A Treatment-Decision Score for HIV-Infected Children With Suspected Tuberculosis

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abstract

BACKGROUND: Diagnosis of tuberculosis should be improved in children infected with HIV to reduce mortality. We developed prediction scores to guide antituberculosis treatment decision in HIV-infected children with suspected tuberculosis.

METHODS: HIV-infected children with suspected tuberculosis enrolled in Burkina Faso, Cambodia, Cameroon, and Vietnam (ANRS 12229 PAANTHER 01 Study), underwent clinical assessment, chest radiography, Quantiferon Gold In-Tube (QFT), abdominal ultrasonography, and sample collection for microbiology, including Xpert MTB/RIF (Xpert). We developed 4 tuberculosis diagnostic models using logistic regression: (1) all predictors included, (2) QFT excluded, (3) ultrasonography excluded, and (4) QFT and ultrasonography excluded. We internally validated the models using resampling. We built a score on the basis of the model with the best area under the receiver operating characteristic curve and parsimony.

RESULTS: A total of 438 children were enrolled in the study; 251 (57.3%) had tuberculosis, including 55 (12.6%) with culture- or Xpert-confirmed tuberculosis. The final 4 models included Xpert, fever lasting >2 weeks, unremitting cough, hemoptysis and weight loss in the past 4 weeks, contact with a patient with smear-positive tuberculosis, tachycardia, miliary tuberculosis, alveolar opacities, and lymph nodes on the chest radiograph, together with abdominal lymph nodes on the ultrasound and QFT results. The areas under the receiver operating characteristic curves were 0.866, 0.861, 0.850, and 0.846, for models 1, 2, 3, and 4, respectively. The score developed on model 2 had a sensitivity of 88.6% and a specificity of 61.2% for a tuberculosis diagnosis.

CONCLUSIONS: Our score had a good diagnostic performance. Used in an algorithm, it should enable prompt treatment decision in children with suspected tuberculosis and a high mortality risk, thus contributing to significant public health benefits.

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WHAT'S KNOWN ON THIS SUBJECT: Despite their potential diagnostic value, the numerous scores and classifications developed to help standardize diagnosis of tuberculosis in children are not currently recommended in the World Health Organization childhood tuberculosis guidance because of their heterogeneity, lack of validation, and poor performance in children infected with HIV.

WHAT THIS STUDY ADDS: We developed a score that was based on Xpert MTB/RIF, easily collected clinical features, chest radiograph features, and abdominal ultrasonography. With a sensitivity of 89% and a specificity of 61%, our score could enable early treatment decision in most HIV-infected children with tuberculosis.

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Tuberculosis is the leading cause of death in children infected with HIV worldwide, accounting for one-third of all deaths in this group.[1,2] Diagnosis is a major challenge in childhood tuberculosis because of the low sensitivity of microbiologic examinations resulting from the paucibacillary nature of the disease and the difficulty to self-expectorate in children, the lack of a point-of-care test, and the limitations of clinical approaches.[3] Underdiagnosis leads to poor access to treatment and subsequent mortality.[4] In recent mathematical modeling, it was estimated that of 239 000 pediatric tuberculosis deaths every year, >96% occurred in children not receiving antituberculosis treatment.[5]

Diagnostic challenges are greater in children infected with HIV.[6] Microbiologic diagnosis, including with the World Health Organization (WHO)–endorsed Xpert MTB/RIF (Xpert) assay, performs similarly in both children infected with HIV and HIV-uninfected children, but clinical and radiologic features lack specificity in the context of severe immunodeficiency, frequent opportunistic infections, and HIV infection itself.[6–8] Furthermore, immunodeficiency reduces sensitivity of immunologic tests for tuberculosis infection.[9,10] Poor access to antituberculosis treatment is also responsible for a large part of tuberculosis-related mortality in children infected with HIV. Of 40 000 tuberculosis-related deaths in children infected with HIV, an estimated 90% occurred in children not receiving antituberculosis treatment.[1,5]

Initiation of antituberculosis treatment significantly reduces mortality in HIV-infected children with confirmed and unconfirmed tuberculosis. It is, however, frequently followed by delays in antiretroviral therapy (ART) despite the WHO recommendation to initiate ART as soon as possible in children with tuberculosis. This is a serious issue because ART is associated with major reduction in mortality when started during the first month of follow-up.[11,12] Xpert could enable quick diagnostic confirmation and treatment decision in children with high bacillary load who are most at risk of dying.[12] In others, optimized algorithms or scoring systems for empirical antituberculosis treatment decision will help clinicians initiate treatment appropriately and accelerate initiation of ART.

Various scoring systems and diagnostic approaches have been developed for tuberculosis diagnosis in children.[13,14] However, these approaches lack coherence, standard definition of symptoms, and adequate validation and perform poorly in children infected with HIV.[13–15] Although still in use in some countries, these scores are currently not recommended by the WHO.[16,17] A recent study, however, revealed the potential for tuberculosis diagnosis, in children infected with HIV, of several diagnostic systems, including the historical Kenneth Jones criteria, and others used in South Africa, in Brazil, and previously in WHO studies.[18–22]

We aimed to build a diagnostic prediction score and algorithm for antituberculosis treatment decision in HIV-infected children with suspected tuberculosis on the basis of microbiologic, clinical, and radiologic features. We assessed whether the Quantiferon Gold In-Tube (QFT) (Qiagen, Hilden, Germany), an interferon-γ release assay that can replace the tuberculin skin test (TST) for the diagnosis of tuberculosis infection, and abdominal ultrasonography, whose diagnostic value has been shown for tuberculosis in adults and children infected with HIV, had an added value on this score.[9,23,24]

METHODS

The ANRS 12229 PAANTHER 01 Study was a cohort study aimed at developing an algorithm to improve diagnosis of tuberculosis in children infected with HIV that was conducted in 8 hospitals in Burkina Faso, Cambodia, Cameroon, and Vietnam (April 2011–December 2014) (Supplemental Methods section of the Supplemental Information). Inclusion procedures and the study design have been described elsewhere.[25] In brief, we enrolled HIV-infected children aged ≤13 years with suspected tuberculosis on the basis of at least 1 of the following: (1) persistent cough; (2) fever for >2 weeks; (3) failure to thrive, defined as recent deviation in the growth curve or a weight-for-age *z* score (WAZ) <−2 SDs; (4) failure of antibiotics for a pulmonary infection; or (5) a suggestive chest radiograph (CXR). We excluded those with antituberculosis treatment started within 2 years before inclusion.

