Diagnostic accuracy of computer-aided detection of tuberculosis on chest X-rays and C-reactive protein as tuberculosis triage tests at health facilities in Lesotho and South Africa: 2021 - 2022

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BACKGROUND

- TB is the leading cause of death from a single infectious agent worldwide
- Almost 1/3 of people with active TB go undiagnosed each year
- Improving active case finding for TB is important to identify and treat undiagnosed TB cases.
- To scale these activities, rapid, low-cost, non-sputum tuberculosis (TB) screening tests need to be developed

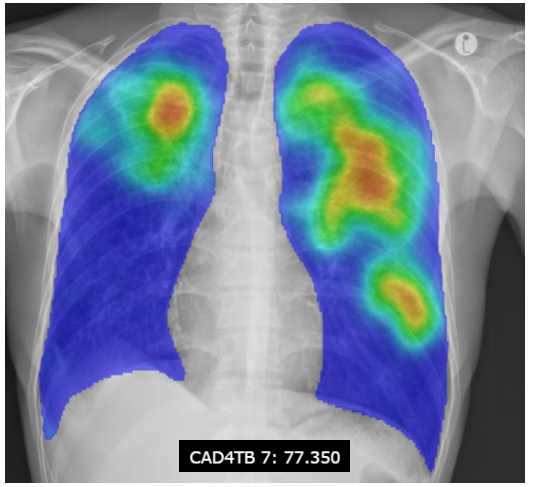
BACKGROUND

- According to the WHO target product profile (TPP) for tuberculosis referral or triage tests, these tests should ideally be non-sputum based, rapid, accurate and easy to use at low costs
- Required minimum >90% sensitivity and >70%
- Screening and triage tests are expected to reduce diagnostic costs, offer early access to diagnosis, enable timely treatment initiation, improve patient outcomes and ultimately reduce further transmission

BACKGROUND

CAD4TB

- WHO recommends chest x-ray in combination with computer-aided detection (CAD) software to identify tuberculosis-related radiographic abnormalities for screening and triage
- CAD has become a promising approach to the diagnosis of tuberculosis as the software has evolved significantly through artificial intelligence and as mobile or portable x-ray systems have allowed its use in the community
- However, it is still necessary to establish a threshold that is context-specific



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BACKGROUND

CRP

- WHO also recommends screening for tuberculosis with C-reactive protein in people living with HIV, but there is no recommendation for HIV-negative individuals

- The test is available as a point-of-care assay that can be used at community level

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BACKGROUND

The TB TRIAGE+ ACCURACY study evaluated:

- Artificial intelligence-based computer-aided detection software (CAD4TB)
- Point-of-care C-reactive protein (CRP)

as potential triage tests for TB screening, in patients with presumptive TB, attending health facilities in South Africa and Lesotho

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Methods

- We conducted a prospective, multi-centre study
- Enrolling adults (≥ 18 yrs)
- With one or more TB symptom (cough, fever, night sweats, loss of weight)
- In South Africa participants were recruited from primary health care clinics in the Msunduzi Municipality, KwaZulu Natal
- In Lesotho, participants were recruited from the Butha Buthe Government Hospital
- Both sites are in countries with high HIV and tuberculosis incidence and serve a primarily rural or semi-rural population

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Methods

CAD4TB: AI software that uses a data set of reference x-rays, to create an algorithm, for abnormality screening

