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C-reactive protein as a triage test in guiding who should get a confirmatory test for pulmonary tuberculosis diagnosis among adults: a case-control proof - of - concept study from urban Tanzania

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C-REACTIVE PROTEIN AS A TRIAGE TEST IN GUIDING WHO SHOULD GET A CONFIRMATORY TEST FOR PULMONARY TUBERCULOSIS DIAGNOSIS AMONG ADULTS: A CASE - CONTROL PROOF - OF - CONCEPT STUDY FROM URBAN TANZANIA

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A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree in Master of Science in Public Health Research at Nelson Mandela African Institution of Science and Technology

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ABSTRACT

The current screening tools for tuberculosis (TB) are inadequate resulting in insufficient TB case detection and continued community transmission of TB. As the world is geared into finding missing TB cases, new strategies are called for to aid in rapid identification of TB cases. This study aimed to evaluate the role C-reactive protein (CRP) in triaging patients to get a confirmatory test for active PTB diagnosis in urban Tanzania. A case-control study was conducted among PTB (PTB) patients and contacts without active PTB. The diagnosis of PTB was performed using GeneXpert MTB/RIF assay and culture. Blood was collected from cases and controls for measuring CRP levels during recruitment. We compared socio-demographic characteristics, clinical and laboratory parameters obtained during recruitment and performed diagnostic accuracy analyses for CRP. Out of all 193 study participants who were involved in final analysis, 147 (76.2%) were males. PTB cases had significantly lower median body mass index (BMI) than controls (median 17.4 kg/m^2 [IQR: 15.8-19.2 kg/m^2] vs., 24.9 kg/m^2 [IQR: 22.1-28.5 kg/m^2), $p < 0.001$). There was no statistical difference in prevalence of human immunodeficiency virus (HIV) between PTB cases and controls i.e., 13.33% vs., 11.7%, $p = 0.48$. CRP was significantly higher in PTB cases vs., controls (median 67.8 mg/L, [IQR: 36.5-116.9 mg/L] vs., 1.55 mg/L, [IQR: 0.59-6.0mg/L], $p = 0.003$). Furthermore, CRP at cut-off ≥ 10 mg/L was associated with adequate combination of sensitivity, specificity and area under the curve (AUC) of 89.9%, 95% CI: 82.2-95.0, 80.9%, 95% CI: 71.4-88.2 and 0.85, 95%CI: 0.80-0.90 respectively. A multivariate logistic regression model adjusted for fever, night sweats and body mass index showed that CRP above 10 mg/L was significantly associated with PTB, adjusted odds ratio (aOR) 5.2, 95% CI 1.2-22.8. C-reactive protein at cut-off ≥ 10 mg/L can be used to screen PTB. These findings can be utilized to improve TB screening algorithm by incorporating CRP in combination with TB symptoms to identify patients who need further confirmatory TB tests. However, additional prospective studies are required to support our findings and contribute into policy recommendations on use of CRP in a screening algorithm for PTB.

DECLARATION

I, Evarist Chiweka declare that this work has been prepared entirely by me and that it has not been submitted, in whole or in part, in any previous application for degree. Besides where explained otherwise by citation or acknowledgments, the document submitted is completely my own.

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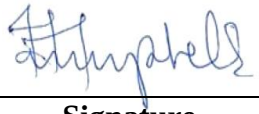
Dr. Jerry Hella		19 July 2022
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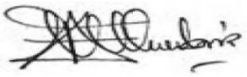
Dr. Francis Mhimbira		19 July 2022
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CERTIFICATION

The undersigned certify that we have read and approve that the dissertation entitled "C-reactive protein as a triage test in guiding who should get a confirmatory test for pulmonary tuberculosis diagnosis among adults: A case-control proof-of-concept study from urban Tanzania" submitted by Evarist Chiweka to Nelson Mandela African Institution of Science and Technology, Tanzania in partial fulfillment of the requirements for the award of Master of Science in Public Health Research is a genuine work done under our guidance.

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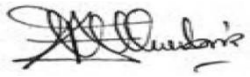
Dr. Francis Mhimbira		19 July 2022
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LIST OF ABBBREVIATIONS

AFB	ACID Fast Bacilli
aOR	Adjusted Odds Ratio
AUC	Area Under Curve
BMI	Body Mass Index
CRF	Case Report Form
CRP	C-reactive Protein
CXR	Chest X-ray
Hb	Haemoglobin
HIV	Human Immunodefiency Virus
IFN-γ	Gamma Interferon
IGRA	Interferon Gamma Release Assay
IHI	Ifakara Health Institute
IOR	Interquatile Range
IRB	Institutional Review Board
LAM	Lipoarabinomannan
LMICs	Low and Middle Income Countries
LTBI	Latent Tuberculosis Infection
MTB	*Mycobacterium Tuberculosis*
NAAT	Nucleotide Acid Amplification Test
NIMR	National Institute of Medical Research
NM-AIST	Nelson Mandela African Institute of Science and Technology
NPV	Negative Predictive Value
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
PTB	Pulmonary Tuberculosis
ROC	Receiver Operating Characteristics

SD	Standard Deviation
SSM	Sputum Smear Microscopy
TB	Tuberculosis
TST	Tuberculin Skin Test
URTI	Upper Respiratory Tract Infection
WHO	World Health Organization
ZN	Ziehl Neelsen

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CHAPTER ONE

INTRODUCTION

1.1 Background of the problem

It is estimated that 10 million people fell ill with tuberculosis (TB) and 1.5 million died of the disease globally in 2018 (World Health Organization [WHO], 2019). Despite the progress made to control the burden of TB worldwide, it is still a leading cause of mortality from infectious diseases group (World Health Organization, 2019). There is a large geographical differences in the burden of TB among the World Health Organizations (WHO) regions, with the highest burden being in the South-East Asia (43%), followed by Africa (25%), Western Pacific (18%) and Eastern Mediterranean (8.3%) (World Health Organization, 2021). As per individual countries, there are still 30 countries which account for 86% of all cases notified in 2020 worldwide (WHO, 2019). Prompt case detection and subsequent start of effective treatment especially in TB high burden countries are among the major strategies for its control (Lönnroth *et al.*, 2010; Teo *et al.*, 2019; Theron *et al*., 2014b; WHO, 2019).

Symptoms and chest radiography are the widely available methods to screen for active TB in most resources limited settings while sputum smear microscopy, mycobacterium culture and molecular Xpert MTB/RIF assay (Cepheid, Sunnyvale, Califormia) are confirmation tests (Boehme *et al*., 2011; Dunn *et al*., 2016; van't Hoog *et al.*, 2014). However, most individuals suspected of having TB based on symptoms screening do not have TB and many bacteriological confirmed PTB patients do not have symptoms that are commonly used in TB screening especially in areas with high prevalence of HIV infection (Ayles *et al.*, 2009; Cheng *et al.*, 2015; Corbett *et al.*, 2010; Hoffmann *et al*., 2013; Hoog *et al.*, 2014; Kim *et al.*, 2012). Therefore, TB diagnostic algorithm strategy which relies on TB symptoms subject a lot of suspects to unnecessary costly confirmatory tests hence calling for alternative TB screening tool especially in TB high burden countries with limited resources.

Inflammatory markers are emerging as tools of choice for TB screening and they can be used at point of care (Wallis *et al*., 2010). C-reactive protein (CRP) is an inflammatory marker whose levels rise significantly in response to infections, a fact that has clinical use (Black *et al.*, 2004; El-Shafey *et al.*, 2015; Skogmar *et al*., 2015). Several observational studies have shown that CRP has high association with TB (Drain *et al*., 2014; Lawn *et al.*, 2001; Mesquita *et al*., 2016; Skogmar *et al*., 2015). However, despite the evidence shown in the previous observations on

the potential of CRP as a TB screening tool, performance of screening tool varies across different settings. It is therefore important to determine performance of CRP as a triage tool for guiding who should get a confirmatory test for PTB in our settings.

