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High-sensitivity C-reactive protein in HIV care: Tuberculosis diagnosis and short-term mortality in a cohort of Kenyan HIV patients in the DREAM programme

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ABSTRACT

Objective: Tuberculosis (TB) is the leading cause of death in HIV-positive people. In Kenya, 140 000 new TB cases occurred in 2019, and 13 000 HIV-positive patients died due to TB. The objective of this study was to investigate the role of high-sensitivity C-reactive protein (HS-CRP) in TB diagnosis and the prediction of mortality in HIV-positive patients.

Methods: The IDEA-TB Study enrolled HIV-positive adult patients attending three DREAM centres in Kenya who were suspected of having TB. A lateral flow urine lipoarabinomannan assay (LF-LAM), serum HS-CRP, and GeneXpert MTB/RIF assay (Xpert MTB/RIF) were performed. Six-month survival was evaluated.

Results: A total of 574 patients were enrolled. The median (interquartile range) age, body mass index, and CD4 count were 45 years (37–54 years), 20.5 kg/m^2 (18.5–23.69 kg/m^2), and 477 cells/mL (290–700 cells/mL), respectively. TB was confirmed in 87 (15.2%) patients. Concordance between the Xpert MTB/RIF and LF-LAM tests was 87.1%. HS-CRP was higher in TB patients (35.39 mg/l vs 9.21 mg/l). Malnutrition and elevated HS-CRP were associated with TB: odds ratio (OR) 2.5 (95% confidence interval (CI) 1.14–5.72) and OR 6.6 (95% CI 3.87–11.52), respectively. Nine (1.6%) patients died during follow-up. No single factor was associated with mortality. Only the combination of malnutrition and elevated HS-CRP was highly predictive of death (odds ratio (OR) 9.8, 95% CI 1.88–50.95); the association was stronger in TB patients (33.3% vs 1.0%; OR 47.6, 95% CI 7.03–322.23).

Conclusion: TB diagnosis in HIV-positive patients remains challenging. HS-CRP could play a role in predicting early mortality in symptomatic patients.

Introduction

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* and is one of the major causes of ill health and among the top 10 causes of death worldwide, as well as the leading cause of death by a single agent. The World Health Organization (WHO) estimated that about 10 million people fell ill

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with TB in 2019, and approximately a quarter of the world population is infected with *M. tuberculosis* (World Health Organization, 2020). This is particularly evident in the countries of Sub-Saharan Africa, where the combination of TB and HIV has led to high mortality. In 2018, 211 000 people with TB and HIV co-infection died, and more than 71% of all TB/HIV patients lived in the WHO African Region (World Health Organization, 2020).

According to the WHO, Kenya is in the list of the 30 high burden countries for TB, TB/HIV, and drug-resistant TB. In 2019, it was estimated that the TB incidence in the country was 140 000 cases, out of which only 86 000 were detected. In terms of mortality in 2019, approximately 30 000 died of TB, including 13 000 HIV-positive TB patients. Case detection and treatment coverage is still a challenge in the country; only 60% of estimated TB patients were notified and consequently received anti-TB therapy in 2019 (Organization WH, 2020). The TB/HIV co-infection rate in the country is 26%.

TB case detection and diagnostic tools are still a challenge. In 2018, only seven million people with TB were notified to national TB programmes. In 2014, the WHO urged that "new health-system strategies and diagnostic tools are critically important" (World Health Organization, 2014).

In HIV-infected patients, the WHO recommends four-symptom screening (4SS) as the initial screening tool (World Health Organization, 2013b). However, the 4SS tool has demonstrated a low performance in many studies, missing up to 22% of TB cases (Floridia et al., 2017). Conventional sputum tests (smear microscopy and culture) are limited because of time and resource demands, and the low detection rate of active cases (Wassermann and Meintjies, 2014).