The study was approved by relevant national ethics committees, institutional review boards, and national authorities. The ANRS 12229 PAANTHER 01 Study is registered at ClinicalTrials.gov (identifier NCT01331811).

Procedures and Definitions

After parent or guardian informed consent, a detailed history on presence and duration of symptoms 4 weeks before enrollment was collected from parent(s) or guardian(s) through a standardized questionnaire. Cough patterns were characterized by using a graphic illustration shown to parent(s) or guardian(s).[26] All children had a complete physical examination; CXR, abdominal ultrasonography, and TST performed; and blood samples collected for HIV RNA, CD4, complete blood cell count, transaminases, and QFT. Each child had 2 to 3 gastric aspirates or expectorated sputa, 1 nasopharyngeal aspirate, 1 stool sample, and 1 string test, if aged

≥4 years, collected over a period of 3 days for Xpert, smear microscopy, and a mycobacterial culture.[25] ART and antituberculosis treatment were initiated at the discretion of the treating physician. All children were followed-up for 6 months. All data were collected by using standardized paper case-report forms and entered in an online database developed on the Voozanoo software (Epiconcept, Paris, France).

At the end of the study, children were retrospectively classified as having confirmed, unconfirmed, or unlikely tuberculosis by using the updated Clinical Case Definition for Classification of Intrathoracic Tuberculosis (Supplemental Table 4).[27] For model development, the reference diagnosis was tuberculosis, defined either as confirmed or unconfirmed. CXRs were reviewed independently by 2 readers blinded to patient data; discordant opinions were resolved by a third reader. Results of the TST were considered positive if the transverse diameter of induration, read at 48 to 72 hours, was >5 mm. QFT results, interpreted per the manufacturer's recommendation, were not taken into account for the reference diagnosis. We used age-defined standards for tachycardia and tachypnea (Supplemental Table 5).[28] Sample-size calculations are detailed in the Supplemental Methods section of the Supplemental Information.

Statistical Analysis

We compared baseline characteristics between groups using Student's *t* test or the Kruskal-Wallis test and Pearson's χ^2 or Fisher's exact test, as appropriate.

We used logistic regression to develop diagnostic prediction models for tuberculosis. We restricted the analysis to those children with data available for candidate predictors. We included, as candidate predictors, characteristics used in previous childhood tuberculosis scoring systems and characteristics previously described as associated with tuberculosis in children infected with HIV as well as QFT and abdominal ultrasonography results (Supplemental Methods section of the Supplemental Information).[22,23,29–34] To identify additional predictors, we performed a nested case-control study, selecting as case patients all children with culture-confirmed tuberculosis and as controls those with unlikely tuberculosis who were still alive at month 6 and had not been treated for tuberculosis. We included as predictors CXR features, as assessed by the local reader. We tested various symptom durations (>2, >3, and >4 weeks) in the models and selected the one with the best Akaike information criterion. We also included ART and immunodeficiency as predictors in the models and tested interactions with other predictors.

To account for the fact that QFT and abdominal ultrasonography may not be systematically available in low- and middle-income countries (because they were not recommended by the WHO for tuberculosis diagnosis), we developed 4 different models: (1) all predictors integrated, (2) QFT excluded, (3) abdominal ultrasonography excluded, and (4) both QFT and abdominal ultrasonography excluded. We obtained final models by stepwise backward selection. As recommended for prediction models, we used less stringent *P* values of <.157 or .135 when incorporating variables with 1 or 2 degrees of freedom to avoid overfitting and to reduce model optimism.[35] We included Xpert and smear microscopy results secondarily in final models using Firth's penalized likelihood to solve the problem of data separation.[36] We performed internal validation using bootstrap resampling (Supplemental Methods section of the Supplemental Information).[35]

We compared areas under the receiver operating characteristic curves (AUROCs) of models obtained and selected the best model on the basis of discriminative ability and parsimony. We developed an associated diagnostic score by assigning to each variable category a predictor score equal to its β coefficient in the model. We set the tuberculosis diagnosis threshold using a predicted probability cutoff that reached a sensitivity of 90% in the case-control subpopulation. To facilitate final score calculations, we multiplied all predictor scores by a factor setting the threshold to 100 (Supplemental Table 12).

We assessed diagnostic performance of the score obtained in the whole cohort, considering missing data for predictors as all negative or all positive. Finally, we proposed a diagnostic algorithm that included the score.

We performed all analyses using SAS software version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

We enrolled 438 children in the study (Table 1). Tuberculosis was confirmed by culture and/or Xpert in 55 (12.6%) children, and 196 (44.7%) children were classified as having unconfirmed tuberculosis, for a total of 251 (57.3%) children with tuberculosis.

Individual predictors with the best sensitivity for tuberculosis diagnosis were cough in the previous 4 weeks, cough lasting >2 weeks, cough in the past 24 hours, fever in the previous 4 weeks, and weight loss, as reported by the parent(s) or guardian(s), in the previous 4 weeks (Table 2). Specificities of these signs were poor overall.

Diagnostic Prediction Models

A total of 335 of 438 children had data available for all selected

predictors and were included in model development, including 201 (60.0%) children with tuberculosis and 134 (40.0%) who were classified as not having tuberculosis. Compared with children who were not included in model development, children with all predictors available were older, had a higher WAZ and higher hemoglobin count, more frequently had nontuberculous mycobacteria isolated, and had antituberculosis treatment initiated, and their risk of death was lower (Supplemental Tables 6 and 7).