We aimed to evaluate the accuracy of CRP in triaging TB suspects who need confirmatory tests for active PTB in an observational study of patients with PTB and controls without PTB in urban Tanzania. To address this need first, baseline characteristic and distribution of CRP and other hematological parameters of PTB cases and controls were compared. Secondly, discriminatory accuracy of CRP and TB symptoms for PTB among adults were determined.

1.2 Statement of the problem

Tuberculosis is a major public health problem worldwide, sub Saharan Africa is bearing the most TB burden together with South East Asia (WHO, 2019). Much efforts have been done by the global TB community to reduce its burden using different strategies associated with significant achievement (Espinal *et al.*, 2000; McNerney *et al*., 2015; Ryu, 2015; WHO, 2019). However, TB incidence rate is declining slowly and it's still a leading cause of mortality among infectious diseases (WHO, 2019).

One of the major drawbacks in TB control is lack of early case detection and early start of effective treatment in TB high burden countries because the current screening tools are ineffective (Huddart *et al.,* 2016). Recent studies have evaluated the performance of non-sputum based tests as TB control strategies (Kik *et al.,* 2014). However, performance of a screening test is determined by local factors (Leeflang *et al.,* 2009). Despite the evidence shown in the previous observations on the role of CRP as a biomarker for TB, performance of screening using CRP has varied across different settings. It is therefore important to determine performance of CRP for screening PTB in our settings and thus improve diagnostic yield of TB case detection.

1.3 Rationale of the study

Diagnosis of TB is a challenge especially in resources limited settings where unfortunately there is a high burden of the disease, which is not matching the limited resources available. The current TB symptom screening has acceptable sensitivity but low specificity particularly in HIV positive patients. Furthermore, symptoms screening depends on skills and clinical acumen of an attending clinician and most often is not fully implemented. Due to its low specificity,

symptoms screening potentially leads to more confirmatory tests than what would be logistically and economically feasible. The CRP, which is already available as an inexpensive, routinely used test has great potential for point of care triaging before PTB confirmation tests due to its good sensitivity and specificity for detection of TB. Hence, CRP might have the potential to become a cost-effective triage test at lower levels of the health care system before a follow-on TB diagnosis. Systematic understanding of CRP performance for triaging in our context will provide valuable information which will aid in formulating diagnostic algorithms which suit our settings to aid in TB diagnosis.

1.4 Research objectives

1.4.1 General objective

The overall objective of this study was to evaluate the performance of CRP in triaging PTB suspects who need confirmatory tests among adults in Temeke district, Tanzania.

1.4.2 Specific objectives

To achieve the above overall objective, the study had 3 specific objectives:

(i) To describe the baseline socio-demographic and clinical characteristics of adult PTB cases and controls.

(ii) To study the distribution of haematological and inflammatory markers among adult PTB cases and controls.

(iii) To determine the discriminatory accuracy of CRP and TB symptoms for PTB among adults at Temeke district, Tanzania.

1.5 Research questions

(i) What are the baseline socio-demographic and clinical characteristics of adult PTB cases and controls?

(ii) How are the haematological and inflammatory markers distributed among adult PTB cases and controls?

(iii) What is the discriminatory accuracy of CRP in triaging PTB suspects among adults?

1.6 Research hypothesis

The research hypotheses are the followings:

(i) That adult PTB cases have distinct socio-demographic characteristics that are different from controls.

(ii) That PTB cases exhibit different distribution of haematological and inflammatory markers as compared to controls without PTB.

(iii) That CRP is elevated among PTB cases than controls and that elevation can have triaging role for TB suspects who need confirmatory tests for PTB among adults.

1.7 Significance of the study

Data from this study is going to inform clinicians on the use of CRP for triaging PTB suspects on who need confirmatory tests for PTB. Specifically, the test will improve the diagnostic yield of TB diagnostics (microscopy and GeneXpert) by ensuring those who need these tests end up getting the test, as opposed to missing this opportunity. Furthermore, it is going to inform health policy decision-makers on formulation of TB diagnosis algorithm in alignment with our context.

1.8 Delineation of the study

This study was in line with global strategies to end TB burden by 2035. Research and development on TB diagnostic tools is a cornerstone of the strategies as early TB diagnosis reduces ongoing transmission and mortality. Haematological inflammatory marker can serves as a non-sputum point of care TB screening tool. Several studies investigated the potential of inflammatory markers as TB biomarkers. This study is first in our context to test performance of screening tool within the environment where it operates. The findings will guide possibility of more large-scale study on this subject.

CHAPTER TWO

LITERATURE REVIEW

2.1 Sputum smear microscopy

Sputum smear microscopy (SSM) is the most available, affordable and cornerstone TB diagnostic in resource limited setting (WHO, 2016). Sputum smear microscopy has several operational advantages over culture and other diagnostic tools. The results are available soon, correlate with infectiousness, and identify patients at high risk of death from tuberculosis if untreated and patients who require more drugs in the initial treatment regimen because of greater bacterial load (Cattamanchi *et al*., 2009). Furthermore, sputum smear microscopy has an important role in follow up of TB treatment. Only when the smears are negative can the intensive phase of the treatment be suspended (Cattamanchi *et al*., 2009). Sputum smear microscopy can be concentrated or directly examined after Ziehl-Neelsen (ZN) staining by convectional microscopy or fluorescence microscopy. Concentrated SSM increase yield and its sensitivity increased by approximately 12% (Chandra *et al*., 2013).

Fluorescence microscopy is on average 10% more sensitive than conventional microscopy (Steingart *et al*., 2006). The main shortcomings of fluorescence microscopy are relatively high costs of the microscopy unit and its maintenance costs compared with the conventional microscopy unit (Dzodanu *et al.,* 2019). To ensure accurate diagnosis, the quality and number of collected specimens are important aspects that may affect diagnostic results. In that regard it was observed that average sensitivity of the first slide is 53.5% which may increase to 64.9% following the addition of the second slide, but not further with a third slide. These findings apply to HIV-positive and negative patients and have prompted WHO to propose deduction of specimen numbers for examination in settings with well-established laboratory networks (Islam *et al.,* 2013). However, the sensitivity of sputum smear microscopy is very variable varying between 20% and 60%. Smear-negative tuberculosis has been associated with poor treatment outcomes, including death, especially in areas with high prevalence of HIV (De Castro *et al*., 2018; Rieder *et al*., 2007).

2.2 Mycobacterium tuberculosis culture

Mycobacterium tuberculosis (MTB) culture is regarded as the gold standard TB diagnostic test and used widely as a reference to assess performance of other TB diagnostic tools (Rewata *et*

al., 2009). Mycobacterium culture exists in varieties of forms such as solid culture or liquid culture with various modifications and performances. Generally, liquid culture has on average better MTB culture recovery with shorter turnaround time compared to conventional solid culture methods. However, it suffers more contamination rate (Diriba *et al*., 2017; Hanna *et al*., 1999; Lee *et al*., 2003). The MTB culture can simultaneously be used to test drug resistance, a growing concern in a fight against the disease (Makamure *et al*., 2013; Mekonnen *et al*., 2019). The major drawbacks of MTB culture are time consuming and the need for biosafety and training requirements. Furthermore, culture capacity is limited in underserved remote areas in TB high burden countries (Huddart *et al*., 2016).

2.3 Immune-based tests for TB

Immune-based tests are widely available and have potential for suitability in resource limited settings because they are faster and simpler to perform (Perkins *et al.,* 2006). Tuberculin skin test (TST) and gamma interferon (IFN-γ) release assay (IGRA) indicate a cellular immune response to MTB. Both tests are useful in diagnosing TB infection but they are not capable of accurately differentiating between latent TB infections (LTBI) and active TB. Furthermore, they have reduced sensitivity in patients with any kind of immunosuppression as well as low specificity in TB high burden countries (Joshi *et al*., 2011). Humoral immunity based tests have inconsistency performance, while tests to detect antigen in specimens other than blood are useful in subgroups of TB patients (Boehme *et al*., 2005).