The GeneXpert *Mycobacterium tuberculosis*/rifampicin assay (Xpert MTB/RIF) is a rapid PCR-based assay that detects the presence of *M. tuberculosis* complex DNA and mutations associated with resistance to rifampicin in biological samples within <2 h (Steingart et al., 2013). Xpert MTB/RIF was endorsed by the WHO in 2010 and is now recommended as the preferred diagnostic tool in HIV-infected patients (World Health Organization, 2013a). This is despite some limitations in sensitivity and logistical requirements, such as difficulties in installation, provision of air conditioning, and uninterrupted electricity and internet connections for calibration (Ardizzoni et al., 2015; Organization WH, 2014).

The lateral flow urine lipoarabinomannan assay (LF-LAM) detects lipoarabinomannan in persons with active TB. The test is low-cost, simple, requires no special equipment, yields results in approximately 30 min, and has shown high specificity in HIV-positive patients when the CD4 count is lower than 200 cells/mm^3 (Shah et al., 2016). The WHO recommends use of the LF-LAM as a component of the package of care for people with advanced HIV disease (World Health Organization, 2017). Limitations of the test are its low specificity in HIV-infected patients with higher CD4 counts and its low sensitivity.

Rapid serological assays may represent a key tool for the rapid identification or triage of individuals with active TB. Non-antibody biomarkers could be helpful to support the diagnosis of TB. One such biomarker is the level of high-sensitivity C-reactive protein (HS-CRP), which appears to be influenced by the presence of active TB, especially in HIV-positive patients (Ciccacci et al., 2019a; Liu et al., 2017; Steingart et al., 2013).

Combined strategies are under study, and the introduction and the scaling-up of rapid and accurate point-of-care (POC) tests is strongly recommended by the WHO (Scott et al., 2017; World Health Organization, 2014).

The objective of this study was to investigate the possible role of HS-CRP in TB case detection and in the prediction of early fatal events in HIV-positive patients.

Methods

The IDEA-TB Study (Innovative Diagnostic Enhancement Against TB) is a prospective study aimed at evaluating the possible role of HS-CRP for TB diagnosis and the prediction of early mortality in HIV-positive patients in Kenya. The study was conducted within the DREAM programme (Disease Relief through Excellent and Advanced Means) in three facilities in Meru County, Kenya. The DREAM programme is a public health programme developed by the Community of Sant'Egidio in 11 African countries, delivering a range of health services in many settings (Altan et al., 2016; Ciccacci et al., 2019b; Liotta et al., 2013). The sites of the study are three DREAM centres in Kenya: Meru/Nchiru, Chaaria, and Nkubu). Enrolment started in May 2019 and lasted for 12 months. All consecutive HIV-positive adult patients attending the study sites during the study period, who were clinically presumed to have TB according to national guidelines and were referred for Xpert MTB/RIF, were asked to be enrolled in the study. The suspicion of TB was based on symptom screening (cough, night sweats, fever, weight loss) and other clinical features suggesting TB infection. It was expected that 600 patients would be enrolled over a 12-month period, according to the activity reports of the study sites. Due to their particular immunological status, pregnant or lactating women were excluded from participation.

For each enrolled patient, demographic, anthropometric, and clinical data, and blood, sputum and urine samples were collected on the same day. Urine samples were analysed on site with the LF-LAM urine test and the results were captured on a datasheet. Blood samples were transferred to the Nchiru laboratory for HS-CRP testing and sputum samples were sent to the Meru Regional laboratory for Xpert MTB/RIF testing, and the results were collected on a datasheet. Data entry for the results was done on specific datasheets and de-identified for privacy and confidentiality of the patients. The database was Excel-based and the laboratory test results were recorded directly on the sheet; these were then sent to the researchers once a month. All other anthropometric data were extracted from the DREAM database, which is used in health care delivery at the sites. The two sources of data were then matched according to a unique code that is given to the patients by the DREAM software.

The statistical data analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Data are presented as the median with interquartile range (IQR) or mean ± standard deviation for parametric variables. Odds ratios (OR) are reported with the 95% confidence intervals (CI).