Of predictors associated with tuberculosis diagnosis in the case-control subanalysis, which included 45 culture-confirmed tuberculosis cases and 153 control cases (Supplemental Results section of the Supplemental Information, Supplemental Tables 8 and 9), tachycardia only was not part of our initial list of predictors considered (Supplemental Table 10).

An identical set of 9 predictors remained in the 4 models: fever lasting >2 weeks, unremitting cough, hemoptysis and weight loss in the previous 4 weeks, contact with a patient with smear-positive tuberculosis, tachycardia, miliary tuberculosis, alveolar opacities, and lymph nodes on the CXR (Supplemental Table 11). ART and immunodeficiency did not improve model predictions and thus were not included in the final model; QFT results and abdominal lymph nodes on the ultrasound were ultimately included in the final models because they improved model predictions significantly. There was no interaction between ART or immunodeficiency and other predictors.

AUROCs for models 1, 2, 3, and 4 were 0.839 (95% confidence interval [CI] 0.797–0.880), 0.830 (95% CI 0.787–0.873), 0.819 (95% CI 0.775–0.863), and 0.808 (95% CI 0.762–0.853), respectively. Compared with model 1, only model 4 had a significantly lower discriminative ability (P = .220, P = .072, and P = .0191 for models 2, 3, and 4, respectively).

Models Integrating Smear Microscopy and Xpert

Including smear microscopy as a predictor did significantly change the discriminative ability of models 1, 2, and 3, compared with models without smear microscopy. It only led to a significant AUROC increase for

TABLE 1 Characteristics of Children Enrolled in the Study

	All Children, N = 438		Not Tuberculosis, n = 187		Tuberculosis, n = 251	
	n[a]	n (%) or Median (IQR)	n[a]	n (%) or Median (IQR)	n[a]	n (%) or Median (IQR)
Age, y	—	7.3 (3.3 to 9.7)	—	7.3 (2.2 to 9.9)	—	7.3 (3.9 to 9.6)
Male sex	—	220 (50.2)	—	82 (43.9)	—	138 (55.0)
Country						
Burkina Faso	—	63 (14.4)	—	35 (18.7)	—	28 (11.2)
Cambodia	—	139 (31.7)	—	36 (19.2)	—	103 (41.0)
Cameroon	—	125 (28.5)	—	65 (34.8)	—	60 (23.9)
Vietnam	—	111 (25.3)	—	51 (27.3)	—	60 (23.9)
Underweight (WAZ <−2)	429	276 (63.3)	182	106 (52.2)	247	170 (68.8)
WAZ	429	−2.5 (−3.6 to −1.8)	182	−2.5 (−3.1 to −1.5)	247	−2.5 (−3.5 to −2.0)
Lansky play performance score	432	80 (80 to 100)	186	95 (80 to 90)	246	80 (70 to 90)
BCG vaccine used	401	349 (87.0)	173	156 (90.2)	228	193 (84.7)
Previous tuberculosis treatment	—	57 (13.0)	—	12 (6.4)	—	45 (17.9)
On ART at inclusion	—	172 (39.3)	—	80 (42.8)	—	92 (36.7)
CD4 absolute count, cells per μL	416	463 (53 to 999)	168	576 (104 to 1072)	246	413 (36 to 924)
CD4 percentage	414	14.0% (3.2% to 24.0%)	165	15.1% (4.9% to 24.9%)	249	13.0% (3.0% to 23.0%)
Immune depression[b]	414	—	165	—	249	—
Not significant	—	128 (30.9)	—	55 (33.3)	—	73 (29.3)
Mild and advanced	—	37 (8.9)	—	15 (9.1)	—	22 (8.8)
Severe	—	82 (19.8)	—	35 (21.2)	—	47 (18.9)
Very severe	—	167 (40.3)	—	60 (36.4)	—	107 (43.0)
Hemoglobin, g/dL	427	10.1 (8.5 to 11.5)	178	10.3 (8.9 to 11.5)	249	10.0 (8.2 to 11.4)
Acid-fast bacilli smear results positive	426	27 (6.3)	177	1 (0.6)	249	23 (9.2)
Xpert results positive	425	43 (10.1)	177	0	248	43 (17.3)
Culture-confirmed tuberculosis	426	45 (10.6)	177	0	249	45 (18.1)
Nontuberculous mycobacteria–positive culture	426	46 (10.8)	177	19 (10.2)	249	27 (10.8)
CXR consistent with tuberculosis	405	273 (67.4)	169	77 (45.6)	236	196 (83.1)
TST result positive	389	32 (8.2)	161	11 (6.8)	228	21 (9.8)
Initiated antituberculosis treatment	—	241 (55.0)	—	11 (5.9)	—	230 (91.6)
Time to antituberculosis treatment, d	241	7 (5 to 11)	11	9 (6 to 113)	230	7 (5 to 10)

IQR, interquartile range; —, not applicable.

[a] If n is different from N.

[b] Immunodeficiency was categorized by using the WHO immunologic classification (2006), with the addition of CD4 percentage <10% as very severe immunodeficiency.

TABLE 2 Diagnostic Accuracy of Tuberculosis Tests and Predictors After Full Clinical Evaluation

