testing. In our institutional pathway, direct DPT was typically performed when symptoms occurred more than 6 hours after the last dose of the culprit penicillin-class antibiotic. An exception was made for children with isolated maculopapular rash, who were considered eligible for direct DPT when the rash occurred more than 1 hour after the last dose. In contrast, children with a history suggestive of immediate-type hypersensitivity reactions or other clinically higher-risk phenotypes were first evaluated with skin testing, consisting of SPT followed by IDT if SPT was negative. This group included children with urticaria, angioedema, respiratory symptoms, hypotension, anaphylaxis, or other symptoms occurring within 6 hours after the last dose, except for isolated maculopapular rash as described above. In these patients, graded DPT was performed only after negative skin test results. Confirmed penicillin allergy in this study was defined as a positive skin test and/or a positive DPT. All diagnostic procedures were performed in a supervised outpatient setting equipped for emergency resuscitation.

Skin testing

Skin testing was performed no earlier than four weeks after the reported index reaction. Reagents were prepared in-house according to the suspected culprit penicillin-class antibiotic. The routine skin test panel included penicillin G at 25,000 U/mL and ampicillin at 25 mg/mL. Amoxicillin-clavulanate at 25 mg/mL was additionally included in patients with a history suggestive of hypersensitivity to amoxicillin or amoxicillin-clavulanate, and cloxacillin at 25 mg/mL was added in patients with a history of suspected cloxacillin or dicloxacillin allergy. These concentrations were based on our institutional pediatric beta-lactam skin testing protocol, which was adapted from previously published pediatric beta-lactam allergy diagnostic protocols.[17] The skin test panel, reagent concentrations, testing sequence and interpretation criteria remained unchanged throughout the study period. SPT was performed first, followed by IDT using the same reagent concentration if SPT was negative. Histamine (1 mg/mL) and normal saline solution were used as positive and negative controls, respectively. A wheal at least 3 mm greater than the negative control was considered positive for SPT. For IDT, an increase in wheal diameter of at least 3 mm from the initial bleb, accompanied by surrounding erythema at 20 minutes, was interpreted as positive. All skin tests were performed by trained personnel under pediatric allergist supervision.

Drug provocation testing

The full therapeutic dose for oral challenge was determined according to the standard pediatric dose of the selected penicillin-class antibiotic, based on body weight and the specific formulation used. In the direct DPT group, the selected penicillin-class antibiotic was administered as an open oral challenge in 2 incremental doses (10% and 90%). In the graded DPT group, the selected penicillin-class antibiotic was administered in 4 incremental doses (10%, 20%, 30%, and 40% of the total therapeutic dose). Each dose was administered at 30-minute intervals under close supervision. Patients were observed in the clinic for at least 2 hours after the final dose for acute reactions. In selected children with suspected non-immediate reactions and a negative supervised challenge, an extended home continuation phase using a therapeutic oral dose for 4 additional days was prescribed according to the culprit drug and standard pediatric dosing. Caregivers were instructed to discontinue the medication and return for urgent evaluation if suspicious symptoms developed. A DPT result was considered positive when objective signs or symptoms consistent with hypersensitivity occurred during the supervised challenge or within 48 hours after the final administered dose. The challenge was considered negative if no objective reaction occurred during the observed in-clinic phase or within the defined post-challenge assessment period.

Data collection

Demographic and clinical data were extracted from medical records. Variables collected included age at provocation testing, age at index reaction, sex, type of symptoms (pruritus, maculopapular rash, urticaria, angioedema, respiratory symptoms, hypotension, and anaphylaxis), time interval between drug intake and symptom onset, time from index reaction to allergy evaluation, treatment required (home management, emergency department visit, or hospitalization), and number of reported drug allergy labels.