Statistical tests used to compare groups included the Mann–Whitney *U*-test and the Kruskal–Wallis *H*-test for continuous variables, while the Chi-square test was used for categorical variables. A multivariate survival analysis evaluating premature death as an outcome was performed using a Cox regression model. Early mortality was defined as a fatal event occurring within the first 6 months of follow-up.

The research protocol was approved by the AMREF Ethics and Scientific Review Committee on March 6, 2019 (P591/2019). All patients who were invited to be enrolled in the study received a specific consent form to sign. The study was explained to the patient, both in English and in Kiswahili, and they were asked to join the study.

Results

A total of 574 patients with suspected TB were enrolled. General characteristics of the cohort are reported in Table 1. The median BMI was 20.5 kg/m^2, and 24.9% (143/574) of patients were malnourished.

Table 1
General characteristics of the study cohort (N = 574).

Site, *n* (%)	
Nkubu	236 (41.1%)
Chaaria	215 (37.5%)
Meru/Nchiru	123 (21.4%)
Sex, *n* (%)	
Male	215 (37.5%)
Female	359 (62.5%)
Age (years), median (IQR)	45 (37–54)
BMI (kg/m^2), median (IQR)	20.5 (18.5–23.6)
CD4 cell count (cells/mm^3), median (IQR) (n = 205)	477 (290–700)
Plasma HIV-RNA <1000 copies/mL, *n* (%) (n = 345)	283 (82.0%)

BMI, body mass index; IQR, interquartile range.

Table 2
Tuberculosis test results.

Test	Test result	Number	%
Xpert MTB/RIF	Negative	546	95.1%
	Positive	28	4.9%
LF-LAM test	Negative	502	87.5%
	Positive	72	12.5%
Any TB test	Negative	487	84.8%
	Positive	87	15.2%

Xpert MTB/RIF, GeneXpert *Mycobacterium tuberculosis*/rifampicin assay; LF-LAM, lateral flow urine lipoarabinomannan assay.

Table 2 reports the TB test results. Only 87 (15.2%) patients suspected to have TB were confirmed as TB cases (either LF-LAM or Xpert MTB/RIF positive test). Concordance between Xpert MTB/RIF and LF-LAM was 87.1%.

The mean HS-CRP in the cohort was 13.18 ± 31.7 mg/l. As shown in Table 3, HS-CRP was significantly higher in TB patients. A significant correlation was observed between HS-CRP and both LF-LAM and MTB/RIF test results ($p < 0.0001$) (Figure 1).

Table 4 reports the results of the univariate analysis, studying the associations of BMI, haemoglobin (Hb), CD4 count, HS-CRP, and HIV viral load with TB diagnosis. HS-CRP >20 mg/l was the strongest factor (OR 6.68, 95% CI 3.87–11.52).

At the end of follow-up (6 months), 538 (93.7%) patients were still in care; 19 (3.3%) had transferred, nine (1.6%) had died, and eight (1.4%) were lost to follow-up. No single factor was significantly associated with mortality, however the combination of nutritional status and elevated HS-CRP was highly predictive of death in the first 6 months of follow-up. Early mortality among patients with BMI < 18.5 kg/m^2 and simultaneous HS-CRP >20 mg/l was 11.1% vs 1.3% in patients without one of the two factors (OR 9.8, 95% CI 1.88–50.95). When considering only TB-negative patients, the association was even stronger (33.3% vs 1.0%, OR 47.6, 95% CI 7.03–322.235).

Table 3
HS-CRP and TB test results.

	Test result	HS-CRP Mean ± SD	*p*-Value
Whole cohort		13.18 ± 31.7	
TB	Negative	9.21 ± 25.7	<0.00001
	Positive	35.39 ± 49.0	
LF-LAM	Negative	9.42 ± 25.9	<0.00001
	Positive	39.38 ± 50.8	
Xpert MTB/RIF	Negative	11.36 ± 28.4	<0.0001
	Positive	48.67 ± 60.9	

HS-CRP, high-sensitivity C-reactive protein; Xpert MTB/RIF, GeneXpert *Mycobacterium tuberculosis*/rifampicin assay; LF-LAM, lateral flow urine lipoarabinomannan assay.