	Sensitivity			Specificity			Positive Predictive Value		Negative Predictive Value	
	n/*N*	%	95% CI	*n*/*N*	%	95% CI	%	95% CI	%	95% CI
Cough										
In past 24 h	224/250	89.6	85.8–93.4	16/187	8.6	4.5–12.6	56.7	51.8–61.6	38.1	23.4–52.8
Any in past 4 wk	235/250	94.0	91.1–96.9	12/187	6.4	2.9–9.9	57.3	52.5–62.1	44.4	25.7–63.2
Lasting >2 wk	212/250	84.8	80.3–89.3	35/187	18.7	13.1–24.3	58.2	53.2–63.3	47.9	36.5–59.4
Lasting >3 wk	151/250	60.4	54.3–66.5	78/187	41.7	34.6–48.8	58.1	52.1–64.1	44.1	36.8–51.4
Lasting >4 wk	130/250	52.0	45.8–58.2	96/187	51.3	44.2–58.5	58.8	52.3–65.3	44.4	37.8–51.1
Unremitting cough	65/250	26.0	20.6–31.4	152/187	81.3	75.7–86.9	65.0	55.7–74.3	45.1	39.8–50.4
Fever										
In past 24 h	148/250	59.2	53.1–65.3	112/187	59.9	52.9–66.9	66.4	60.2–72.6	52.3	45.6–59.0
Any in past 4 wk	209/250	83.6	79.0–88.2	64/187	34.2	27.4–41.0	63.0	57.8–68.1	61.0	51.6–70.3
Lasting >2 wk	163/250	65.2	59.3–71.1	124/187	66.3	59.5–73.1	72.1	66.3–78.0	58.8	52.1–65.4
Lasting >3 wk	99/250	39.6	33.5–45.7	151/187	80.7	75.1–86.4	73.3	65.9–80.8	50.0	44.4–55.6
Lasting >4 wk	82/250	32.8	27.0–38.6	161/187	86.1	81.1–91.1	75.9	67.9–84.0	48.9	43.5–54.3
Abdominal pain >2 wk	43/213	20.2	14.8–25.6	129/150	86.0	80.4–91.6	67.2	55.7–78.7	43.1	37.5–48.8
Loss of appetite in past 4 wk	137/250	54.8	48.6–61.0	109/187	58.3	51.2–65.4	63.7	57.3–70.1	49.1	42.5–55.7
Loss of appetite lasting >2 wk	67/250	26.8	21.3–32.3	162/187	86.6	81.8–91.5	72.8	63.7–81.9	47.0	41.7–52.2
Chest pain in past 4 wk	48/206	23.3	17.5–29.1	112/141	79.4	72.8–86.1	62.3	51.5–73.2	41.5	35.6–47.4
Diarrhea in past 4 wk	76/250	30.4	24.7–36.1	134/186	72.0	65.6–78.5	59.4	50.9–67.9	43.5	38.0–49.0
Dyspnea in past 4 wk	76/247	30.8	25.0–36.5	150/186	80.6	75.0–86.3	67.9	59.2–76.5	46.7	41.3–52.2
Fatigue in past 4 wk	132/247	53.4	47.2–59.7	111/187	59.4	52.3–66.4	63.5	56.9–70.0	49.1	42.6–55.6
Fatigue lasting >2 wk	99/247	40.1	34.0–46.2	131/187	70.1	63.5–76.6	63.9	56.3–71.4	47.0	41.1–52.8
Headaches lasting >2 wk	19/205	9.3	5.3–13.2	131/136	96.3	93.2–99.5	79.2	62.9–95.4	41.3	35.9–46.7
Hemoptysis in past 4 wk	13/250	5.2	2.4–8.0	182/186	97.8	95.8–99.9	76.5	56.3–96.6	43.4	38.7–48.2
Loss of playfulness in past 4 wk	124/248	50.0	43.8–56.2	122/187	65.2	58.4–72.1	65.6	58.8–72.4	49.6	43.3–55.8
Sleep disorders in past 4 wk	57/249	22.9	17.7–28.1	162/186	87.1	82.3–91.9	70.4	60.4–80.3	45.8	40.6–51.0
Drenching night sweats in past 4 wk	98/249	39.4	33.3–45.4	131/187	70.1	63.5–76.6	63.6	56.0–71.2	46.5	40.6–52.3
Vomiting in past 4 wk	38/250	15.2	10.7–19.7	145/186	78.0	72.0–83.9	48.1	37.1–59.1	40.6	35.5–45.7
Wt loss in past 4 wk	178/250	71.2	65.6–76.8	81/187	43.3	36.2–50.4	62.7	57.1–68.3	52.9	45.0–60.9
Temperature >37.8°C	78/250	31.2	25.5–36.9	146/182	80.2	74.4–86.0	68.4	59.9–77.0	45.9	40.4–51.4
Tachycardia	42/249	16.9	12.2–21.5	168/181	92.8	89.1–96.6	76.4	65.1–87.6	44.8	39.8–49.8
Tachypnea	79/242	32.6	26.7–38.6	124/172	72.1	65.4–78.8	62.2	53.8–70.6	43.2	37.5–48.9
Chest-wall indrawing	36/249	14.5	10.1–18.8	173/185	93.5	90.0–97.1	75.0	62.8–87.3	44.8	39.9–49.8
Abnormal lung sounds on auscultation	149/249	59.8	53.8–65.9	79/187	42.2	35.2–49.3	58.0	51.9–64.0	44.1	36.9–51.4
Reduced breath sounds	50/246	20.3	15.3–25.4	145/186	78.0	72.0–83.9	54.9	44.7–65.2	42.5	37.3–47.8
Crackles	119/249	47.8	41.6–54.0	101/187	54.0	46.9–61.2	58.0	51.3–64.8	43.7	37.3–50.1
Rhonchus	69/249	27.7	22.2–33.3	152/187	81.3	75.7–86.9	66.3	57.3–75.4	45.8	40.4–51.1
Wheezing	18/249	7.2	4.0–10.4	173/187	92.5	88.7–96.3	56.3	39.1–73.4	42.8	38.0–47.6
Dullness on percussion	36/249	14.5	10.1–18.8	166/186	89.2	84.8–93.7	64.3	51.7–76.8	43.8	38.8–48.8
Any lymph node	92/248	37.1	31.1–43.1	132/187	70.6	64.1–77.1	62.6	54.8–70.4	45.8	40.1–51.6
Cervical lymph node	78/247	31.6	25.8–37.4	136/184	73.9	67.6–80.3	61.9	53.4–70.4	44.6	39.0–50.2
Hepatomegaly	99/246	40.2	34.1–46.4	133/183	72.7	66.2–79.1	66.4	58.9–74.0	47.5	41.7–53.3
Splenomegaly	47/248	19.0	14.1–23.8	157/183	85.8	80.7–90.9	64.4	53.4–75.4	43.9	38.7–49.0
Abdominal distension	48/246	19.5	14.6–24.5	164/187	87.7	83.0–92.4	67.6	56.7–78.5	45.3	40.2–50.4

