Clinical utility of C-reactive protein-based triage for presumptive pulmonary tuberculosis in South African adults

Claire J Calderwood , Byron WP Reeve , Tiffeney Mann , Zaida Palmer , Georgina Nyawo , Hridesh Mishra , Ibrahim Abubakar , Mahdad Noursadeghi , Grant Theron , Rishi K Gupta

PII: S0163-4453(22)00639-9
DOI: https://doi.org/10.1016/j.jinf.2022.10.041
Reference: YJINF 5763

To appear in: *Journal of Infection*

Accepted date: 31 October 2022

Please cite this article as: Claire J Calderwood , Byron WP Reeve , Tiffeney Mann , Zaida Palmer , Georgina Nyawo , Hridesh Mishra , Ibrahim Abubakar , Mahdad Noursadeghi , Grant Theron , Rishi K Gupta , Clinical utility of C-reactive protein-based triage for presumptive pulmonary tuberculosis in South African adults, *Journal of Infection* (2022), doi: https://doi.org/10.1016/j.jinf.2022.10.041

Highlights

- CRP has good diagnostic accuracy for pulmonary TB among symptomatic adults
- At ≥10mg/L CRP approaches, but fails to meet, WHO benchmarks for a TB triage test
- CRP may still offer clinical utility to prioritize use of confirmatory tests
- Performance is similar across key risk groups for TB including people living with HIV
- Clinical utility of CRP is dependent on target population TB prevalence

Clinical utility of C-reactive protein-based triage for presumptive pulmonary tuberculosis in South African adults

Authors

Claire J Calderwood, MRCP* (1)

Byron WP Reeve, PhD* (2)

Tiffeney Mann, MSc (3)

Zaida Palmer, MSc (2)

Georgina Nyawo, MSc (2)

Hridesh Mishra, PhD (2)

Ibrahim Abubakar, PhD (1)

Mahdad Noursadeghi, PhD (3)

Grant Theron, PhD† (2)

Rishi K Gupta, PhD† (1)

* Contributed equally

† Contributed equally

Affiliations

1. Institute for Global Health, University College London, London, UK

2. DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research; South African Medical Research Council Centre for Tuberculosis Research; Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town

3. Division of Infection and Immunity, University College London, London, UK

Corresponding author

Dr Rishi K Gupta, PhD

Institute for Global Health, University College London, London, UK

Email: r.gupta@ucl.ac.uk

Word count: 3362

Abstract: 296 words

Keywords: Diagnosis, Screening, CRP, HIV, TB

Running title: CRP-based triage for presumptive pulmonary TB

Abstract

Background:

Identification of an accurate, low-cost triage test for pulmonary TB among people presenting to healthcare facilities is an urgent global research priority. We assessed the diagnostic accuracy and clinical utility of C-reactive protein (CRP) for TB triage among symptomatic adult outpatients, irrespective of HIV status.

Methods:

We prospectively enrolled adults reporting at least one (for people with HIV) or two (for people without HIV) symptoms of cough, fever, night sweats, or weight loss at two TB clinics in Cape Town, South Africa. Participants provided sputum for culture and Xpert MTB/RIF Ultra. We evaluated the diagnostic accuracy of CRP (measured using a laboratory-based assay) against a TB-culture reference standard as the area under the receiver operating characteristic curve (AUROC), and sensitivity and specificity at pre-specified thresholds. We assessed clinical utility using decision curve analysis and benchmarked against WHO recommendations.

Results:

Of 932 included individuals, 255 (27%) had culture-confirmed pulmonary TB and 389 (42%) were living with HIV. CRP demonstrated an AUROC of 0·80 (95% confidence interval 0·77–0·83), with sensitivity 93% (89–95%) and specificity 54% (50–58%) using a primary cut-off of ≥10mg/L. Performance was similar among people with HIV to those without. In decision curve analysis, CRP-based triage offered greater clinical utility than confirmatory testing for all up to a number willing to test threshold of 20 confirmatory

tests per true positive pulmonary TB case diagnosed (threshold probability 5%). If it is possible to perform more confirmatory tests than this, a 'confirmatory test for all' strategy performed better.