2.4 Nucleic acid amplification tests (NAATs)

Recently there is a huge development in tests that depend on detection and amplification of a targeted region of MTB genome, particularly those using real-time polymerase chain reactions (PCR) testing platforms (Dicks & Stout, 2019; Laraque *et al.,* 2009). Compared to conventional PCR which need well trained technical staff and sophisticated equipment, real time PCR platforms have the potential for reducing turn around-time, automation of the procedure and point of care utilization (Bainomugisa *et al*., 2015; Carniel *et al*., 2014; Lv *et al.,* 2017).

In 2011, WHO endorsed the use of Xpert MTB/RIF assay for simultaneous detection of MTB and rifampicin resistance mutations. This test is a fully automated molecular technology using real time PCR which is supposed to provide result within 2 hours and has a potential of use close to point of care (Albert *et al*., 2016; Cox *et al*., 2014; McNerney *et al*., 2015). Different studies have demonstrated that Xpert MTB/RIF assay has high sensitivity and increased case

detection rate compared with sputum smear (Chikaonda *et al.*, 2017; Matabane *et al.*, 2015). However, despite its proven high accuracy several groups have demonstrated controversial findings on its impact on morbidity and mortality due to TB at patient and population level (Albert *et al*., 2016; Di Tanna *et al*., 2019; Theron *et al*., 2014a).

2.5 C-reactive protein

C-reactive protein (CRP) is an acute-phase protein found in serum that is elevated in presence of tissue damage, infection, inflammation and malignancy, a fact that is utilized in clinical practices. It was shown that its rise in response to TB infection is independently of HIV (Lawn *et al*., 2001; Skogmar *et al*., 2015; Wallis *et al*., 2010). Several groups have demonstrated that serum CRP levels have a positive association for the presence of PTB (Lawn *et al.*, 2013). Recently, studies are evaluating CRP as potential non-sputum based biomarker for TB diagnosis and monitoring its treatment response (Santos *et al*., 2019).

One cohort study in South Africa showed a rise in CRP levels above a pre-set level of the upper limit of normal corresponded to a sensitivity of 98% and specificity of 59% for diagnosing either smear negative or culture-positive PTB (Wilson *et al.*, 2011). Another South African study conducted among HIV infected patients showed that CRP had excellent negative predictive value (NPV) at very low CRP levels < 1.5 mg/L and again vey excellent positive predictive value (PPV) at very high levels > 400 mg/L (Lawn *et al*., 2013). However, performance of a screening tool was influenced by environment and prevalence of the disease (Leeflang *et al.*, 2009).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study design

This was a case-control study nested within an ongoing tuberculosis cohort study in Dar es Salaam (TB DAR) where samples of cases and controls were tested for CRP and other inflammatory markers. The TB DAR cohort study was initiated in October 2013.

3.2 Study setting

The TB DAR cohort study site is in Temeke district of Dar es Salaam, the economic capital of Tanzania. Dar es Salaam has approximately 4.4 million people and notifying 22% of all TB cases in Tanzania (Ministry of Health Community Development, Gender, 2018).

3.2.1 Selection of study participants

Participants included were adults (≥ 18 years) sputum positive for geneXpert and culture TB patients (TB cases) and controls that did not have active disease excluded by negative geneXpert and culture results. Among 359 PTB patients recruited between 2014 and 2015, a convenience sampling method was used to get 103 PTB cases and 103 controls. Controls were household contacts exposed to a PTB cases but without active disease. The selection procedure matched participants by age and sex. The final analysis was restricted to 193 participants i.e., 99 (51.3%) PTB cases and 94 controls, for which laboratory data from serum CRP and sputum samples examination were available.

3.3 Study procedures and data collection

All participants were clinically evaluated during recruitment as either PTB cases or controls after ruling out presence of active PTB among controls. Socio-demographic data, clinical data and biological samples were collected at the time of recruitment. Serum samples were taken at the time of PTB diagnosis before starting TB treatment (TB cases) or at the time of recruitment (controls) and stored at -80 ˚C. GeneXpert MTB/RIF (Cepheid, Sunnyvale, California, United States of America) was used to rule out PTB in controls. During recruitment, we collected urine and stool for diagnosis of helminths as well as nasopharyngeal swabs (Copan, USA) to detect respiratory viruses and bacteria.

3.4 Laboratory procedures

We used extensive laboratory techniques to evaluate the presence of various soil transmitted helminths from urine and stool samples. Kato-Katz method (in triplicates), Baermann technique (in duplicates), urine filtration (in duplicates), and circulating cathodic rapid antigen test (POC-CCA; Rapid Medical Diagnostics, South Africa) were used to diagnose helminths (*Strongyloides stercoralis, Trichuris trichiura, Schistosoma mansoni, Schistosoma. haematobium, Ascaris lumbricoides*).

Sputum samples from TB cases and controls were collected and stored at 4° Celsius and transported in temperature-controlled cool boxes to a biosafety level 2+ laboratory at Bagamoyo Research and Training Center, IHI. Specimens were homogenized and decontaminated using N-acetyl L-cysteine Sodium Hydroxide and then incubated according to standard procedures on Löwenstein-Jensen medium and read once each week until there was MTB growth otherwise they were declared as negative after 8 weeks. In case of MTB growth, the isolate was subject to a Capilia TB/MPT64 antigen test to confirm the presence of MTB complex species.

Nasopharyngeal swabs were analyzed to detect presence of respiratory pathogens using a multiplex real-time PCR with a broad panel of 16 viral (Anyplex II RV16) and seven bacterial (Allplex panel 4) respiratory pathogens (Supplementary material 1) according to the manufacturer's instructions (Seegene, Seoul, South Korea).

Haematological tests were performed immediately after sample collection when possible while those tests which needed specialized laboratory and not available within the country were stored at -80 °C until shipping them to Switzerland. The HIV screening was done using Alere Determine HIV rapid test, and the Uni-gold HIV (Trinity Biotech, USA) rapid test served as a confirmatory test in case of a positive screening test. Full blood counts were done with a MS4 Vet hematology analyzer (Diamond Diagnostics, Massachusetts, USA) at the Temeke Regional Referral Hospital laboratory. All analyses for acute phase inflammatory parameters were performed at the Labor Risch, Bern (Switzerland) using the Siemens Nephelometer BN II (soluble transferrin receptor) and the Cobas 6000, Roche diagnostics, Switzerland.

3.5 Definitions

World Health Organization (WHO) criteria were used to classify anemia: anemia (hemoglobin [Hb] ≤ 13.0 g/dL for men, ≤ 12.0 g/dL for women). A CRP cut- off of ≥ 10 mg/L was used to indicate presence of active TB vs., < 10 mg/L indicated absence of active PTB (Yoon *et al.*, 2017). Helminth infection was defined as infection with any helminth species, and respiratory infection as detection of any respiratory viral or bacterial pathogen. PTB symptoms were classified as the presence of fever, weight loss, and night sweats. BMI ≤ 18.5 kg/m² was used to indicate underweight. The outcome variable or target condition of interest was PTB. Predictor variables were CRP levels ≥ 10 mg/L, fever, night sweat and BMI category (underweight vs., over weight). Reference test was positive culture and index tests were CRP concentration cut-offs (CRP ≥ 5 mg/L, CRP ≥ 10 mg/L, CRP ≥ 15 mg/L, CRP ≥ 20 mg/L and CRP ≥ 25 mg/L).

3.6 Statistical analysis

Socio-demographic characteristics, clinical and laboratory parameters of PTB cases and controls were compared with data obtained during recruitment. Wilcoxon rank-sum test or Student's *t*-tests were used for comparison of values of continuous variables while chi-square or Fisher's exact tests for comparison of values of categorical variables. We evaluated utility and accuracy of different CRP concentration cut-offs for PTB discrimination using sensitivity, specificity and receiver operating characteristic curves. We used odds ratios and 95% confidence interval associated with CRP cut-off ≥ 10 mg/L and TB symptoms to determine their role in predicting PTB cases using univariate and multivariable logistic regression analyses. All statistical tests were two-sided, and we set threshold of a statistically significant difference at an alpha level of 0.05. We performed all analyses using Stata version 15.1 (Stata corporation, Texas, USA).