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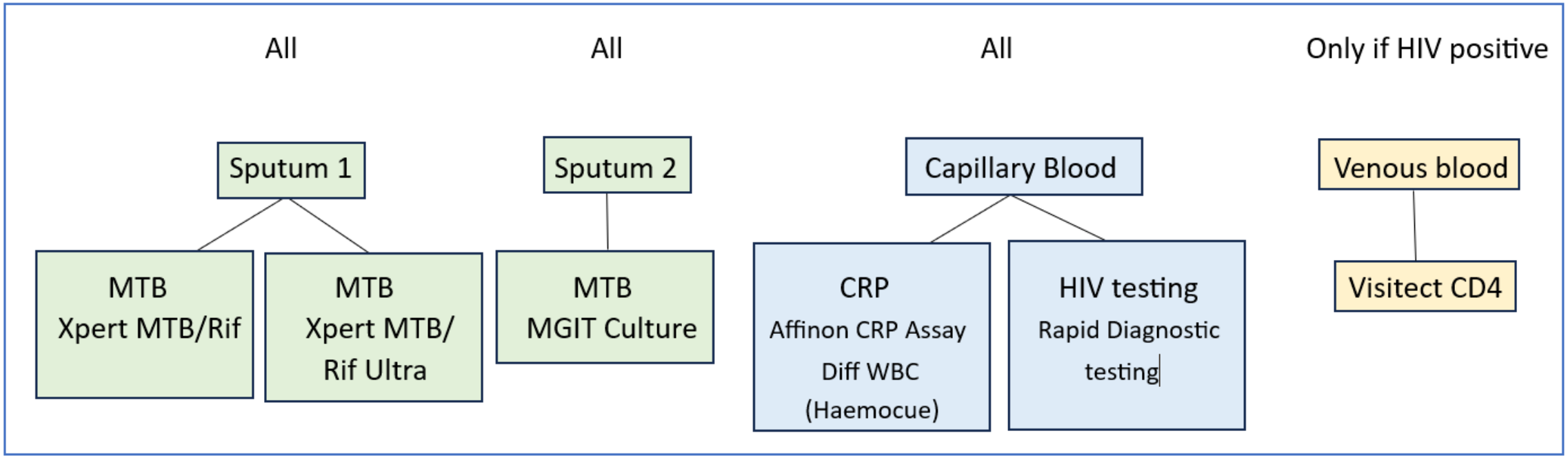
Methods