Conclusions:

CRP achieved the WHO-defined sensitivity, but not specificity, targets for a triage test for pulmonary TB and showed evidence of clinical utility among symptomatic outpatients, irrespective of HIV status.

Funding:

South African Medical Research Council, EDCTP2, Royal Society Newton Advanced Fellowship, Wellcome Trust, National Institute of Health Research, Royal College of Physicians.

Research in context

Existing evidence

We performed a systematic search using terms for "C-reactive protein" and "tuberculosis" in OVID Medline on 1st April 2021 with no language or date restrictions. Two previous systematic reviews assessed the diagnostic accuracy of C-reactive protein for pulmonary TB, the most recent of which reported pooled sensitivity of 89% (95%CI 80–96%) and specificity 57% (36–65%) using a threshold of ≥10mg/L. Most included studies were restricted to provider-initiated systematic screening (active case finding) for TB among people living with HIV at the time of ART initiation. One subsequent case-control diagnostic accuracy study found that CRP-based triage did not achieve the WHO target product profile criteria for a triage test. An individual participant data meta-analysis evaluated CRP as a screening test for pulmonary TB among PLHIV, irrespective of signs and symptoms, describing 83% sensitivity (95%CI 79–86) and 67% specificity (95%CI 60–73; n=3187) in that setting. Overall, CRP is a promising tool for TB screening and triage, however there are fewer data on the symptomatic triage use case, and no studies have prospectively evaluated CRP-based triage among outpatients presenting with symptoms compatible with TB, without pre-selection based on HIV status or other factors. Moreover, previous data have focused on diagnostic accuracy in isolation, without considering programmatic clinical utility.

Added value of this study

To our knowledge, this is the first study to report the diagnostic accuracy and clinical utility of CRP for pulmonary TB in a large, consecutive cohort of symptomatic outpatients, irrespective of

HIV status. At a threshold of ≥10mg/L, CRP approached, but did not meet, WHO target product profile (TPP) criteria for a triage test, achieving the minimum required sensitivity (target: 90%; CRP: 93% [95% CI 89–95%]) but not specificity (target: 70%; CRP: 54% ;50–58%]). The discriminatory ability of CRP was similar across key risk groups for TB including people living with HIV, and among those with previous TB. In our study population, with very high prevalence of pulmonary TB (27%), a CRP-based triage strategy would lead to 41% fewer confirmatory tests than a test all approach but would miss 7% of TB cases. CRP-based triage demonstrated clinical utility in similar settings if it is necessary or desirable to prioritise use of confirmatory testing so that those tested have at least a 5% risk of pulmonary TB (i.e. a number willing to test of fewer than 20 confirmatory tests per true TB case detected), whilst confirmatory testing for all individuals who met our symptom-based enrolment criteria appears best below this threshold probability. We also demonstrate that clinical utility is highly dependent upon TB prevalence, suggesting that there is likely even more clinical utility for CRP- based triage in settings with lower TB prevalence than that in our study.

Implications

Previously published data have supported the use of CRP testing to systematically screen for TB among people living with HIV initiating ART. In our study, CRP approaches the WHO benchmarks for a triage test and may offer clinical utility to prioritize use of confirmatory tests among symptomatic adults, without the need for prior knowledge of HIV status. Further urgent prospective evaluations of CRP-guided triage using point-of-care assays, including interventional trials and health-economic analyses, are required to support policy development, and as a benchmark against which to assess the performance of other candidate triage tests.

Background

Of the estimated 10 million people who developed tuberculosis (TB) in 2020, 4.1 million were not reported to TB programmes.[1] The World Health Organization (WHO) has emphasised the urgent need for better tools to identify people with TB. A key priority is development of a rapid, point-of-care, low-cost, non-sputum-based "triage" test to guide confirmatory testing. An effective triage test may confer dual benefits in reducing unnecessary confirmatory testing for people at lower risk of disease, while focusing attention on those who need investigations most.[2,3] Computer assisted diagnostic radiography, protein and mRNA biomarkers are under active evaluation for this purpose. A triage test prioritises sensitivity over specificity, but to date the desired performance parameters have been informed only by expert opinion and a modelling analysis of potential financial savings. A more holistic framework for evaluating the clinical utility of candidate triage tests has been lacking.