Discussion

In the study cohort, only 15.2% of TB presumptive patients were actually confirmed to have TB. This finding is in line with those of other studies in Kenya and in other countries, which have found a positive predictive value for clinical screening of around 15% or lower (Cheng et al., 2015; Corbett et al., 2010; Floridia et al., 2017; Modi et al., 2016). Moreover, a systematic review found that the general performance of 4SS was poor, in particular in HIV-positive patients (Hamada et al., 2018).

Concordance of Xpert MTB/RIF and LF-LAM in this cohort was low, but in line with other studies (Cresswell et al., 2020). In a previous study in Mozambique, a higher concordance was found between the two tests (Floridia et al., 2017); however, these variations could be attributed to different rates of extrapulmonary TB, due to different patient selection criteria.

In the study cohort, HS-CRP was associated with TB diagnosis, consistent with other studies (Ciccacci et al., 2019a; Khuder et al., 2013; Yoon et al., 2017a). The mean HS-CRP value in this cohort was higher than 10 mg/l, which is the diagnostic threshold set in some studies for TB diagnosis (Yoon et al., 2017b). This finding could be explained by the fact that the patients were all suspected to have TB, hence they had certain clinical symptoms and likely some disease, whether TB or not. This could have driven the increase in HS-CRP to a certain degree.

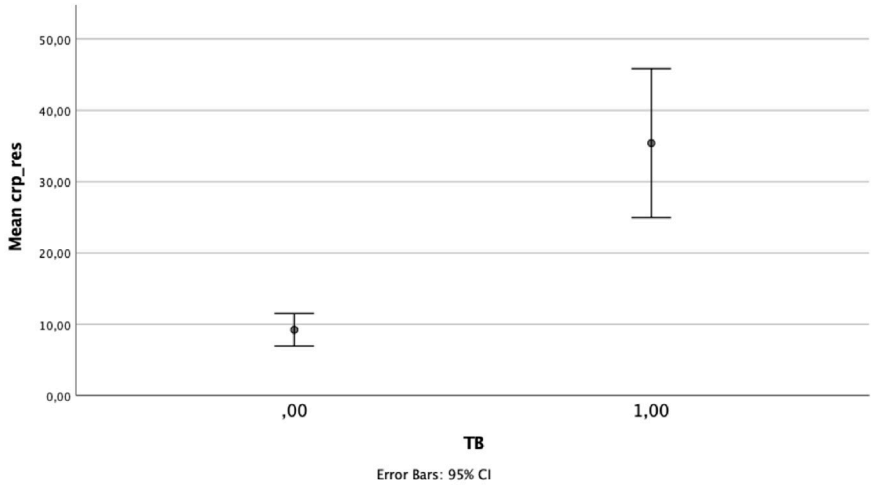
Consistent with other studies (Kerkhoff et al., 2013; Lawn et al., 2013a), HS-CRP was found to be more associated with the LF-LAM urine test result than with the Xpert MTB/RIF result.

Unlike other studies (Bedell et al., 2018; Chaisson et al., 2019; Lawn et al., 2013b), the present study did not find any association between HS-CRP and mortality. However, it should be noted that the cohort was not composed of new HIV patients starting antiretroviral therapy (ART), but patients already on ART. This could explain the differences in prognostic value of HS-CRP, as the first months after ART initiation are the period in which mortality is generally higher.