Figure 1: Study specimen collection



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RESULTS

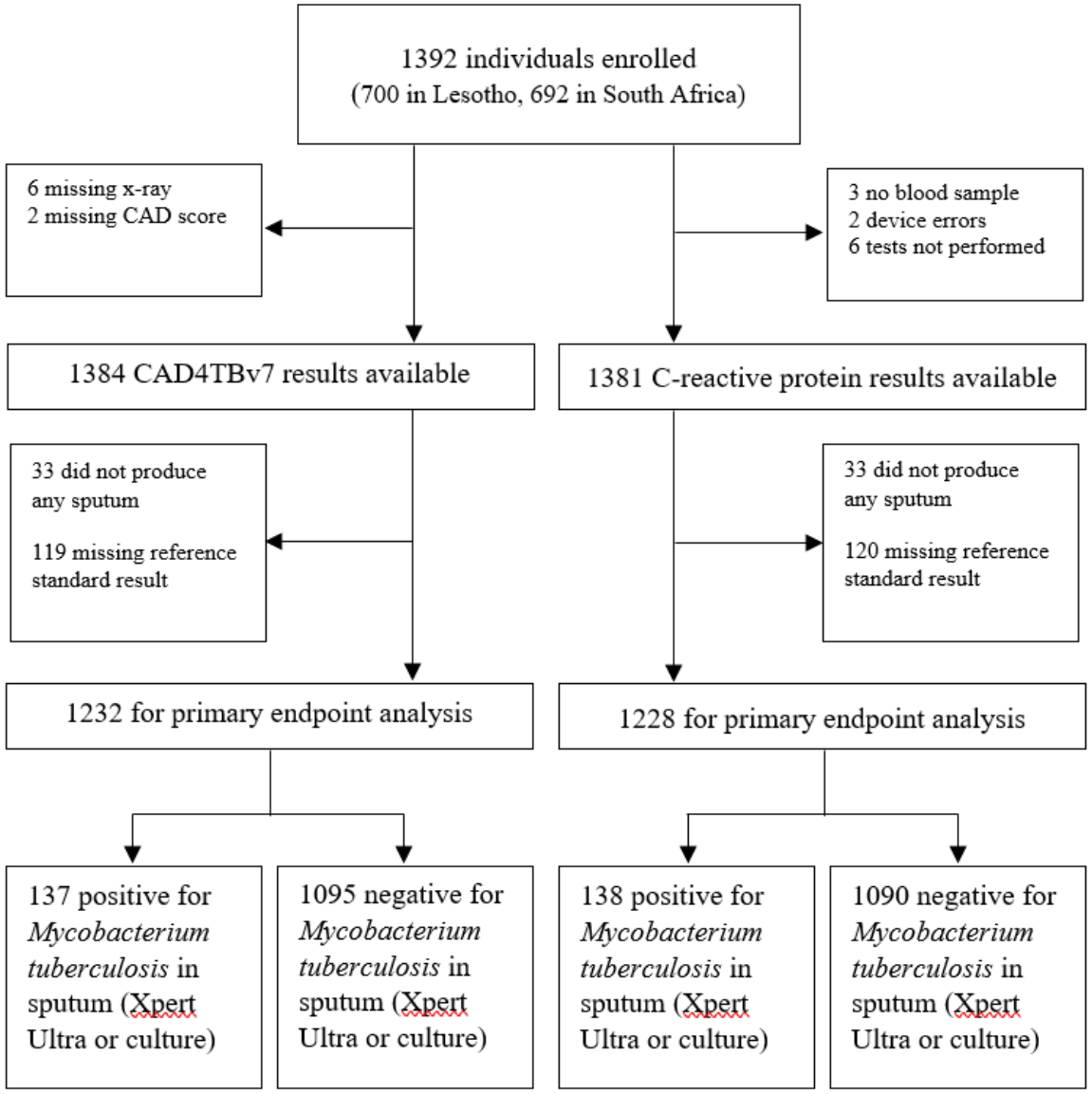

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Table 1: Demographics and TB symptoms

	Lesotho (n=700)	South Africa (n=692)	Total (n=1392)
Age			
Median age (years)	44 (32-60)	46 (33-55)	45 (33-57)
Gender (self-reported)			
Female	377 (53·9%)	375 (54·2%)	752 (54·0%)
Male	323 (46·1%)	317 (45·8%)	640 (46·0%)
Tuberculosis symptoms			
Cough	670 (95·7%)	604 (87·3%)	1274 (91·5%)
Weight Loss	359 (51·3%)	304 (43·9%)	663 (47·6%)
Night sweats	301 (43·0%)	327 (47·3%)	628 (45·1%)
Fever	202 (28·9%)	107 (15·5%)	309 (22·2%)
BCG vaccination			
Yes	599 (85·6%)	530 (76·8%)	1129 (81·2%)
No	101 (14·4%)	110 (15·9%)	211 (15·2%)

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Table 2: Risk Factors

	Lesotho (n=700)	South Africa (n=692)	Total (n=1392)
Previous tuberculosis			
Yes	122 (17·4%)	209 (30·3%)	331 (23·8%)
No	576 (82·3%)	473 (68·6%)	1049 (75·5%)
Risk factors			
Miner	161 (23·0%)	9 (1·3 %)	170 (12·2%)
Health care worker	13 (1·9 %)	16 (2·3 %)	29 (2·1 %)
History of tobacco use	254 (36·3%)	252 (36·5%)	506 (36·4%)
Risky drinking behaviour*	205 (29·3%)	127 (18·4%)	332 (23·9%)
HIV status			
People living with HIV	335 (47·9%)	337 (48·8%)	672 (48·3%)
HIV negative	357 (51·0%)	336 (48·7%)	693 (49·9%)
Refused testing	8 (1·1 %)	17 (2·5 %)	25 (1·8 %)
ART among people living with HIV			
Not receiving ART	70 (20·9%)	19 (5·6%)	89 (13·2%)
Receiving ART	265 (79·1%)	302 (89·6%)	567 (84·4%)