TABLE 2 Continued

	Sensitivity			Specificity			Positive Predictive Value		Negative Predictive Value	
	n/*N*	%	95% CI	*n*/*N*	%	95% CI	%	95% CI	%	95% CI
Abdominal tenderness	32/248	12.9	8.7–17.1	171/187	91.4	87.4–95.5	66.7	53.3–80.0	44.2	39.2–49.1
QFT										
Without indeterminate	39/180	21.7	15.6–27.7	129/142	90.8	86.1–95.6	75.0	63.2–86.8	47.8	41.8–53.7
Indeterminate = negative result	39/244	16.0	11.4–20.6	163/176	92.6	88.7–96.5	75.0	63.2–86.8	44.3	39.2–49.4
Contact with smear-positive patient with TB	24/251	9.6	5.9–13.2	183/187	97.9	95.8–99.9	85.7	72.8–98.7	44.6	39.8–49.4
Ultrasonography										
Abdominal lymph nodes	84/237	35.4	29.4–41.5	144/168	85.7	80.4–91.0	77.8	69.9–85.6	48.5	42.8–54.2
CXR										
Ghon focus	10/242	4.1	1.6–6.6	175/175	100	100–100	100	100–100	43.0	38.2–47.8
Excavation	10/242	4.1	1.6–6.6	174/174	100	100–100	100	100–100	42.9	38.0–47.7
Miliary pattern	14/242	5.8	2.8–8.7	170/175	97.1	94.7–99.6	73.7	53.9–93.5	42.7	37.9–47.6
Paratracheal nodes	31/242	12.8	8.6–17.0	171/175	97.7	95.5–99.9	88.6	78.0–99.1	44.8	39.8–49.8
Tracheal compression	4/242	1.7	0.0–3.3	175/175	100	100–100	100	100–100	42.4	37.6–47.1
Perihilar lymph nodes	89/242	36.8	30.7–42.9	154/175	88.0	83.2–92.8	80.9	73.6–88.3	50.2	44.6–55.8
Nodular opacities	24/242	9.9	6.2–13.7	163/175	93.1	89.4–96.9	66.7	51.3–82.1	42.8	37.8–47.8
Alveolar opacity	94/242	38.8	32.7–45.0	134/175	76.6	70.3–82.8	69.6	61.9–77.4	47.5	41.7–53.3
Pleural effusion	13/242	5.4	2.5–8.2	167/175	95.4	92.3–98.5	61.9	41.1–82.7	42.2	37.3–47.0
Bronchial compression	23/242	9.5	5.8–13.2	175/175	100	100–100	100	100–100	44.4	39.5–49.3
Gibbus	0/240	0.0	0.0–0.0	174/174	100	100–100	—	—	42.0	37.3–46.8
Any lymph node	93/242	38.4	32.3–44.6	152/175	86.9	81.9–91.9	80.2	72.9–87.4	50.5	44.8–56.1
Any compression	26/242	10.7	6.8–14.6	175/175	100	100–100	100	100–100	44.8	39.8–49.7

TB, tuberculosis; —, not applicable.

model 4 (Supplemental Results section of the Supplemental Information). Including Xpert in the final models led to better discriminative ability for all models, with significant increases in AUROCs to 0.866 (95% CI 0.829–0.904), 0.861 (95% CI 0.822–0.899), 0.850 (95% CI 0.809–0.890), and 0.846 (95% CI 0.805–0.887) for models 1, 2, 3, and 4, respectively, compared with models without Xpert (P = .0015, P = .0011, P = .0007, and P = .0002) (Fig 1), without changes in other model predictors selected (Table 3). Compared with model 1, only model 4 had a significantly lower discriminative ability (P = .2800, P = .0799, and P = .0499 for models 2, 3, and 4, respectively). Model optimism was estimated to 0.0584 (95% CI 0.0147–0.0872) for model 2, which had the best discriminative ability and parsimony.

Performance of the Scores

The score was developed on model 2 (Supplemental Table 13) by using the predicted probability cutoff that obtained a sensitivity >90% in the case-control population (Supplemental Figs 3 and 4, Supplemental Table 12). It had the following diagnostic accuracy measures: sensitivity: 178 of 201 (88.6%; 95% CI 84.2%–93.0%); specificity: 82 of 134 (61.2%; 95% CI 52.9%–69.4%); positive predictive value: 77.4% (95% CI 72.0%–82.8%); negative predictive value: 78.1% (95% CI 70.2%–86.0%).

The score sensitivity did not differ between the 4 countries (P = .144); specificities were significantly lower in Cambodia and Cameroon (43.3% [95% CI 25.6%–61.1%]; 40% [95% CI 23.8%–56.2%]; $P < .0001$) (Supplemental Results section of the Supplemental Information). Sensitivity did not differ between patients with a CD4 percentage <10% and those with a CD4 percentage ≥10% (P = .568); specificity was lower in those with

a CD4 percentage <10% (53.1%; 95% CI 39.1%–67.0%; P = .014). Sensitivity and specificity did not differ between children with chronic cough as an inclusion criterion and the others (P = .838 and P = .485).

The score applied to the overall cohort correctly identified 228 (85.7%) children with tuberculosis and 116 (62.0%) children without tuberculosis when all missing predictors were considered as negative. Conversely, when all missing data were considered as positive, it correctly identified 228 (90.8%) children with tuberculosis and 82 (43.9%) children without tuberculosis.