Assuming a triage test threshold is selected to maximise sensitivity, the fundamental question becomes the range of false-positive rates within which a triage test (that triggers confirmatory testing) still achieves a net benefit, compared to confirmatory testing for all. Decision curve analysis (DCA) of test performance in natural observational cohort studies can be used to compare relative net-benefit between two approaches. In DCA, net benefit is calculated as the true positive rate minus the false positive rate weighted by the perceived cost: benefit ratio of an intervention, in this case, confirmatory testing for tuberculosis. The perceived cost: benefit ratio is represented by the "threshold probability" of disease that will trigger an intervention. More intuitively, this is the inverse of the number of confirmatory tests we are willing to

undertake to find a true positive TB case. DCA can help us find the number willing to test (NWT) range, where a triage test leads to greater net benefit than confirmatory testing for all.

C-reactive protein (CRP) is an acute phase reactant commonly used as a non-specific marker of inflammation. Proposed use cases in TB have therefore focused on screening and triage rather than confirmatory testing, owing to a lack of specificity. It is measurable on finger-prick blood using point-of-care platforms at a cost of US$2 per test with results in minutes, thus meeting many of the WHO-recommended operational characteristics of a triage test.[2] Recent WHO guidance has recommended CRP (with a threshold of >5mg/L) for TB screening among people living with HIV (PLHIV), with a meta-analysis demonstrating 90% sensitivity (95% confidence interval [95%CI] 78–96%) and 50% specificity (29–71%) among outpatients initiating anti-retroviral therapy (ART).[4] However, the value of CRP as a triage test among symptomatic people presenting to healthcare, including populations with mixed HIV status, is less clear. In two systematic reviews, no identified studies prospectively evaluated CRP-based triage in this context.[5–9] One subsequent case-control study evaluated the diagnostic accuracy of CRP for pulmonary TB using a threshold ≥12mg/L and described sensitivity 85% [95%CI 80–88%] and specificity 70% [65–74%]). The context in which CRP-based triage may provide clinical utility by reducing the need for confirmatory testing has not been evaluated.[10]

We sought to address these important evidence gaps by testing the diagnostic accuracy and clinical utility of CRP for identifying adult patients with symptomatic tuberculosis in a large prospective observational cohort in South Africa, representative of a setting with high burden of tuberculosis and HIV. In this context, we sought to identify NWT range where CRP achieves greater clinical utility than confirmatory testing for all.

none (black solid line) of the participants meeting study inclusion criteria (i.e. presenting with TB-related symptoms, as defined in text). Dot-dash vertical line represents the threshold

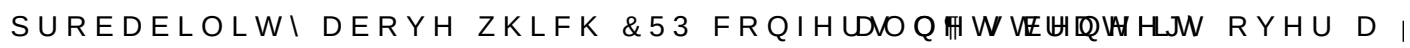

Figure 4: Correlation of CRP with markers of TB severity among culture -confirmed pulmonary TB cases (body mass index ([BMI] culture days to positivity, haemoglobin and TB Score II).

TB Score II was only calculated for individuals with complete data for all score components. Spearman rank correlation was calculated.

References

1 World Health Organization. Global tuberculosis report. Geneva, 2021.

2 World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. 2014.

3 Nathavitharana RR, Yoon C, Macpherson P, et al. Guidance for Studies Evaluating the Accuracy of Tuberculosis Triage Tests. J Infect Dis 2019; **220**: S116–25.

4 World Health Organization. WHO consolidated guidelines on tuberculosis: Module 2: Screening. 2021.

5 Santos VS, Goletti D, Kontogianni K, et al. Acute phase proteins and IP-10 as triage tests for the diagnosis of tuberculosis: systematic review and meta-analysis. Clin Microbiol Infect 2019; **25**: 169–77.

6 Yoon C, Chaisson LH, Patel SM, et al. Diagnostic accuracy of C-reactive protein for active pulmonary tuberculosis: A meta-analysis. Int J Tuberc Lung Dis 2017; **9**: 1013–1019.

7 Drain PK, Mayeza L, Bartman P, et al. Diagnostic accuracy and clinical role of rapid C-reactive protein testing in hiv-infected individuals with presumed tuberculosis in south africa. Int J Tuberc Lung Dis 2014; **18**: 20–6.