3.7 Ethics considerations

This was an observational study without any intervention to study participants. The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong and South Africa), the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceutical for Human Use (ICH) guidelines, and the laws and regulations of the United Republic of Tanzania.

Only volunteers were included in the study where each participant received written information about the study and the information was explained in presence of a witness, if required. Among all participants, an informed consent was obtained from each participant prior to any study procedure being done. Study participants were informed of their right to withdraw from the study at any time without providing any explanation and that their withdrawal will not affect any clinical care that they were to receive. Lastly, all study records were properly kept maintaining confidentiality and were not made publicly available. All laboratory specimens and clinical forms were identified by coded numbers only.

The study was approved by the institutional review board of the Ifakara Health Institute (IHI, reference number IHI/IRB/04-2015), the Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania (NIMR, reference number NIMR/HQ/R.8c/Vol. I/357) and the Ethics Committee of the Canton of Basel (EKNZ, reference number UBE-15/42). All participants gave written informed consent before enrolment.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Study population and clinical characteristics

The median age of study population was 32.7 years (interquartile range [IQR] 26.5–40.0); and 147 (76.2%) were males out of all 193 recruited study participants who were involved in final analysis. Overall, the median body mass index (BMI) at the time of recruitment was 20.1 kg/m^2, IQR 17.3-25.1 kg/m^2. PTB cases had significantly lower median BMI than recruited controls (median 17.4 kg/m^2 [IQR: 15.8–19.2 kg/m^2] vs., 24.9 kg/m^2 [IQR: 22.1–28.5 kg/m^2), $p < 0.001$) (Table 1).

The prevalence of HIV infection among study participants was 12.44%, with no any statistical difference in prevalence of HIV between PTB cases and controls i.e., 13.33% vs., 11.7%, $p = 0.48$. We found a higher prevalence of helminths infections among PTB cases than controls i.e., 32.2% vs., 21.28%, however this difference in prevalence between the two study groups were not significantly different. *Strongyloides stercoralis* contributed more into the burden of soil transmitted helminths among PTB cases than controls i.e., 22.22% vs., 9.57%, $p = 0.019$. PTB cases recruited in our study frequently reported PTB symptoms with weight loss reported by all PTB cases, $p < 0.001$ (Table 1).

4.2 Hematological characteristics and acute phase proteins

The overall median CRP concentration was 18.7 mg/L (IQR 1.4–80 mg/L) where this biomarker was significantly higher in PTB cases compared to controls (median 67.8 mg/L, IQR 36.5– 116.9 mg/L vs., 1.55 mg/L, IQR 0.59–6.0, $p = 0.003$). C-reactive protein when used at a cut - off of 10 mg/L could statistically differentiate active PTB vs., no active PTB disease among adults recruited (Table 2). Similarly, the average hemoglobin (Hb) level was 12.3 mg/dL ± 2.18 mg/dL and it was found that PTB cases were more likely to have lower average Hb levels than controls (mean 11.8 mg/mL ± 2.1 mg/dL vs., 12.8 mg/mL ± 2.1 $p = 0.001$). Serum ferritin levels were higher in PTB cases than in controls (median 355.5 µg/L vs., 103.5 µg/L, $p<0.001$).

Furthermore, serum albumin levels at the time of PTB diagnosis and recruitment of controls was significantly lower among PTB cases than among controls (mean 28.58 ± 6.14 g/L vs., 39.25 ± 5.54 g/L, $p < 0.001$, (Table 2).

Table 1: Baseline socio-demographic and clinical characteristics of adult PTB cases and controls at Temeke, Dar es Salaam

Characteristics	All, n = 193 (100%)	Controls, n = 94 (48.7%)	PTB cases, n = 99 (51.3%)	*P*-value
Age, years, median (IQR)	32.7 (26.5-40)	32.7 (26.5-39.3)	33 (26-40)	0.98††
Sex, n (%)				0.59§
Female	46 (23.8)	24 (25.5)	22 (22.2)	
Male	147 (76.2)	70 (74.5)	77 (77.8)	
BMI, kg/m², median (IQR)	20.1 (17.3-25.1)	24.9 (22.1-28.5)	17.4 (15.8-19.2)	< 0.001††
BMI category, n (%)				< 0.001§§
Underweight	73 (37.8)	6 (6.38)	67 (67.68)	
Normal weight	71 (36.8)	41 (43.62)	30 (30.30)	
Overweight	34 (17.6)	32 (34.04)	2 (2.02)	
Obese	15 (7.8)	15 (15.96)	-	
Education, n (%)				0.403§§
No formal education	36 (18.65)	15 (15.96)	21 (21.21)	
Primary	117 (60.62)	62 (65.96)	55 (55.56)	
Secondary	31 (16.06)	12 (12.77)	19 (19.19)	
University	9 (4.66)	5 (5.32)	4 (4.04)	
Occupation, n (%)				0.031§§
Housewife	14 (7.29)	5 (5.38)	9 (9.09)	
Unskilled labor	17 (8.85)	7 (7.53)	10 (10.10)	
Semiskilled manual	63 (32.81)	36 (38.71)	27 (27.27)	
Semiskilled non-manual	76 (39.58)	32 (34.41)	44 (44.44)	
Student	4 (2.08)	-	4 (4.04)	
Unemployed	18 (9.38)	13(13.98)	5 (5.05)	
Income ($), mean ± SD	85.99 ± 73.53	91.18 ± 96.58	81.07 ± 41.12	0.341†
Cigarette smoking, n (%)	39 (20.21)	14 (14.89)	25 (25.25)	0.073§
HIV infection, n (%)	24 (12.44)	11 (11.70)	13 (13.13)	0.48§
Helminthiasis, n (%)	52 (26.94)	20 (21.28)	32 (32.32)	0.084§
Strongyloidiasis	31 (16.06)	9 (9.57)	22 (22.22)	0.019§§
Schistosomiasis	11 (5.70)	5 (5.32)	6 (6.06)	1.0
URTI, n (%)				
Bacterial, (n=124)	58 (46.77)	18 (62.07)	40 (42.11)	0.059§
Viral	42 (21.76)	18 (19.15)	24 (24.24)	0.391§
TB Symptoms, n (%)				
Night sweats	108 (55.96)	12 (12.77)	96 (96.97)	< 0.001§§
Fever	111 (57.51)	17 (18.09)	94 (94.95)	<0.001§§
Weight loss	114 (59.07)	15 (15.96)	99 (100)	<0.001§§

n, number; SD, standard deviation; IQR, Interquartile range; †Student *t* test †† Wilcoxon rank sum test; § Pearson Chi-squared test; §§Fisher's exact test; USD, United States Dollars (1 USD=2,171 Tanzanian Shillings, June 2016)

Table 2: Distribution of hematological acute and chronic inflammatory markers and disease status among PTB cases and controls at Temeke, Dar es Salaam

Serum parameters	No. included* Controls / Cases	Controls, n = 94 (48.7%)	PTB cases, n = 99 (51.3%)	*P*-value
CRP, mg/L, median (IQR)	94 / 99	1.55 (0.59-6)	67.8 (36.5-116.9)	<0.001††
Haemoglobin, g/dL, mean ± SD	94 / 99	12.8 ± 2.1	11.8 ± 2.1	0.001†
PTB disease by CRP, n (%)	94 / 99			<0.001§§
No active disease		76 (80.85)	10 (10.10)	
Active disease		18 (19.15)	89 (89.90)	
Ferritin, µg/L, median (IQR)	89 / 99	103.5 (59.5-159.5)	355.3 (162.2-642.7)	<0.001††
Albumin, mean ± SD	94 / 99	39.25 ±5.54	28.58 ± 6.14	<0.001†

n, number; SD, standard deviation; IQR, Interquartile range; †Student *t* test,††Wilcoxon rank sum test; § Pearson Chi-squared test;§§Fisher's exact test; sTfR, soluble transferrin receptor; CRP, C-reactive protein