PAANTHER Algorithm

In children infected with HIV presenting with a clinical suspicion of tuberculosis based either on chronic cough for >2 weeks or other study eligibility criteria, including a suggestive CXR (if done previously), the score can be applied in a stepwise approach (Fig 2). Antituberculosis treatment should be initiated immediately in children with a score of >100. Tuberculosis may be ruled out in children who score below 100 after full assessment, with a recommended subsequent clinical reassessment for persistent symptoms. If abdominal ultrasonography cannot be available, an alternative score may be used (Supplemental Table 14), with a sensitivity of 90.0% (95% CI 85.9%–94.2%) but a lower specificity of 48.5% (95% CI 40.0%–57.0%).

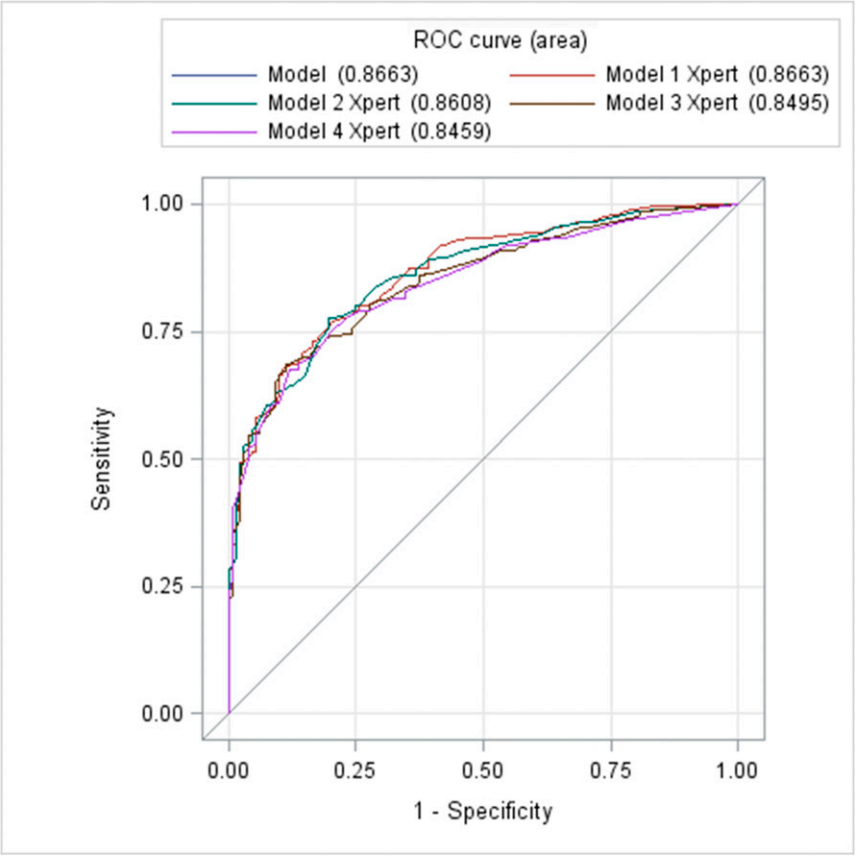

FIGURE 1
Receiver operating characteristic (ROC) curves for comparisons of 4 tuberculosis diagnostic prediction models with Xpert: (1) model 1 integrated all predictors, (2) model 2 excluded QFT, (3) model 3 excluded abdominal ultrasonography, and (4) model 4 excluded both QFT and abdominal ultrasonography.

DISCUSSION

We developed a diagnostic prediction score for antituberculosis treatment decision in HIV-infected children with suspected tuberculosis. We aimed to provide clinicians from high–tuberculosis burden and resource-limited settings with a decision-making tool to initiate antituberculosis treatment quickly in HIV-infected children with suspected tuberculosis. The score obtained had a sensitivity of ~90% and a specificity of 61%.

To our knowledge, this is the first study in which a diagnostic score is developed exclusively in children infected with HIV by using methods recommended for diagnostic prediction models. Previous pediatric tuberculosis diagnostic scores and algorithms were mostly based on expert opinion and often lacked validation.[13,14] A prospective study in South Africa revealed that the combined presence of 3 symptoms constituted a good tuberculosis diagnostic approach in HIV-uninfected children aged ≥3 years, but it performed poorly in those infected by HIV (sensitivity: 56%; specificity: 62%).[22] Recently, a retrospective study of scoring systems in Brazilian children infected with HIV who were evaluated for tuberculosis revealed that an extended version of the South African approach had a sensitivity of 94% or 84%, depending on whether a microbiologic evaluation was included in the evaluation, and a specificity of 30%.[18] Our score therefore has good performances overall, compared with these scoring systems, with a good sensitivity and an acceptable specificity if Xpert is used. Despite increasing availability of the GeneXpert platform in high–tuberculosis burden countries, access to Xpert may still be challenging in some resource-limited settings.[37]