8 Wilson D, Badri M, Maartens G. Performance of serum c-reactive protein as a screening test for smear-negative tuberculosis in an ambulatory high HIV prevalence population. PLoS One 2011; **6**: 1–7.

9 Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative

tuberculosis using case definitions and treatment response in HIV-infected adults. Int J Tuberc Lung Dis 2006; **10**: 31–8.

10 Samuels TH, Wyss R, Ongarello S, Moore DA, Schumacher SG, Denkinger CM. Evaluation of the diagnostic performance of laboratory-based c-reactive protein as a triage test for active pulmonary tuberculosis. PLoS One 2021; **16**: 1–15.

11 Turner C, Gupta R, Tsaliki E, et al. Blood transcriptional biomarkers for active pulmonary tuberculosis in a high-burden setting: a prospective, observational, diagnostic accuracy study. Lancet Respir Med 2020; **8**: 407–19.

12 Mishra H, Reeve BWP, Palmer Z, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF for diagnosis of tuberculosis in an HIV-endemic setting with a high burden of previous tuberculosis: a two-cohort diagnostic accuracy study. Lancet Respir Med 2020; **8**: 368–82.

13 World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva, Switzerland: World Health Organization (WHO), 2011.

14 Rudolf F, Lemvik G, Abate E, et al. TBscore II: Refining and validating a simple clinical score for treatment monitoring of patients with pulmonary tuberculosis. Scand J Infect Dis 2013; **45**: 825–36.

15 Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011; **12**: 77.

16 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves : A Nonparametric Approach.

Biometrics1988; **44**: 837–45.

17 Yoon C, Semitala FC, Atuhumuza E, et al. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. Lancet Infect Dis2017; **17**: 1285–92.

18 Shine B, de Beer FC, Pepys MB. Solid phase radioimmunoassays for human C-reactive protein. Clin Chim Acta1981; **117**: 13–23.

19 Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ2016; **352**: 3–7.

20 Marshall Brown. rmda: Risk Model Decision Analysis. R package version 1.6. 2018.

21 Barker G, Ricardo, Christine; Nascimento M. Engaging men and boys in changing gender-based inequity in health: evidence from programme interventions. In: World Health Organization. 2007.

22 Kerkhoff AD, Wood R, Vogt M, Lawn SD. Predictive value of anemia for tuberculosis in HIV-infected patients in Sub-Saharan Africa: an indication for routine microbiological investigation using new rapid assays. J Acquir Immune Defic Syndr2014; **66**: 33–40.

23 Doumatey AP, Zhou J, Adeyemo A, Rotimi C. High sensitivity C-reactive protein (Hs-CRP) remains highly stable in long-term archived human serum. Clin Biochem2014 Mar;47(4-5):315-8.

24 Ishikawa S, Kayaba K, Gotoh T, Nakamura Y, Kario K, Ito Y, Kajii E; JMS Cohort. Comparison of C-reactive protein levels between serum and plasma samples on long-

term frozen storage after a 13.8 year interval: the JMS Cohort Study. J Epidemiol 2007 Jul;17(4):120-4.

25 Chegou NN, Sutherland JS, Malherbe S, et al. Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB. Thorax 2016; **71**: 785–94.