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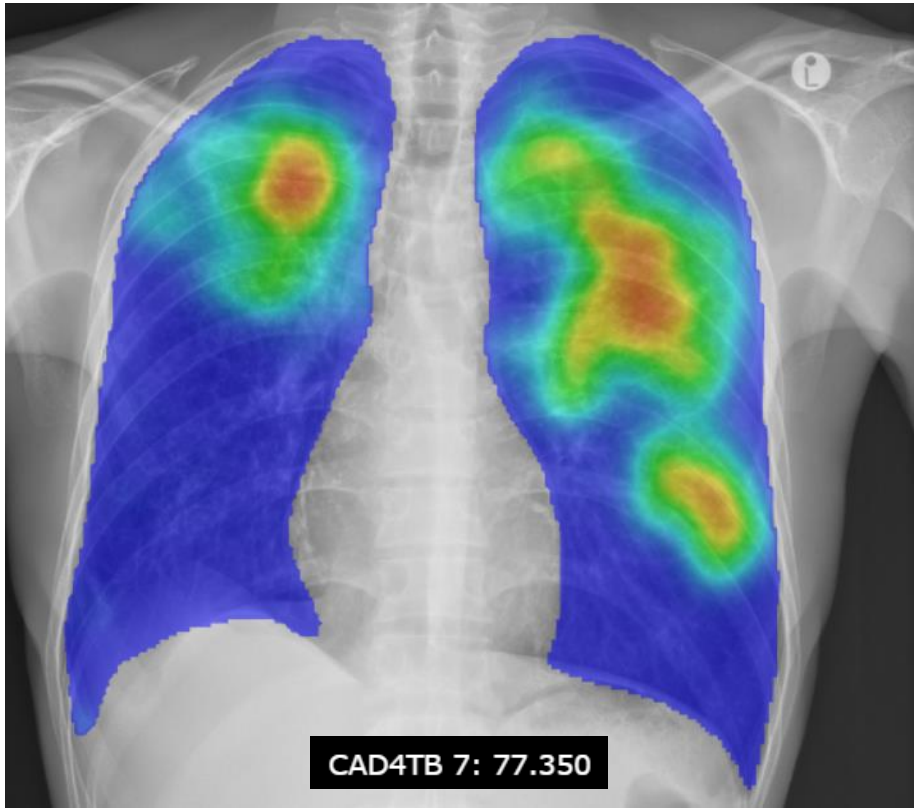
RESULTS: CAD4TB Threshold

CAD4TBv7 was assessed against WHO minimum TPP criteria

At a CAD4TBv7 score $\geq$ 27

- Sensitivity of 89·8% (95% CI 83·4-94·3)
- Specificity of 68·2% (95% CI 65·4-71·0)
- Positive predictive value of 26·1% (95% CI 22·2-30·3)
- Negative predictive value of 98·2% (95% CI 96·9-99·0)



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RESULTS: CRP Threshold

CRP was assessed against WHO minimum TPP criteria

CRP threshold was determined at 7 mg/L

- Sensitivity of 89·9% (95% CI 83·6-94·3)
- Specificity of 38·2% (95% CI 35·3-41·1)
- Positive predictive value of 15·5% (95% CI 13·1-18·2)
- Negative predictive value of 96·7% (95% CI 94·6-98·2).

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RESULTS: Combination CAD4TB and CRP

Table 3: Diagnostic accuracy of the combination of CAD4TBv7 and CRP

Reference standards	Combination of CAD4TB and CRP			
	Sensitivity	95% CI	Specificity	95% CI
Culture alone (n=1240)	94·8%	88·4-98·3	30·1%	27·4-32·9
Xpert alone (n=1335)	98·1%	93·4-99·8	31·3%	28·7-33·9
Xpert Ultra alone (n=1339)	96·6%	91·6-99·1	31·2%	28·6-33·9
Composite microbiological reference standard (n=1236)	95·6%	90·7-98·4	30·8%	28·0-33·6
Extended composite reference standard (n=1263)	89·7%	86·4-92·4	36·5%	33·2-39·9

The evaluation of the combination of CAD4TBv7 & CRP showed:

- High sensitivity between 90% and 98%
- At the expense of a lower specificity across all analyses (specificity: between 30% and 38%)

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RESULTS: Number Needed to Test

The number needed to test after triaging to identify one microbiologically confirmed case was

- 4 for CAD4TBv7 (95% CI 3-5) and
- 6 for C-reactive protein (95% CI 5-8).

In a triage scenario

- CAD4TBv7 would have avoided 62% (95% CI 59-64) and
- C-reactive protein 35% (95% CI 33-38%) of confirmatory tests