TABLE 3 Prediction Models Integrating Xpert Results

Predictor	Model 1 With QFT and Abdominal Ultrasonography				Model 2 With Abdominal Ultrasonography (No QFT)				Model 3 With QFT (No Abdominal Ultrasonography)				Model 4 (No QFT or Abdominal Ultrasonography)			
	β[a]	OR	95% CI	*P*	β[b]	OR	95% CI	*P*	β[c]	OR	95% CI	*P*	β[d]	OR	95% CI	*P*
Xpert results				.0073				.0061				.0065				.0052
Negative	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Positive	3.960	52.46	2.90–948.60	—	4.127	62.03	3.25–>999.99	—	3.868	47.833	2.95–775.81	—	4.052	57.52	3.35–986.52	—
Fever lasting >2 wk				<.0001				.0001				.0003				.0003
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.152	3.16	1.78–5.63	—	1.137	3.13	1.76–5.53	—	1.031	2.81	1.61–4.88	—	1.025	2.79	1.61–4.84	—
Unremitting cough				.0462				.0592				.0650				.0650
No	—	1	—	—	—	1	—	—	—	1	—	.053	—	1	—	—
Yes	.713	2.04	1.01–4.11	—	.671	1.96	0.97–3.93	—	.670	1.95	0.99–3.85	—	.634	1.89	0.96–3.70	—
Hemoptysis in previous 4 wk				.0949				.1174				.154				.1812
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.449	4.26	0.78–23.33	—	1.358	3.89	0.71–21.26	—	1.2080	3.35	0.64–17.62	—	1.133	3.10	0.59–16.34	—
Wt loss in previous 4 wk				.2440				.1863				.116				.0876
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	.369	1.45	0.78–2.69	—	.414	1.51	0.82–2.80	—	.482	1.62	0.89–2.95	—	.519	1.68	0.93–3.05	—
Contact with smear-positive patient with TB				.0170				.0142				.040				.0342
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.930	6.89	1.41–33.65	—	2.027	7.59	1.50–38.37	—	1.624	5.07	1.08–23.85	—	1.708	5.52	1.14–26.78	—
Tachycardia				.1020				.0737				.107				.0781
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	.849	2.34	0.85–6.46	—	.925	2.52	0.92–6.95	—	.814	2.26	0.84–6.06	—	.890	2.43	0.91–6.55	—
Miliary pattern on CXR				.0915				.0564				.141				.0921
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.370	3.93	0.80–19.31	—	1.544	4.68	0.96–22.86	—	1.156	3.18	0.68–14.76	—	1.317	3.73	0.81–17.30	—
Alveolar opacities on CXR				.0003				.0001				.002				.0009
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.200	3.32	1.73–6.38	—	1.280	3.60	1.88–6.88	—	.978	2.66	1.42–4.96	—	1.046	2.85	1.53–5.28	—
Lymph nodes on CXR				<.0001				<.0001				<.0001				<.0001
No	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—
Yes	1.771	5.88	2.98–11.58	—	1.715	5.56	2.85–10.83	—	1.920	6.82	3.54–13.15	—	1.863	6.44	3.37–12.30	—
Abdominal lymph nodes on ultrasound				.0002				.0003								
No	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Yes	1.281	3.60	1.82–7.11	—	1.250	3.49	1.73–6.83	—	—	—	—	—	—	—	—	—
QFT result				.1624								.207				
Negative	—	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—
Positive	.792	2.21	0.78–6.25	—	—	—	—	—	.714	2.04	0.77–5.45	—	—	—	—	—
Indeterminate	.509	1.66	0.83–3.35	—	—	—	—	—	.450	1.57	0.79–3.11	—	—	—	—	—

OR, odds ratio; TB, tuberculosis; —, not applicable.

[a] Intercept (constant) = −2.3555.

[b] Intercept = −2.1993.

[c] Intercept = −1.9602.

[d] Intercept = −1.8234.

The vast majority of children had prolonged cough as an inclusion criterion, which therefore lacked specificity. However, unremitting cough, which was assessed by using a graphic illustration, revealed a much higher specificity and remained in the model. Tachycardia, which was not used before in pediatric tuberculosis scores, is part of the 3 danger signs that should trigger antituberculosis treatment initiation in severely ill adults infected with HIV.[38] CXR findings significantly contributed to our score; yet, there is limited access to quality CXR and lack of reading skills in limited-resource settings. We used the local reader's opinion, which constituted an imperfect but more practical test compared with more experienced readers.[39] Presence of lymph nodes on the ultrasound had similar diagnostic accuracy compared with that found in South African children infected with HIV and significantly improved the model's discriminative ability.[23,24] Sensitivity of QFT in our study was much lower than the pooled sensitivity estimated at 47% in a recent meta-analysis in