* Participants with available inflammatory serum parameters

Table 3: Performance characteristics of different CRP cut-offs for PTB suspects triage among adults at Temeke, Dar es Salaam

Cut point mg/dl	Sensitivity, (95% CI)	Specificity, (95% CI)	AUC, (95% CI)
5 mg/L	93.9%, (87.3-97.7)	69.1%, (58.8-78.3)	0.815, (0.763-0.868)
10 mg/L	89.9%, (82.2-95.0)	80.9%, (71.4-88.2)	0.854, (0.804-0.904)
15 mg/L	86.9%, (78.6-92.8)	85.1%, (76.3-91.6)	0.859, (0.811-0.909)
20 mg/L	85.9%, (77.4-92.0)	89.4%, (81.3-94.8)	0.876, (0.829-0.923)
25 mg/L	84.8%, (76.2-91.3)	89.4%, (81.3-94.8)	0.871, (0.824-0.918)

CI, Confidence interval; AUC, Area under the curve

4.3 Test characteristics of different CRP concentration thresholds and logistic regression analyses

We evaluated the utility of different concentration thresholds of CRP and their use in triaging in and out PTB cases using gradual increase of cut - offs from 5 mg/L to a 25 mg/L. CRP at cut - off ≥ 5 mg/L was associated with sensitivity, specificity, and AUC of 93.9%, 95% CI: (87.3 - 97.7), 69.1%, 95% CI: (58.8 - 78.3) and 0.82, 95% CI: (0.76 - 0.87) respectively. Increasing CRP cut-off to ≥ 10 mg/L was associated with sensitivity, specificity and AUC of 89.9%, 95% CI: (82.2 - 95.0), 80.9%, CI: (71.4 - 88.2) and 0.85, 95% CI: (0.80 - 0.90) respectively. CRP cut-offs values of ≥15 mg/L, 20 mg/L and 25 mg/L were associated with increasing specificity and AUC. However, increasing cut - offs are associated with gradual decreasing sensitivity (Table 3 and Fig. 1)

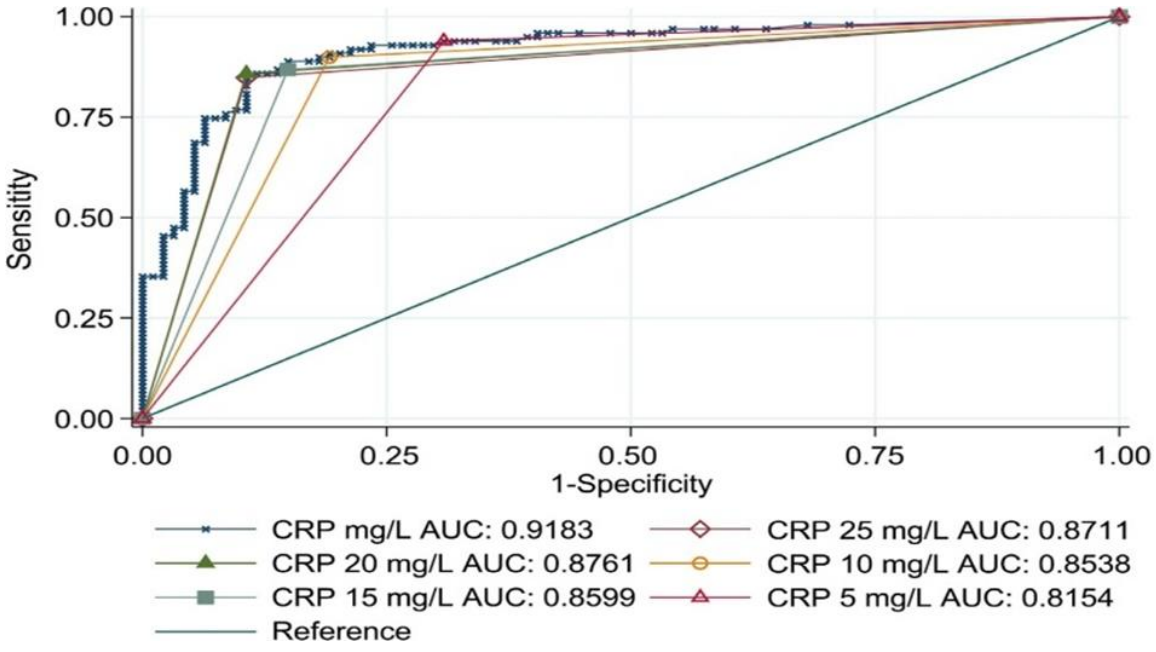

Figure 1: Receiver operator characteristic (ROC) curves for different CRP cut-offs for PTB suspects triage among adults in Temeke, Dar es Salaam

In univariate logistic regression analysis underweight, night sweats, fever and CRP ≥ 10 mg/L were significantly associated with PTB cases (odds ratio [OR] for underweight 15.3, 95% CI: 5.9 - 39.8; OR for night sweats 218.7, 95% CI: 59.7 - 801.6; OR for fever 85.2, 95% CI: 30.0 - 241.3; OR for CRP ≥ 10 mg/L 37.6, 95% CI: 16.4 - 86.3). In a multivariate logistic regression all symptoms remained significantly associated with PTB cases (adjusted odds ratio [aOR] for underweight 9.2, 95% CI: 1.4 - 61.5; aOR for night sweats 9.7, 95% CI: 1.9 - 49.9; aOR for fever 85.2, 95% CI: 30.0 - 241.3, and aOR for CRP ≥ 10 mg/L 5.2, 95% CI: 1.2-22.8) (Figs. 2 & 3).

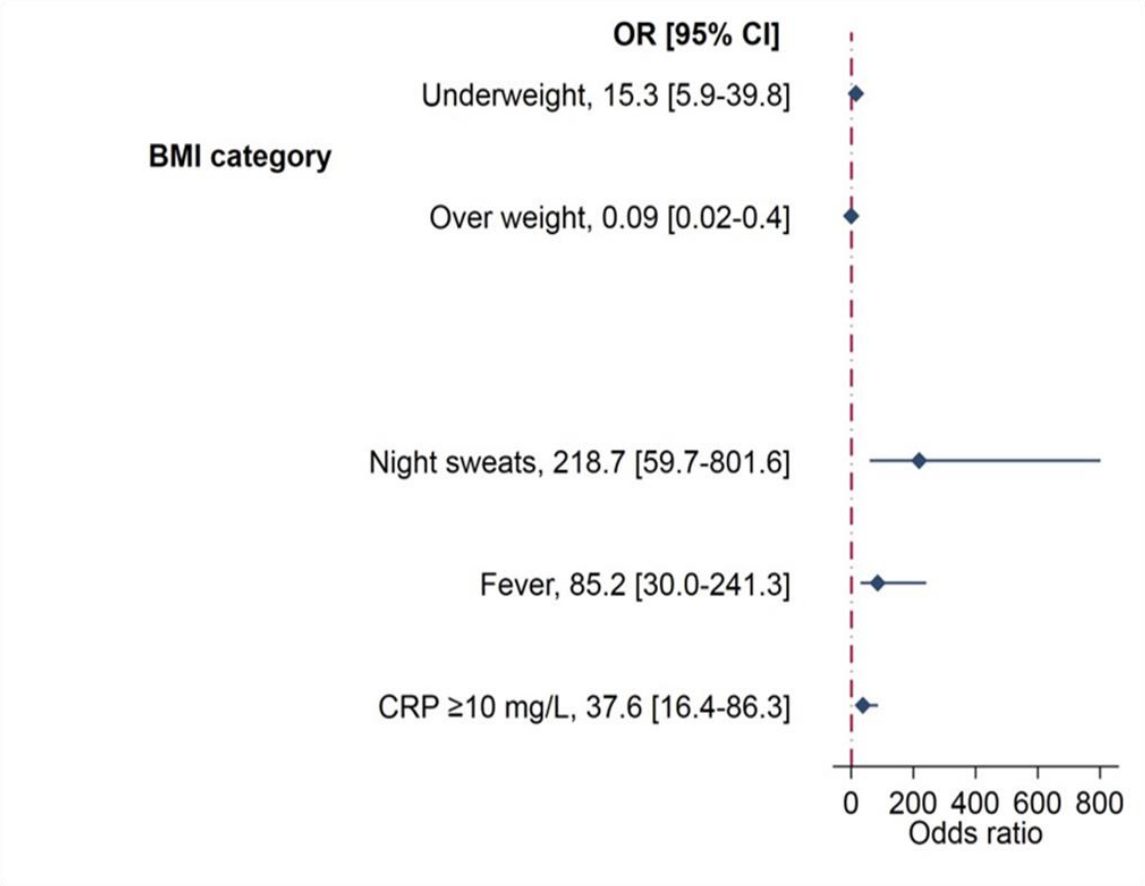

Figure 2: Univariate logistic regression analyses for CRP cut-off ≥ 10 mg/L and PTB symptoms