PEN-FAST scores were calculated retrospectively from medical record data after completion of skin testing and/or DPT. Accordingly, the score was not available to clinicians at the time of test interpretation. Skin test and DPT outcomes were determined during routine clinical care by the attending pediatric allergist according to predefined institutional criteria and were documented in the medical record at the time of testing, independent of the later retrospective PEN-FAST assessment. Only patients with sufficient clinical information to derive all PEN-FAST components were included in the analysis. The PEN-FAST score was calculated using the four clinical components described in the original derivation study, and patients with total scores < 3 were categorized as low risk according to the original adult-derived cutoff.[12]

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. The primary analysis evaluated the diagnostic performance of the PEN-FAST score using the original adult-derived cutoff of ≥ 3, consistent with the intended purpose of external validation. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CIs) were calculated. As secondary exploratory analyses, we also examined alternative PEN-FAST score representations, including the raw 0–5 score and grouped risk categories, to assess whether discriminatory performance differed materially from the prespecified primary analysis. Exploratory subgroup analyses were additionally performed in selected clinically relevant strata, including age at provocation test, onset of symptoms after drug exposure, and whether treatment was required for the index reaction. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 267 pediatric patients were included in the analysis. Most patients were male (61.1%). The median age at provocation testing was 8.0 years (IQR, 4.7–11.0), and the median age at first reported penicillin hypersensitivity was 3.0 years (IQR, 1.2–7.1). Single-drug allergy labeling was reported in 69.7% of patients, and amoxicillin was the most frequently implicated drug (65.2%). Reactions occurring more than 6 hours after drug exposure were reported in 43.1% of patients. The most commonly reported symptoms were maculopapular rash (61.8%), urticaria (36.0%), pruritus (31.5%), and angioedema (26.6%). Anaphylaxis was reported in 1.9% of patients. Treatment requiring medical evaluation occurred in 55.8% of cases, including emergency department visits (47.6%) and hospitalization (8.2%) (**Table 1**).

Among the 267 children included in the final analysis, 212 underwent sequential evaluation with skin testing (SPT with or without IDT), whereas 55 underwent direct DPT without prior skin testing. Of the 212 children in the sequential pathway, 1 had a positive SPT and 6 had a positive IDT. The remaining 205 children with negative skin testing underwent graded DPT. Overall, 260 children underwent DPT, of whom 12 had positive challenge results. In total, 19 children (7.1%) were confirmed to have penicillin allergy based on positive skin testing and/or DPT (**Figure 1**).

Table 1. Literature review of allergic contact dermatitis caused by clonidine transdermal patch.

Characteristic	Total (N = 267)
Sex, n (%)	
Male	163 (61.1)
Female	104 (38.9)
Age at provocation test (years), median (IQR)	8.0 (4.7–11.0)
Age of first penicillin hypersensitivity (years), median (IQR)	3.0 (1.2–7.1)
Number of reported drug allergy labels, n (%)	
1 drug	186 (69.7)
> 2 drugs	81 (30.3)
Reported culprit drug, n (%)	
Amoxicillin	174 (65.2)
Amoxicillin-clavulanic acid	46 (17.2)
Dicloxacillin	33 (12.4)
Penicillin	14 (5.2)
Onset of symptoms of reaction, n (%)	
< 1 hour	44 (16.5)
1-6 hours	108 (40.4)
> 6 hours	115 (43.1)
Reported symptoms, n (%)	
Maculopapular rash	165 (61.8)
Urticaria	96 (36.0)
Pruritus	84 (31.5)
Angioedema	71 (26.6)
Anaphylaxis	5 (1.9)
Treatment required, n (%)	
No treatment	97 (36.3)
Self-treatment at home	21 (7.9)
Emergency department or outpatient visit	127 (47.6)
Hospitalization	22 (8.2)