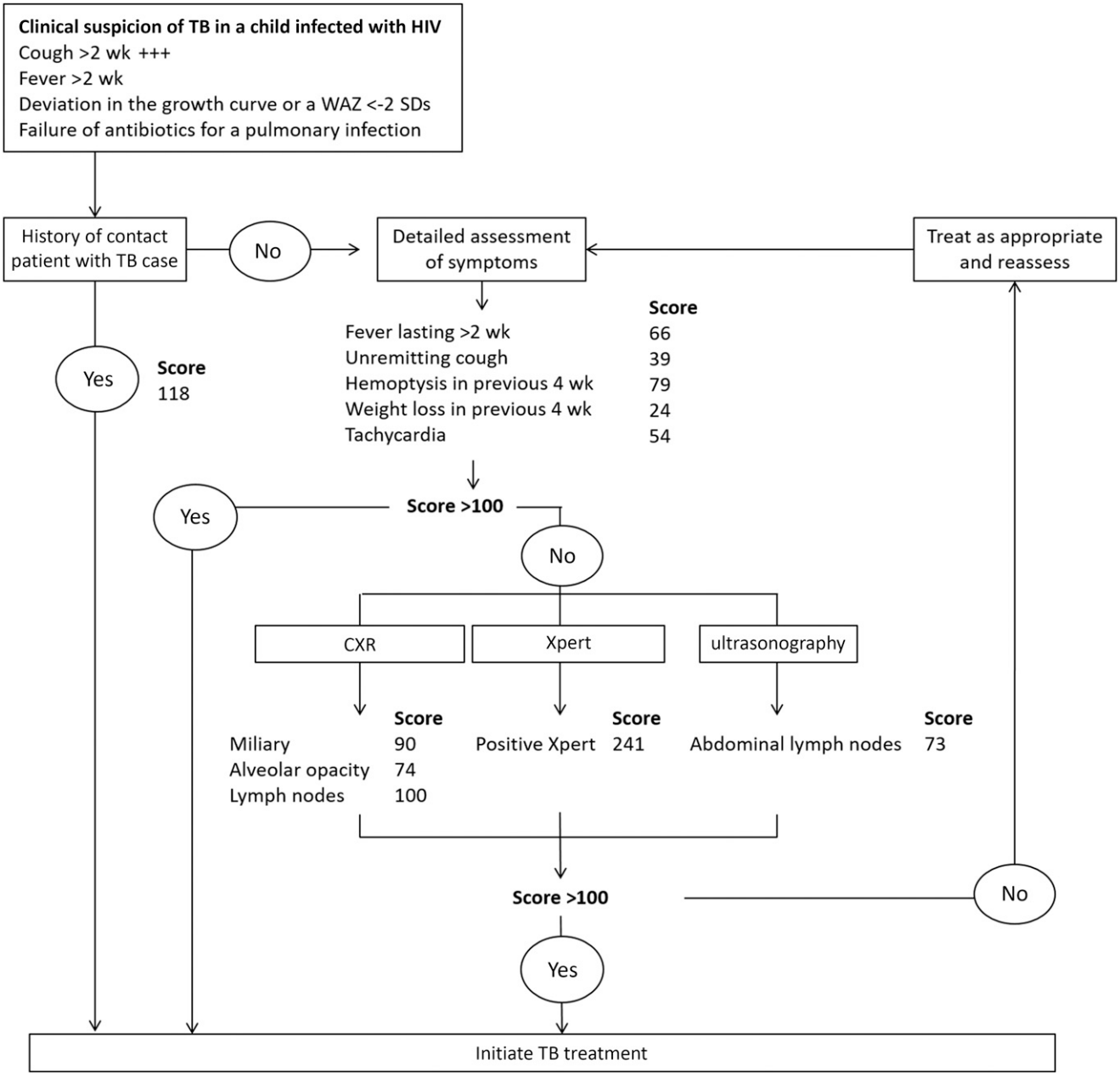

FIGURE 2
Proposed PAANTHER tuberculosis (TB) treatment-decision algorithm, including the diagnostic score.

children infected with HIV and did not improve the model's discriminative ability, confirming its poor diagnostic performance for tuberculosis in children with immunodeficiency.[9]

With its high sensitivity, our score should enable standardized treatment initiation in most HIV-infected children with tuberculosis. We showed previously that mortality in ART-naïve children was associated with the lack of treatment rather than the delay to antituberculosis treatment.[12] However, initiation of antituberculosis treatment within a median of 1 week led to delayed ART, which was associated with increased mortality. It was recently estimated that in high–tuberculosis burden countries, it may be more cost-effective to treat all children with presumptive tuberculosis.[40] In children infected with HIV, however, pill burden and potential impact on ART have led to a call for a more discriminant approach. With the step-by-step approach, the score could enable same-day treatment decision without CXR and abdominal ultrasonography in children presenting clinical criteria. Overall, our score did not perform as well as clinicians from study tertiary health care facilities who treated 92% of children with tuberculosis and only 6% of those without; however, we expect that it will contribute to faster treatment decision at lower levels of care, especially when used with feasible and sensitive specimens for Xpert, such as nasopharyngeal aspirates and stools.[25] In practice, access to treatment does not depend exclusively on treatment decision and may be delayed for other structural reasons.

Our study has limitations. First, an incorporation bias resulting from the lack of a reference standard for childhood tuberculosis, independent from candidate predictors, may have led to overestimation of the models' diagnostic performance.[41] The good discriminative ability of the model in the case-control subset, however, reveals limited impact on the score performances. Second, almost one-quarter of study participants, mostly younger children with severe clinical status, had missing data for the considered predictors. Our analysis reveals, however, that the score has similar sensitivity in these children and that missing data would mostly impact specificity, which varied between 43% and 61%. Lastly, our study eligibility criteria differed from WHO criteria for investigation of tuberculosis, namely poor weight gain, fever, current cough, and history of contact with a patient with tuberculosis.[42] Our score is therefore not directly applicable to children presenting with these criteria. Despite these limitations our study has strengths. Development by using data from 4 countries ensured better external validity and generalizability of the scores, and internal validation revealed that the models developed would provide good predictions.[43] The lower score specificity in Cambodia could be due to higher rates of nontuberculous mycobacteria disease, which is difficult to distinguish from tuberculosis.[44]

CONCLUSIONS

With its high sensitivity and algorithmic approach, the PAANTHER score should enable rapid treatment decision in children with presumptive tuberculosis. This algorithm constitutes a consequentialist approach to tuberculosis in children infected with HIV, considering the need to initiate treatment to reduce mortality, rather than an essentialist approach, considering the trueness of tuberculosis diagnosis.[45] However, further external validation is needed to validate both the scoring system and the overall approach and to confirm its clinical usefulness.

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ABBREVIATIONS

ART: antiretroviral therapy
AUROC: area under the receiver operating characteristic curve
CI: confidence interval
CXR: chest radiograph/radiography
QFT: Quantiferon Gold In-Tube
TST: tuberculin skin test
WAZ: weight-for-age *z* score
WHO: World Health Organization
Xpert: Xpert MTB/RIF

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Dr Marcy designed and wrote the study protocol, led the study, analyzed the data, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Borand, Msellati, and Tejiokem designed and wrote the study protocol, coordinated study implementation at the regional and country level, interpreted the data, and reviewed and revised the manuscript; Dr Ung led the study, enrolled patients, implemented the study, and reviewed and revised the manuscript; Drs Truong, Do Chau, Ngoc Tran, Ateba-Ndongo, Tetang-Ndiang, Sanogo, Neou, and Dim enrolled patients, implemented the study, and reviewed and revised the manuscript; Dr Nacro designed and wrote the study protocol, enrolled patients, implemented the study, and reviewed and revised the manuscript; Dr Goyet analyzed data on chest radiographs and reviewed and revised the manuscript; Dr Pean implemented and supervised laboratory immunologic tests and reviewed and revised the manuscript; Ms Quillet coordinated study implementation at the regional and country level and reviewed and revised the manuscript; Dr Fournier designed and wrote the study protocol and reviewed and revised the manuscript; Dr Berteloot reviewed chest radiographs and reviewed and revised the manuscript; Dr Carcelain designed and wrote the study protocol, supervised immunologic aspects, and reviewed and revised the manuscript; Dr Godreuil designed and wrote the study protocol, supervised microbiologic aspects, and reviewed and revised the manuscript; Dr Blanche designed and wrote the study protocol, interpreted the data, and reviewed and revised the manuscript; Dr Delacourt designed and wrote the study protocol, reviewed chest radiographs, interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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