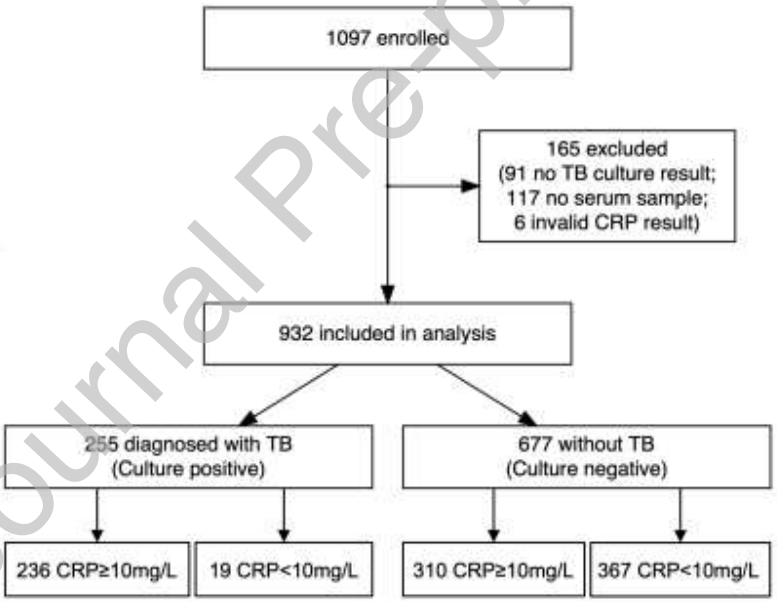

Fig. 1