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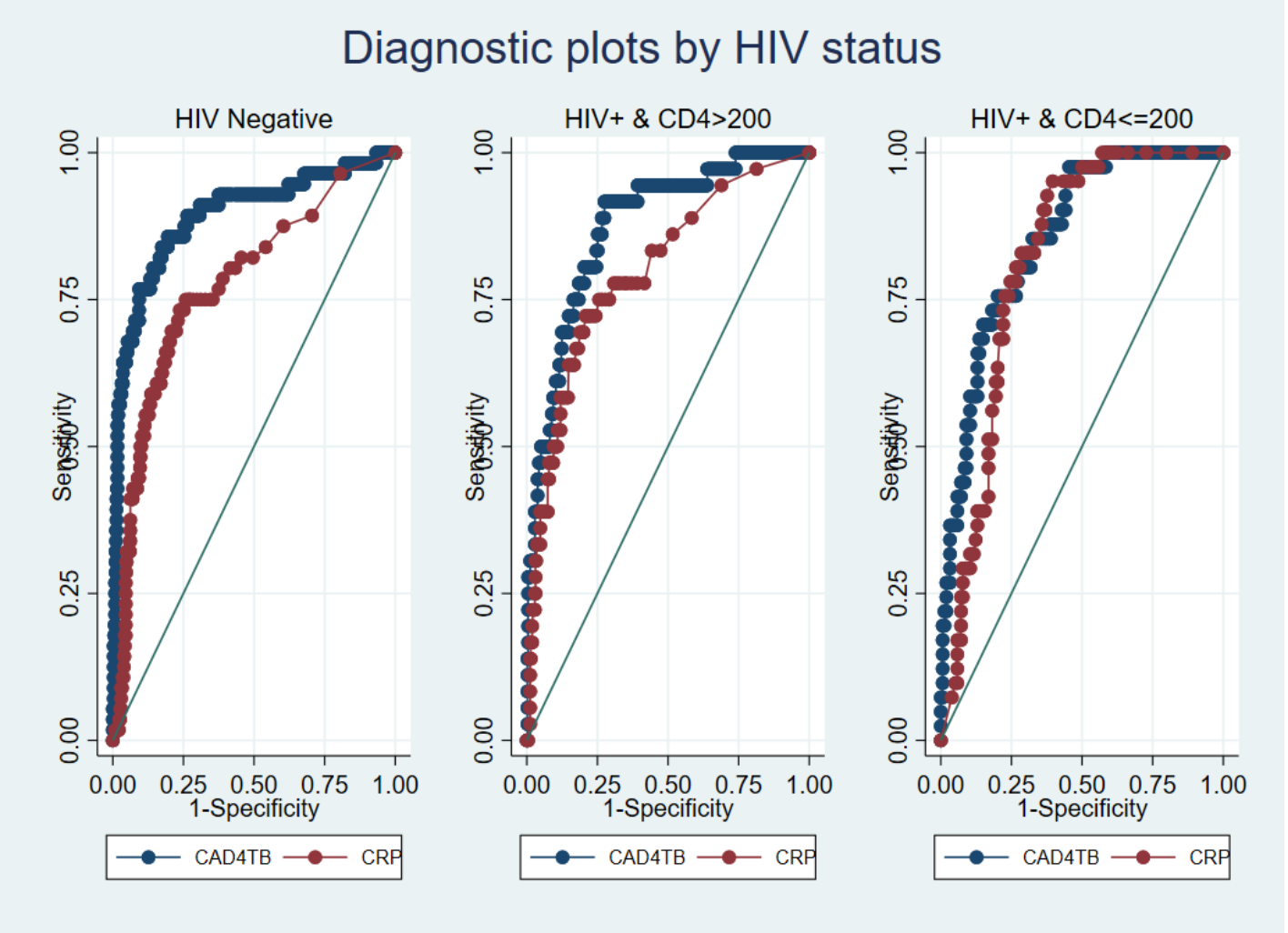
RESULTS