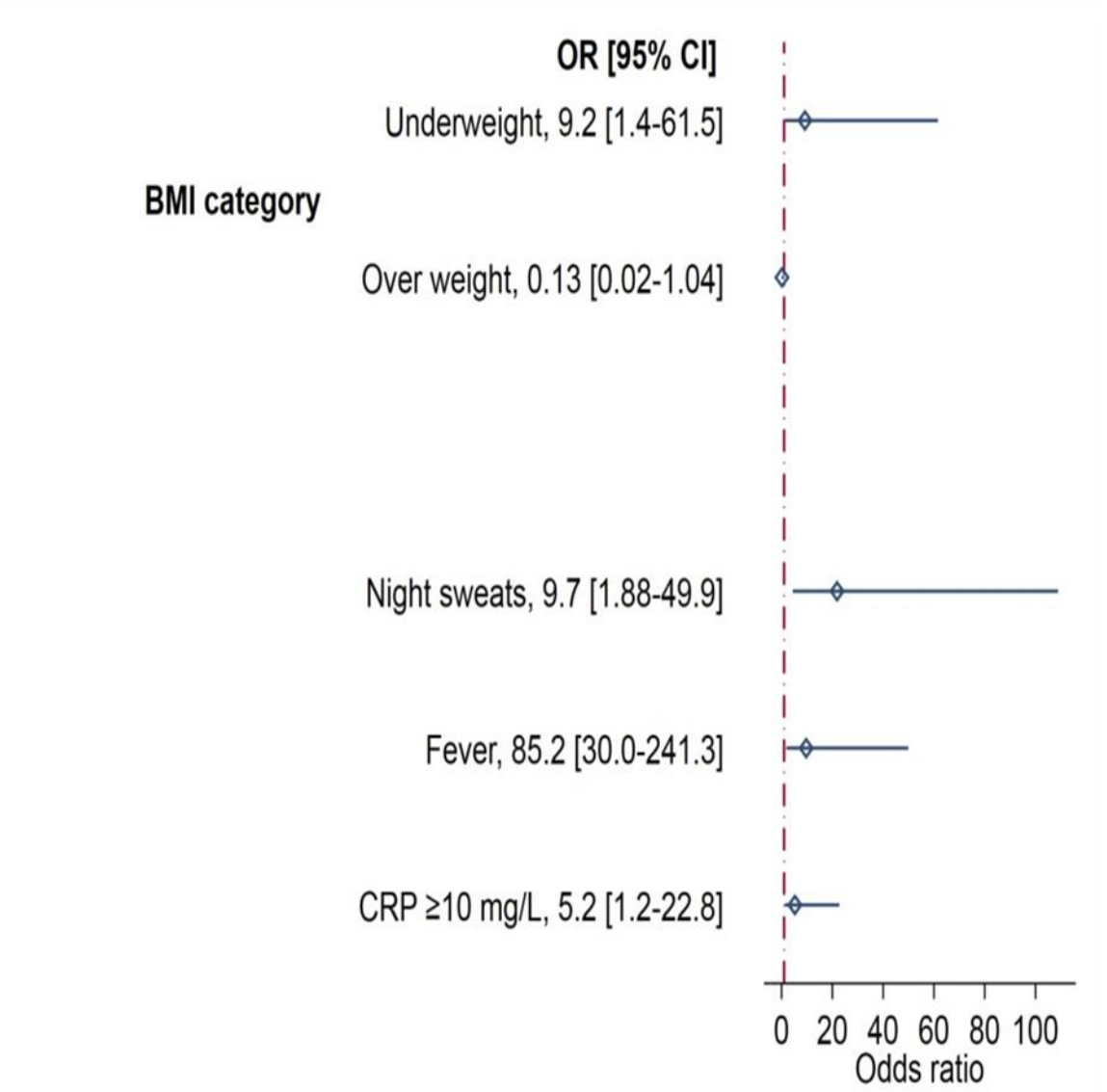

Figure 3: Multivariate logistic regression analyses for CRP cut-off ≥ 10mg/L and PTB symptoms

4.4 Discussion

In this observational study of adult PTB cases and controls in urban Tanzania, we assessed the utility of CRP threshold concentrations in identifying adult PTB cases who will be subjected to confirmatory PTB diagnostics. We demonstrated that CRP conc. ≥ 10 mg/L and TB symptoms can predict PTB cases. These findings are of clinical relevant because CRP can easily be measured and utilized at point of care (Ward, 2018). Furthermore, night sweats, fever and nutritional status are routinely sought by clinicians when evaluating patients.

The findings on association of CRP and PTB are in agreements with other observations elsewhere. Lawn and his colleagues in South Africa demonstrated CRP ≥ 10 mg/L have been

associated with relatively high sensitivity of 85.2% and can reliably rule out active PTB (Lawn *et al.*, 2013). Another study in Ethiopia demonstrated high mean concentration of serum CRP in PTB cases 36 μg/ml compared to controls 0.5 μg/ml (Skogmar *et al*., 2015). However, raised CRP might have been caused by other diseases processes, notably intestinal parasites and respiratory infections (Harrison, 2015; Sbong & Feldman, 2015). Thus, other diseases should be considered and looked for in a patient with significantly raised CRP levels. In the present study we addressed the impact of helminthiasis and respiratory infections on serum levels of CRP. We found no statistically significant differences in frequencies of their distribution in the two groups. These findings were in contrary to observations from other studies. Studies in Tanzania and Ethiopia demonstrated high co-existence of PTB and helminthiasis (Alemu *et al*., 2019; Mhimbira *et al*., 2017). It is known that both diseases have impact on cellular mediated immunity and influence the natural course of one another (Elias *et al.*, 2006). However, similar prevalence in present study could be partially explained by several factors. First, our study setting is urban which is characterized by low exposure to worms and high literacy associated with frequent practice of de-worming. Second, our study participants were recruited from same environment. Last, our two groups have similar distribution of socio-demographic characteristics, which are important determinants of helminthiasis (Hotez, 2014; Id *et al.*, 2019).

The major different in our study is equal prevalence of HIV infection in cases and controls, *i.e.*, 13.33% vs 11.7%. This is in disagreement with the fact that the two diseases are closely related. Previous studies in PTB have reported higher rates of HIV infection and patterns of co-existence were described in many places. Studies in Tanzania observed high prevalence of TB-HIV co-infection (Gunda *et al*., 2018; Ngowi *et al.*, 2008). Similar observations of high prevalence were demonstrated in India (Giri *et al.*, 2013; Manjareeka & Nanda, 2013). Meta-analysis of studies done in Sub-Saharan Africa demonstrated a very high prevalence (34.4%) of HIV infection among PTB patients (Gelaw *et al.*, 2019). However, overall prevalence of HIV in our study population is higher than Tanzanian general population (TACAIDS, 2016). The similar distribution in HIV prevalence between PTB cases and controls can be partly explained by overly selection of study participants of a case-control study design.