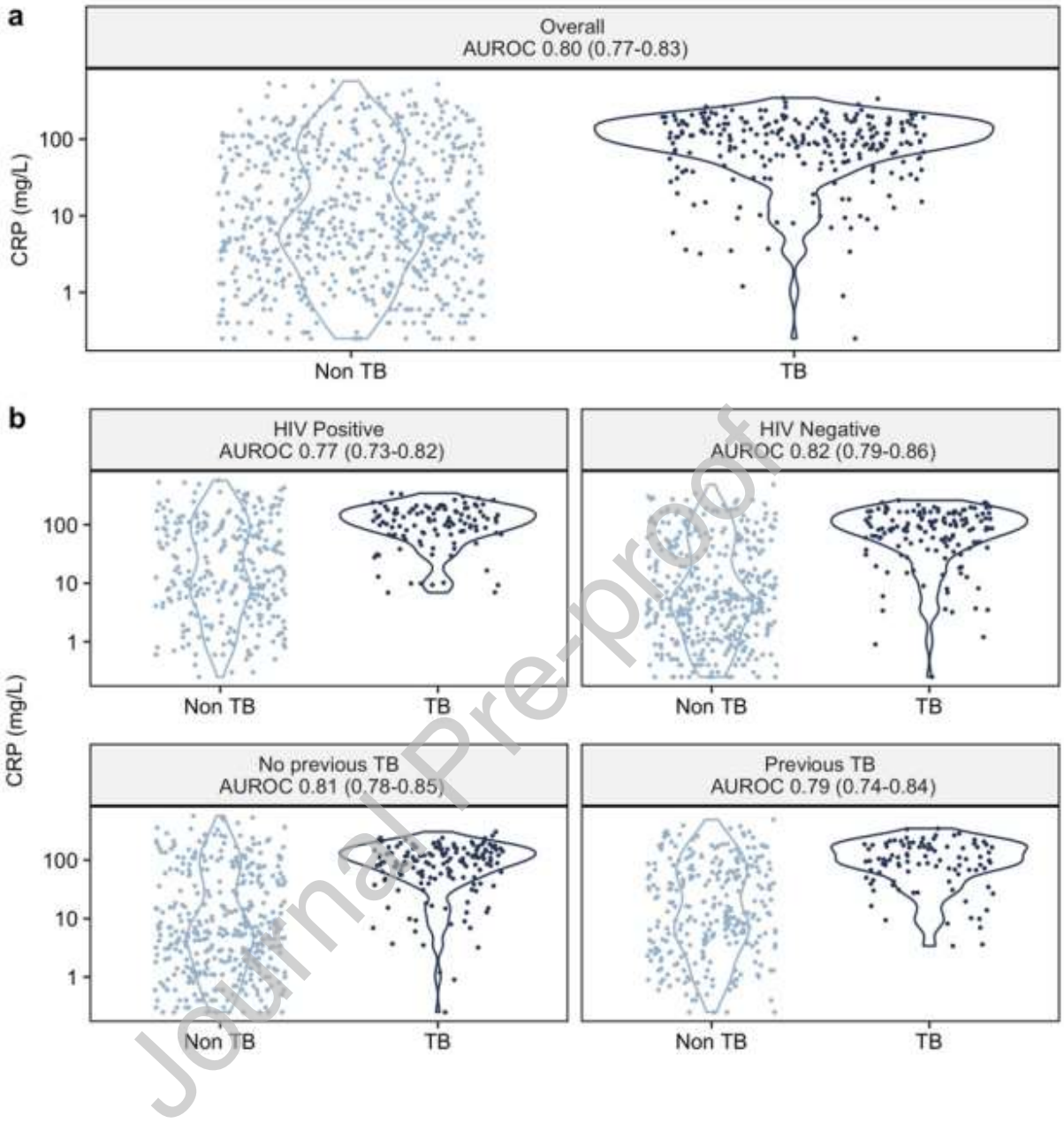

Fig. 2

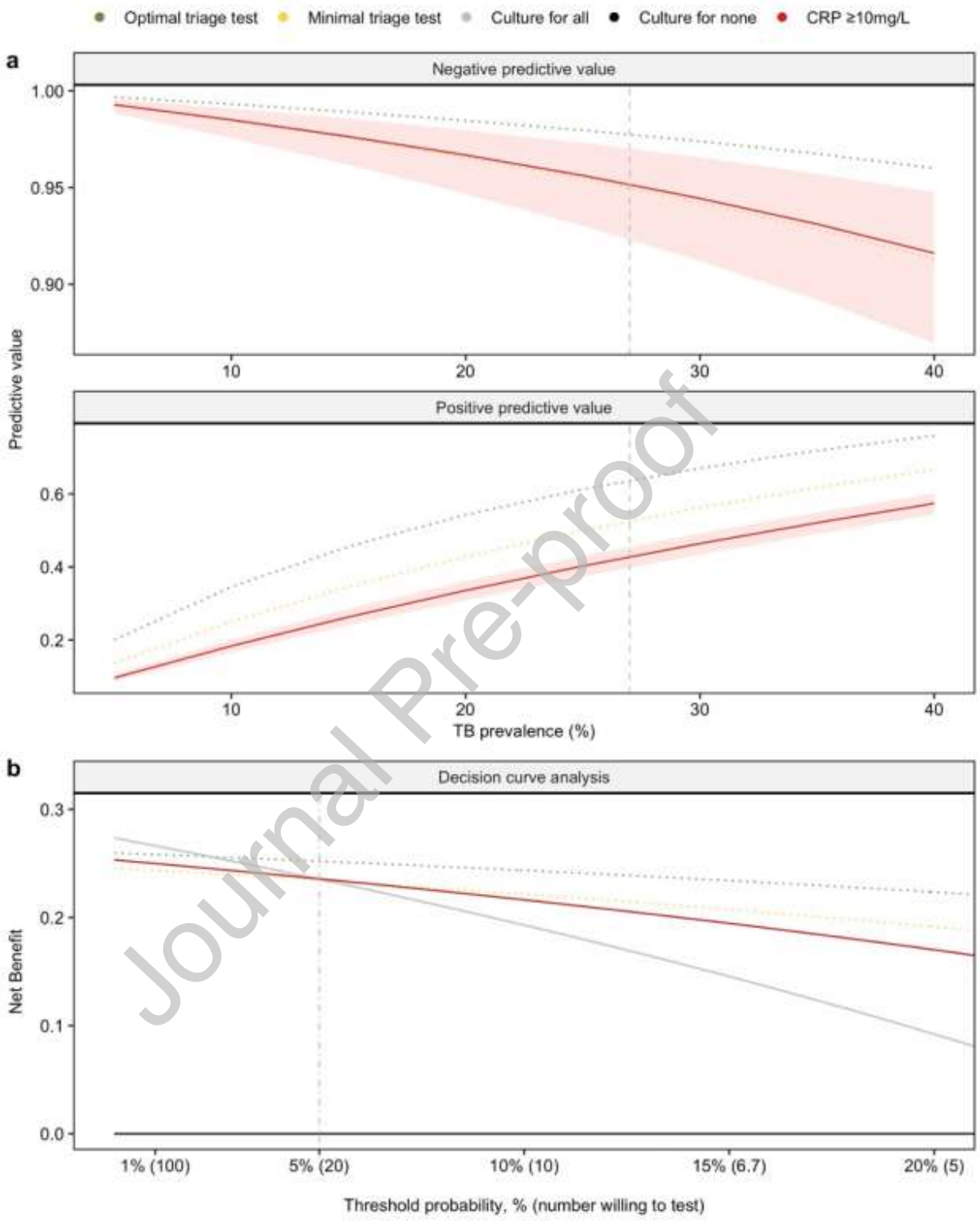