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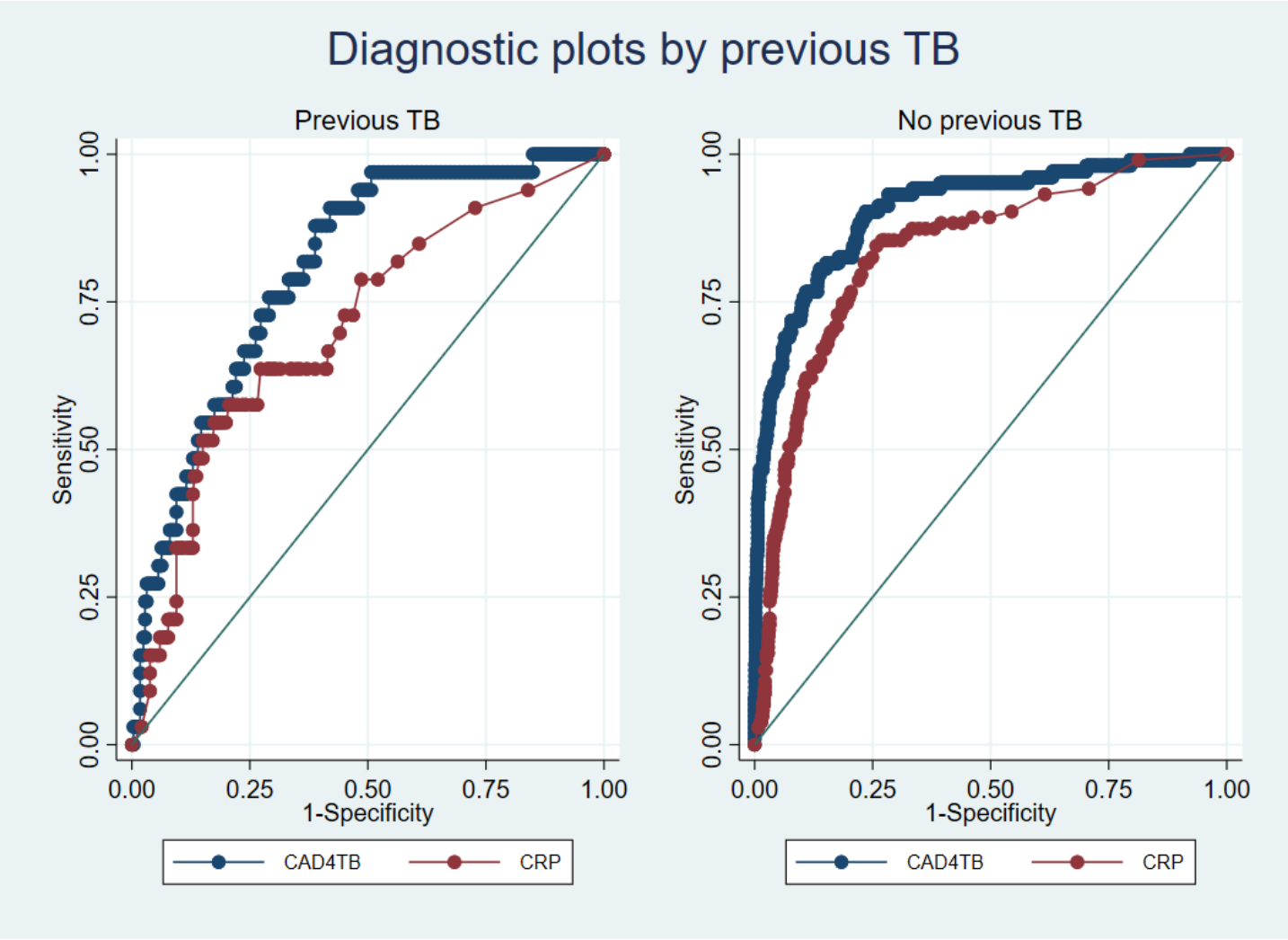

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DISCUSSION

WHO-recommended CAD for digital chest radiography and C-reactive protein are currently among the most promising triage test candidates for tuberculosis

CAD4TBv7 is close to meeting the minimum sensitivity and specificity as defined by WHO's TPP of >90% sensitivity and >70% specificity for a community-based triage or referral tests

In view of the high negative predictive value, CAD4TBv7 can be considered a non-sputum-based triage test to rule out tuberculosis disease

Various barriers still exist to achieve greater adoption of CAD, with developing simplified procedures for local threshold selection and thorough cost-effectiveness analyses being among the most important

CONCLUSION

CRP does not meet TTP criteria, as it shows with at a sensitivity of almost 90% a specificity of only 38%

However, CRP has low costs and performs unaffected by HIV status, there might be a potential clinical utility in refuting tuberculosis

Future research is needed to evaluate the diagnostic value of C-reactive protein for tuberculosis triaging, specifically on how to combine it with CAD for chest x-ray, symptom screening, or promising biomarkers

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CONCLUSION

Combining CAD4TBv7 and CRP using the determined thresholds for each of the two tests increased the sensitivity of the combined test with a substantial sacrifice in specificity, which speaks against a simple combination of the two tests.

An alternative approach could be a combination where CRP is used as a second triage test instead of an immediate Xpert Ultra and test only in a specific range of the CAD4TBvs7 score, an approach currently being evaluated in a large-scale community study

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