Importantly, data from this study demonstrated that CRP at ≥ 10 mg/L is associated with adequate sensitivity and specificity for triaging PTB suspects who need confirmatory tests, while higher cut-off values were associated with increasing specificity in expenses of

sensitivity. Our findings are similar to other observations. Lawn and his colleagues in South Africa also demonstrated that CRP of ≥ 10 mg/L had a sensitivity of 85.2% and can reliably rule out active PTB (Lawn *et al*., 2013). Again, our test characteristics at CRP ≥ 10 mg/L are in line with WHO recommendation for performance of TB triage biomarker test (WHO, 2014). It recommends for non-sputum biomarker triage test for PTB should have sensitivity of > 90% and sensitivity of > 80%. A test with adequate sensitivity and specificity to operate in settings of high burden of a disease has good positive and negative predictive values. However, the current TB symptoms screening has acceptable sensitivity but low specificity particularly in HIV positive patients which potentially leads to more confirmatory tests than what would be logistically and economically feasible. Therefore, CRP at concentration of ≥ 10 mg/L reliably triage PTB suspects in settings with high TB burden help narrow the population that needs costly confirmatory tests.

The observed association between PTB and TB symptoms in our study has been described by other groups. One group in Kenya, 75%, 100% and 83% of PTB cases reported fever, night sweats and weight loss respectively, while in South Africa another group reported 78%, 78% and 100% of the symptoms respectively (Brennan *et al*., 2020). Furthermore, another observation in China reported that TB symptoms were found in 75.8% of cases (Chen *et al*., 2019). The relationship between PTB and nutritional status is known for years. Underweight is a well-recognized risk factor for PTB and PTB can lead to underweight. Night sweats and fever are non-specific symptoms of TB as well as constitutional symptoms of many disease processes. However, symptoms alone have been shown to be less reliable for PTB especially in areas with high prevalence of HIV infection. It is estimated that the prevalence of PTB among suspects with TB symptoms is relatively low (van't Hoog *et al.*, 2014). Therefore, data from our study are informing that CRP at cut-off ≥ 10 mg /L in combination with TB symptoms is a feasible diagnostic algorithm that can increase effectiveness and impact on the ongoing transmission, mortality and morbidity.

In spite of the findings of this study, there are limitations which need to be addressed. First, we could not exclude all possible disease processes that might be responsible for rise in CRP. Second, the study was done in urban setting where the patient population might differ from other rural primary care settings. Third, the present study suffered from small sample size because of the convenient sample of participants who had results of CRP and who were available but this was due to lack of sufficient budget to do these hematological analyses for a

larger sample size. Lastly, the selection of household controls were not ideal, preferably controls should have been adults seeking health care at hospital who do not have active PTB. Thus future studies can draw some positives from our study and address the weaknesses we encountered to further generate the utility of CRP for triaging PTB patients for definitive diagnostics.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In conclusion, the current study demonstrated a high potential for CRP at concentration of ≥ 10 mg/L to triage adult PTB suspects who need confirmatory tests.

5.2 Recommendations

Based on study findings, the following recommendations are made:

(i) C-reactive protein can be used to triage patients for a definitive PTB diagnosis at point of care settings.

(ii) C-reactive protein can be incorporated in PTB testing algorithm for adult patients in our settings.

(iii) Large scale pragmatic trial should be carried to further evaluate the triage potential of CRP in real-time settings to further prove our findings.

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APPENDICES

Appendix 1: Detection of respiratory viral and bacterial pathogens using a multiplex real-time PCR in nasopharyngeal swabs

Viral species	**Bacterial species**
Anyplex II RV16 (panels A and B)	Allplex respiratory panel 4
Adenovirus	*Mycoplasma pneumonia*
Influenza A/B	*Chlamydophila pneumonia*
Rhinovirus A/B/C	*Legionella pneumophila*
Respiratory syncytial virus A/B	*Haemophilus influenza*
Parainfluenza virus 1/2/3/4	*Streptococcus pneumoniae*
Bocavirus 1/2/3/4	*Bordetella pertussis*
Metapneumovirus	*Bordetella parapertussis*
Coronavirus 229	
Coronavirus OC4	
Coronavirus NL63	
Enterovirus	

Appendix 2: Case report form

CRF : Recruitment			
Demographics			
	Date of interview	|___|___| |___|___| |___|___|___|___|	*DD/MM/YYYY*
	Patient ID and visit No.	|___|___|___|___|___|-|___|___|-|___|___|___|	*Scan from the barcode for the specified visit. i.e. VO1, VO2, VO3*
	District	_____	*District where the patient originates*
	Facility	☐Wailes I ☐Wailes II (PASADA) ☐Wailes II	
	TB district number	|__|__|__|__|/|_K_|/|__|__|__|__|/|__|__|__|__|	*TB district number*
	Date of birth	|___|___| |___|___| |___|___|___|___|	*DD/MM/YYYY (choose 15th if day unknow, and July if month unknown)*
	Patient Initials	|___|___|___|	*please enter: first name, middlename, sure name (if no middlename use "_")*
	Sex	☐ Male ☐ Female	
	Tribe	_____	*Select from the list of tribes from the drop down menu*
Social Economic status			

	Education level	☐No formal education ☐Accomplished primary school education ☐Accomplished secondary school education ☐Accomplished college/university	*Select one*
	Occupation	☐Unemployed ☐Petty trader ☐Carpenter ☐Business person ☐Student ☐Retired /long-term disabled	
	House ownership	☐ Your own ☐ Rented ☐ Rented, but paid by somebody else	
	Household monthly income	_____	*In thousands Tanzanian shillings*
	Household size	|__|__|	*How many people currently living in your household*
	Household contribute	|__|__|	*All household members (patient included) that contribute to living expenses*
Contact information			
	Home address	_____	*Free text*
	Town	_____	*Free text*
	Phone no. of patient 1	|__|__|__|__|-|__|__|-|__||__|-|__|__| ☐ Patient ☐ Relative ☐ Friend ☐ Neighbor	*Please verify the information by calling the number*
	Phone no. of patient 2	|__|__|__|__|-|__|__|-|__||__|-|__|__|	*Please verify the information by*

		☐ Patient ☐ Relative ☐ Friend ☐ Neighbor	*calling the number*
HIV information			
	HIV status	☐ HIV-infected ☐ HIV-negative ☐ Test not done ☐ Unknown	*Collect the CTC1 for verification. Make a copy and file it in the patient's folder.*
	HIV treatment center	_____	*Write the HIV treatment center/program and the treatment center code*
	Date of enrolment	|___|___| |___|___| |___|___|___|___|	*Check in the CTC1 card and if not written Inquire from the patient*
	Date of HIV diagnosis	|___|___| |___|___| |___|___|___|___|	*Check in the CTC1 card and if not written Inquire from the patient*
	CPT status	☐ Yes ☐ No	*Check in the CTC1 card and if not written Inquire from the patient*
	Date start started CPT	|___|___| |___|___| |___|___|___|___|	*Check in the CTC1 card and if not written Inquire from the patient*
	ART status	☐ Yes ☐ No	*Check in the CTC1 card and if not written*

			Inquire from the patient
	Date start of ART	|___|___| |___|___| |___|___|___|___|	*Check in the CTC1 card and if not written Inquire from the patient*
	ART treatment	☐Combivir/Efavirenz ☐Combivir/Nevirapine ☐Tenofovir/Emtricitabine/Efavirenz ☐Tenofovir/Emtricitabine/Nevirapine ☐Tenofovir/Lamivudine/Efavirenz ☐Tenofovir/Lamivudine/Nevirapine ☐None of the above	*Select one* *Check in the CTC1 card and if not written Inquire from the patient*
TB symptoms			
	Did you experience any of the following symptoms since the last visit?		*multiple answers possible*
	Productive cough	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Fever	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Haemoptysis	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Excessive night sweat	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Chest pain	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Weight loss	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Night sweat	☐ Yes ☐ No Duration |__|__|__| (weeks)	
	Weight loss	☐ Yes ☐ No Duration |__|__|__| (weeks) Weight loss importance ☐ Severe	