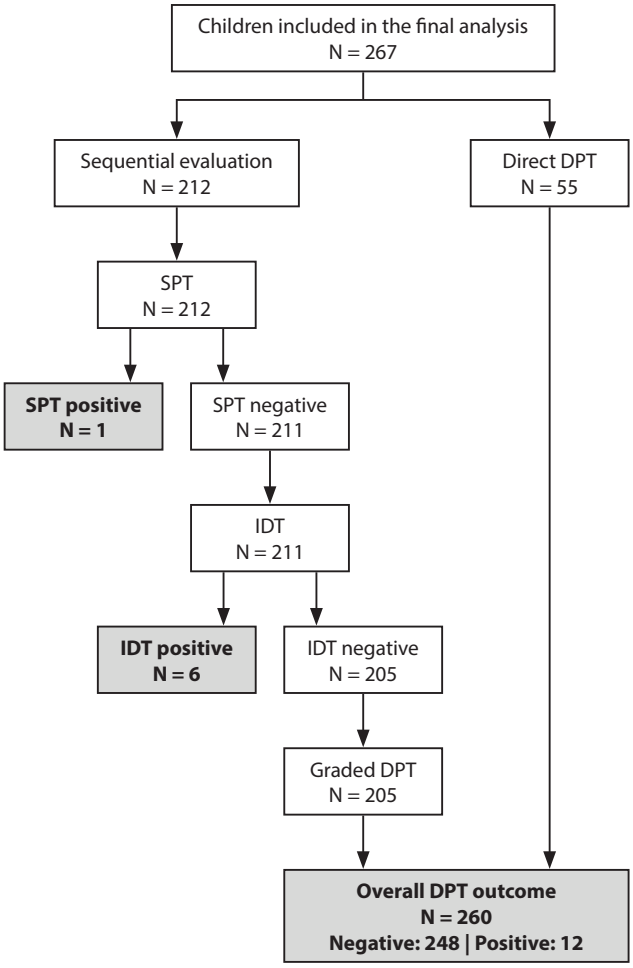

Figure 1. Diagnostic pathway within the included cohort of children with reported penicillin allergy.

Distribution of PEN-FAST Scores

The distribution of PEN-FAST scores was as follows: score 0 in 11.6% of patients, score 1 in 8.2%, score 2 in 34.1%, score 3 in 22.9%, score 4 in 10.1%, and score 5 in 13.1%. Based on predefined risk stratification, 11.6% were categorized as very low risk (score 0), 42.3% as low risk (score 1–2), 22.9% as moderate risk (score 3), and 23.2% as high risk (score 4–5) (**Table 2**).

Among 19 children with confirmed penicillin allergy, the distribution of PEN-FAST scores was as follows: 1 (5.3%) had a score of 0, 5 (26.3%) had a score of 2, 6 (31.6%) had a score of 3, 3 (15.8%) had a score of 4, and 4 (21.1%) had a score of 5 (**Table 3**).

Diagnostic Performance of the PEN-FAST Score

Using the original adult-derived cutoff of ≥ 3, the PEN-FAST score demonstrated modest discrimination for predicting confirmed penicillin allergy, with an area under the receiver operating characteristic curve (AUC) of 0.62 (95%CI, 0.51–0.73). At this cutoff, sensitivity was 68.4%, specificity was 55.7%, positive predictive value (PPV) was 10.6%, and negative predictive value (NPV) was 95.8% (**Figure 2A**). Exploratory analyses using alternative PEN-FAST score representations showed only minimal differences in discrimination compared with the prespecified primary cutoff-based analysis, with an AUC of 0.63 (95%CI, 0.51–0.75) for PEN-FAST grouped into 4 risk levels (**Figure 2B**) and 0.64 (95% CI, 0.52–0.76) for the raw PEN-FAST score (0–5) (**Figure 2C**).

Table 2. Distribution of PEN-FAST Scores and risk categories.

Characteristic	Total (N = 267)
PEN-FAST score, n (%)	
0	31 (11.6)
1	22 (8.2)
2	91 (34.1)
3	61 (22.9)
4	27 (10.1)
5	35 (13.1)
Risk categories, n (%)	
Very low (0)	31 (11.6)
Low (1–2)	113 (42.3)
Moderate (3)	61 (22.9)
High (4–5)	62 (23.2)

Table 3. Confirmed penicillin allergy according to PEN-FAST Score.

Characteristic	Total (N = 19)
PEN-FAST score, n (%)	
0	1 (5.3)
1	0 (0.0)
2	5 (26.3)
3	6 (31.6)
4	3 (15.8)
5	4 (21.1)