Fig. 3

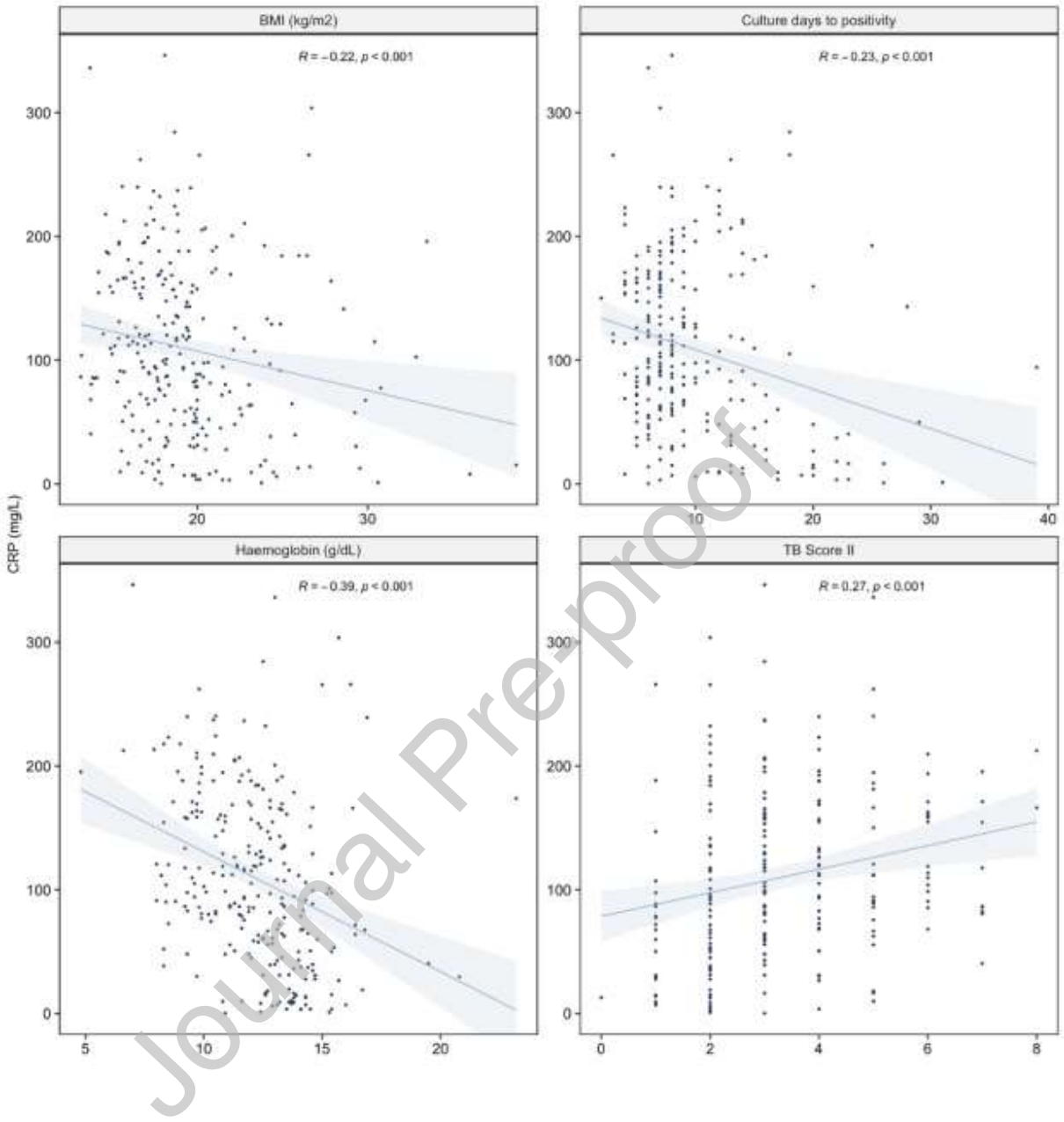

Fig. 4