		☐ Not severe	
	Abdominal pain	☐ Yes ☐ No Duration |__|__|__| (weeks)	
TB diagnosis delay			
	Have you gone to any other facilities	☐ Yes ☐ No If yes please specify how many times you were treated ☐ Once ☐ Twice ☐ Thrice ☐ More than thrice	
	Did you take any medication	☐ Yes ☐ No If yes please specify brand names: _____	
	Have you visited a traditional healer	☐ Yes ☐ No If yes, please specify how many times ☐ Once ☐ Twice ☐ Thrice ☐ More than thrice	
TB treatment history			
	Previous TB episodes	☐ 1 ☐ 2 ☐ 3 ☐ 4	
	Date of episodes	1 episode: |___|___|-|___|___|-|___|___|___|___| 2 episode: |___|___|-|___|___|-|___|___|___|___| 3 episode: |___|___|-|___|___|-|___|___|___|___| 4 episode: |___|___|-|___|___|-|___|___|___|___|	*DD/MM/YYYY (choose 15th if day unknow, and July if month unknown)*
TB diagnosis criteria			
	AFB	☐Positive ☐Negative ☐Unknown ☐Not performed	*Select one*
	Culture	☐Positive ☐Negative ☐Unknown ☐Not performed	*Select one*
	Hain test	☐Positive ☐Negative ☐Unknown	*Select one*

		☐Not performed	
	Chest X-ray (TB suspicion)	☐Positive ☐Negative ☐Unknown ☐Not performed	*Select one (all chest xray films will be digitized and stored electronically)*
	Clinical criteria *(coughing >3wks, fever, night sweats, weight loss)*	☐Positive ☐Negative ☐Unknown ☐Not performed	*Select one*
	Source of specimenn	☐Expectorated sputum ☐Induced sputum ☐Gastric aspirate ☐Pleural fluid ☐Bronchoscopy ☐Lymph node aspirate ☐CSF ☐Unknown ☐Other (specify below) _____	*Select one*
	TB site	☐Pulmonary ☐Extrapulmonary ☐Both ☐Unknown	*Select one*
	AFB results	☐Positive ☐Negative ☐Unknown ☐Not done	
	AFB positivity	☐1+ ☐2+ ☐3+ ☐scanty If scanty specify the number of cells seen ☐1cells ☐2cells ☐3cells ☐4cells ☐5cells ☐6cells ☐7cells ☐8cells ☐9cells	*multiple answers possible*
	TB patient category	☐New case ☐Relapse ☐Treatment after failure ☐Treatment after default ☐Transfer in	*Select one*

		☐Other	
TB medication			
	Standard anti-TB given	☐Category I – 2RHZE/4RH ☐Category II 2SRHZE/1RHZE/5RHE	*Select one*
	Date start of TB treatment	|___|___| |___|___| |___|___|___|___|	*DD/MM/YYYY (choose 15th if day unknow, and July if month unknown)*
	Other anti-TB medication given to the patient	☐Isoniazid ☐Rifampin ☐Pyrazinamide ☐Ethambutol ☐Streptomycin ☐Ethionamide ☐Ofloxacin ☐Moxifloxacin ☐Other 1 _____ ☐Other 2 _____	*Multiple response (select one if the patient has not received the standard treatment)*
	IPT	☐No IPT ☐Completed IPT ☐Incomplete IPT ☐IPT for uncertain period ☐Still on IPT ☐Unknown	*Select one*
	Risk factors for TB	Recent TB in household (within last 2 years) - ☐Yes ☐No ☐Unknown Diabetes mellitus ☐Yes ☐No ☐Unknown Alcohol abuse ☐Yes ☐No ☐Unknown Steroid treatment ☐Yes ☐No ☐Unknown Currently smoking ☐Yes ☐No ☐Unknown IV drug abuse ☐Yes ☐No ☐Unknown In prison (within last 2 years) – ☐Yes ☐No ☐Unknown Underweight ☐Yes ☐No ☐Unknown Silicosis ☐Yes ☐No ☐Unknown	*Multiple response*

		Anti-TNF blocker treatment – ☐Yes ☐No ☐Unknown	
Nutritional assessment			
	Meals per day	|__|__|	*How many meals do you usually eat in a day?*
	Type of foods	☐Ugali☐ Rice ☐ Bananas ☐ Potatoes ☐ Vegetables ☐ Fruits ☐ Chicken ☐ Meat ☐ Fish ☐ Eggs ☐ Milk Other types of foods not listed, please specify (comma separated) _____	*What type of foods do you eat in a week? Multiple response*
Household members			
	Member 1	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 2	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 3	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 4	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 5	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	

	Member 6	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 7	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
	Member 8	Year of birth |___|___| |___|___| |___|___|___|___| Sex ☐ Male ☐ Female HIV Status ☐Positive ☐Negative ☐ Unknown	
Measurements			
	Weight	|___|___|,|___| kg	
	Height	|___|___|___| cm	
	Body temperature	|___|___|,|___| °C	
	Respiratory rate	|___|___| / min	
	Mid upper arm circumference	|___|___|,|___| cm	*multiple answers possible*
	Hip circumference	|__|__|__| (cm)	*In centimeters*
	Waist circumference	|__|__|__| (cm)	*In centimeters*
	Mid Upper Arm circumference (MUAC)	MUAC |__|__|__| (cm) MUAC |__|__|__| (cm) MUAC |__|__|__| (cm)	*Take three separate measurements*
	Skin fold thickness (TSF)	TSF |__|__|__| (cm) TSF |__|__|__| (cm) TSF |__|__|__| (cm)	*Take three separate measurements*
General condition			

	General condition	☐ good ☐ reduced ☐ ill ☐ critically ill	
	Pallor / anaemia	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	Dehydration	☐ Yes, if yes ☐ mild ☐ Moderate ☐severe ☐ No	
	Malnutrition	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	Cyanosis	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	Clubbing	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	General oedema	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	In pain / in discomfort	☐ Yes, if yes ☐ mild ☐ Moderate ☐ severe ☐ No	
	Other, specify	_____	
Systematic examination			
	Lymphatic system *(enlarged lymphnodes)*	Enlarged lymphnodes ☐ Yes ☐ No If yes, specify site ☐ Cervical ☐ Sub-mandibular ☐ Axillar ☐ Inguinal Size ☐<1cm ☐ 1-<2cm ☐ 2-3cm ☐ 3cm and more Characteristic ☐ indurated ☐ soft ☐ painful ☐ matted	
	Respiratory system	Any abnormal findings ☐ Yes ☐ No Dyspnea ☐ Yes ☐ No Percussion abnormal ☐ Yes ☐ No If percussion is abnormal, please specify ☐ dull ☐ hyper resonant ☐ others _____ Auscultation abnormal ☐ Yes ☐ No	

		☐ transmitted sounds ☐ crepitation ☐ wheezes ☐ pleural rub ☐ reduced air entry ☐ prolonged expiration	
	Abdominal system	Any abnormal findings ☐ Yes ☐ No Abdominal tenderness ☐ Yes ☐ No Distension ☐ Yes ☐ No Ascites ☐ Yes ☐ No Hepatomegaly ☐ Yes ☐ No |__|__| cm below rib cage Splenomegaly ☐ Yes ☐ No |__|__| cm below rib cage	
	Other systems, Please specify _____		
	Other systems, Please specify _____		

RESEARCH OUTPUTS

Publication paper

Chiweka, E., Maroa, T., Temba, H., Ponera, J., Athumani, S., Kamwela, L., Sasamalo, M., Naftari, R., Tito, M., Mhimbira, F., & Hella, J. (2021). C-Reactive Protein As a Triage Test in Guiding Who Should Get a Confirmatory Test for Pulmonary Tuberculosis Diagnosis Among Adults: A Case-Control Proof-of-Concept Study from Urban Tanzania. *Journal of Tuberculosis Research,* 10, 28-44. https://doi.org/10.4236/jtr.2022.101003

Poster presentation

C-reactive protein as a triage test in guiding who should get a confirmatory test for pulmonary tuberculosis diagnosis among adults: A case-control proof-of-concept study from urban Tanzania