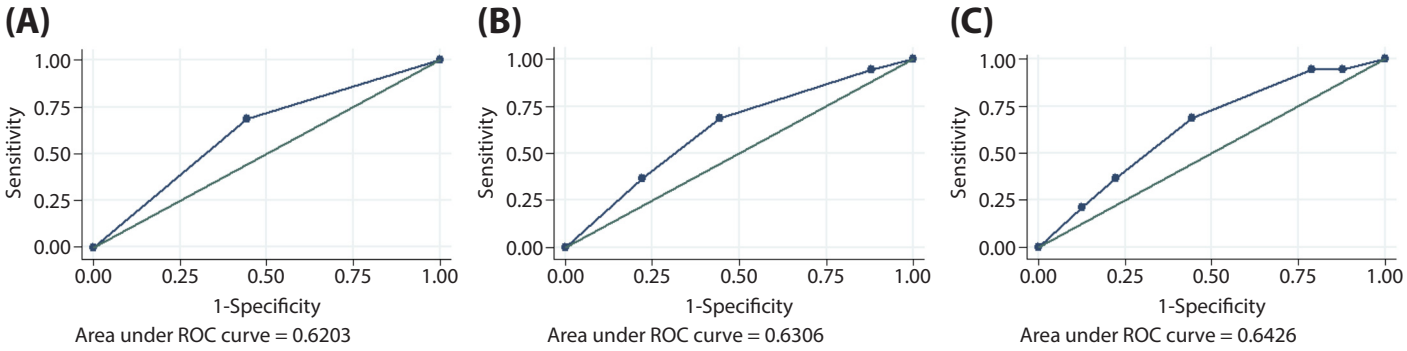

Figure 2. Receiver operating characteristic (ROC) curves of PEN-FAST score performance in children with reported penicillin allergy. (A) Primary analysis using the original adult-derived cutoff of PEN-FAST ≥ 3, with AUC 0.62 (95%CI, 0.51–0.73). (B) Exploratory analysis using PEN-FAST grouped into 4 risk levels, with AUC 0.63 (95%CI, 0.51–0.75). (C) Exploratory analysis using the raw PEN-FAST score (0–5), with AUC 0.64 (95%CI, 0.52–0.76).

Table 4. Exploratory subgroup analyses of PEN-FAST diagnostic performance in selected clinically relevant pediatric subgroups.

Subgroup	N	AUC (95% CI), Raw PEN-FAST score (0 to 5)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Age at provocation test, years						
< 2	89	0.49 (0.00-1.00)	50 (0.01-0.99)	67 (0.56-0.76)	3 (0.00-0.17)	98 (0.91-1.00)
2-10	143	0.67 (0.54-0.79)	71 (0.42-0.92)	54 (0.45-0.63)	14 (0.07-0.25)	95 (0.87-0.99)
> 10	35	0.38 (0.14-0.62)	67 (0.09-0.99)	31 (0.16-0.50)	8 (0.01-0.27)	91 (0.59-1.00)
Onset of symptoms after drug exposure, hours						
<1	44	0.79 (0.61-0.97)	100 (0.16-1.00)	43 (0.28-0.59)	8 (0.01-0.25)	100 (0.81-1.00)
1-6	108	0.51 (0.30-0.73)	43 (0.10-0.82)	60 (0.50-0.70)	7 (0.01-0.19)	94 (0.85-0.98)
> 6	115	0.73 (0.59-0.87)	80 (0.44-0.97)	56 (0.46-0.66)	15 (0.07-0.27)	97 (0.89-1.00)
Treatment required for index reaction						
Yes	114	0.62 (0.48-0.76)	100 (0.69-1.00)	21 (0.14-0.30)	11 (0.05-0.19)	100 (0.85-1.00)
No	153	0.60 (0.42-0.77)	33 (0.07-0.70)	81 (0.73-0.87)	10 (0.02-0.26)	95 (0.90-0.98)

Exploratory subgroup analyses

Exploratory subgroup analyses showed variation in PEN-FAST performance across selected clinically relevant strata. Higher AUC values were observed in children aged 2–10 years and in those with symptom onset more than 6 hours after drug exposure. Diagnostic performance also differed according to whether treatment was required for the index reaction. Detailed subgroup-specific diagnostic performance estimates are presented in **Table 4**.

Discussion

In this pediatric cohort, the PEN-FAST clinical decision rule demonstrated modest discriminatory performance, with an AUC of 0.62 when applying the adult-derived cutoff of ≥ 3. This contrasts with the original adult validation studies, which reported substantially higher discrimination.[12] The reduced performance observed in our study suggests that historical features incorporated in the adult model may not translate directly to pediatric settings.

Our findings are consistent with prior pediatric validation studies showing that PEN-FAST performance in children is more heterogeneous than in adults.[13,15,16] Several factors may contribute to this heterogeneity. First, age distribution may influence performance, as many suspected reactions occur in early childhood when clinical manifestations are less specific and immune phenotypes may differ from those in older children or adults. Second, pediatric histories are often caregiver-reported rather than patient-reported, which may reduce the precision of key historical features used in the score. Third, viral exanthems frequently coincide with antibiotic exposure in children and are commonly misattributed to drug hypersensitivity, potentially weakening the predictive value of variables such as rash morphology and reaction timing.[9] In addition, regional differences in beta-lactam prescribing practices, referral thresholds, and the background epidemiology of viral infections may influence the apparent performance of PEN-FAST across studies and geographic settings.

Although we performed exploratory analyses using alternative PEN-FAST score representations, including grouped risk categories and the raw 0–5 score, these showed only minimal differences in discrimination compared with the prespecified cutoff-based analysis. Given the relatively small number of confirmed allergy cases (n = 19) in this retrospective cohort, formal data-driven threshold optimization or calibration modeling was not emphasized because such analyses would be of limited interpretability and potentially unstable in this dataset.

In our cohort, exploratory subgroup analyses suggested that PEN-FAST diagnostic performance varied across clinically relevant subgroups, with relatively better discrimination in children aged 2–10 years and in those with symptom onset more than 6 hours after drug exposure. Performance also varied according to whether treatment was required for the index reaction. These findings may help explain why pediatric studies have reported variable performance and are broadly consistent with recent studies suggesting that PEN-FAST performance may vary according to reaction phenotype and timing of symptom onset.[15,16] However, because only 19 confirmed allergy outcomes were observed, these subgroup analyses should be interpreted cautiously as exploratory and hypothesis-generating rather than definitive. For the same reason, we did not perform a formal multivariable model combining PEN-FAST with additional clinical predictors, as such modeling would be at substantial risk of overfitting in this dataset.

Although the negative predictive value of the PEN-FAST score was high in our cohort, this finding should be interpreted within the context of disease prevalence. Predictive values are inherently influenced by baseline prevalence; in populations where confirmed penicillin allergy is uncommon, even modestly performing tools may yield high negative predictive values. Therefore, the 7.1% prevalence of confirmed penicillin allergy in our cohort likely contributed to the observed high NPV despite only modest discrimination. In addition, the small number of confirmed allergy outcomes limits the precision of diagnostic performance estimates, particularly for sensitivity and subgroup analyses, and contributes to relatively wide confidence intervals.

Strengths of this study include a standardized institutional diagnostic pathway across the study period, evaluation in a specialized pediatric allergy clinic, and use of skin testing and/or drug provocation testing as the reference standard. Additionally, this cohort represents one of the larger pediatric validation studies reported from Southeast Asia, where external validation data remain limited.

Several limitations should be acknowledged. First, the single-center retrospective design may limit generalizability, particularly because our cohort represents a tertiary referral population, which may differ from primary care or general pediatric settings in case mix and pretest probability. Second, the retrospective design introduces potential information bias related to documentation quality and reliance on existing medical records. Although PEN-FAST scores were calculated retrospectively after completion of skin testing and/or DPT, and therefore were not available to clinicians at the time of test interpretation, formal inter-rater reliability assessment was not performed. Skin test and DPT outcomes were determined during routine clinical care by the attending pediatric allergist according to predefined institutional criteria, which likely reduced but did not eliminate the possibility of assessment variability. Third, the relatively small number of confirmed allergy cases limits the precision of performance estimates, particularly for subgroup analyses. Finally, patients with severe cutaneous adverse reactions (SCARs) were excluded; therefore, these findings should not be extrapolated to such high-risk populations.

Future research should focus on prospective multicenter validation across diverse pediatric settings and geographic regions, as well as the development of pediatric-specific clinical prediction tools. Incorporation of age-stratified variables, reaction morphology, or other clinically relevant features may enhance predictive performance. Until such refinements are available, caution should be exercised when applying adult-derived risk models to children.

In conclusion, the PEN-FAST clinical decision rule demonstrated modest performance in this pediatric cohort. While it may provide supportive clinical information, it should not replace comprehensive evaluation in children with reported penicillin allergy. Continued refinement of pediatric risk stratification strategies remains necessary to optimize antibiotic stewardship and improve patient outcomes.

Ethical Compliance

Ethical approval was obtained from the Institutional Review Board and Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University (REC.66-009-1-1).

Conflict of Interest

The authors declare no conflicts of interest.

Funding Statement

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

- AY conceptualized and designed the study, interpreted the results, and wrote the manuscript.
- KW collected the data, interpreted the results, and wrote the manuscript.
- PS conceptualized and designed the study, and interpreted the results.
- VK conceptualized and designed the study, interpreted the results, and approved the manuscript.
- All authors reviewed the manuscript for important intellectual content and approved the final version.

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