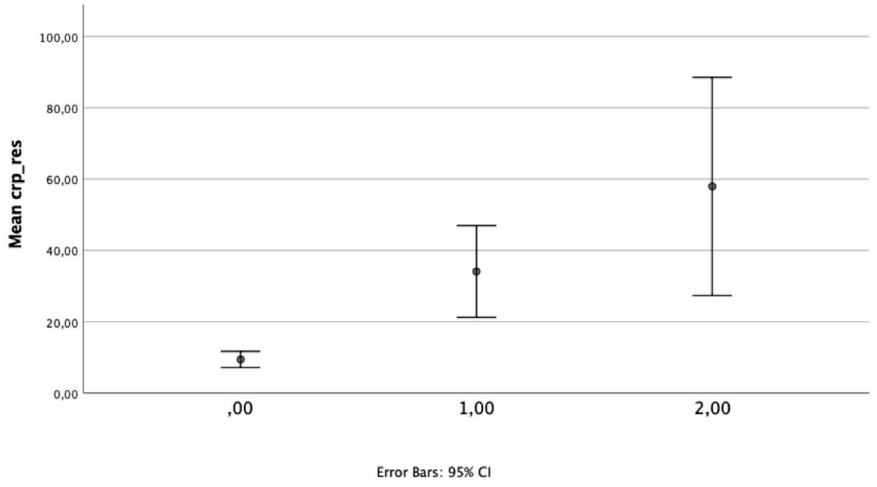
The possible association of HS-CRP with other prognostic factors was studied, especially nutritional status (Liu et al., 2011). In the present study, patients with malnutrition and concomitant higher HS-CRP had a 9.8-fold higher risk of dying in the next 6 months. The role of HS-CRP in TB case-finding and in general TB care is yet to be defined (Yoon et al., 2019). Currently, there have been no previous studies that have attempted to integrate HS-CRP with other clinical features in order to provide clinical information.

Being the first study, there was evidence of a high correlation between concomitant elevated HS-CRP and malnutrition and mortality in TB-negative patients. This finding could be explained by the fact that TB patients were treated after diagnosis, whereas TB-negative patients with malnutrition and elevated HS-CRP were likely affected with other concomitant diseases responsible for elevated mortality (Simon et al., 2004; Sproston and Ashworth, 2018).

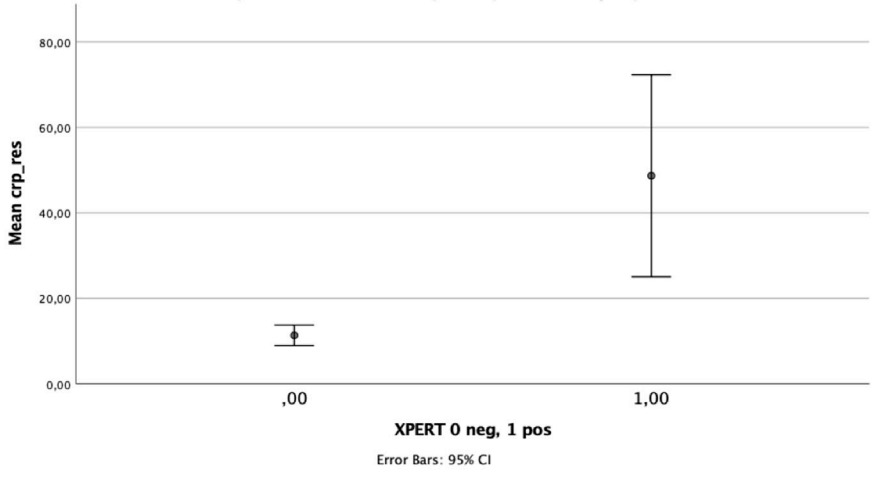
One of the limitations of this study was the lack of some clinical and laboratory information. In particular, CD4 count data were available for only a small number of patients, because the Kenya 2018 ART guidelines recommend a CD4 count only in selected cases. On the flip side, this was also considered a strength of the study, because the results showed an overview of the real use that HS-CRP could have in the field under actual conditions. The attrition of a small number of patients due to death also limited the survival analysis. Although statistically significant, the results should be confirmed in larger studies. Moreover, eight individuals were lost to follow-up and information about their health condition was not available; inevitably, any potential fatal event in this group of patients could not have been included in the survival analysis.



A HS-CRP in TB negative (0) and positive (1) patients



B HS-CRP and LF-LAM result: negative (0), low positive (1), medium and high (2)



C HS-CRP and MTB/RIF result: negative (0), positive (1)

Figure 1. High-sensitivity C-reactive protein (HS-CRP) and TB test results.

Another limitation of the survival analysis was the lack of broader information. A more detailed description of the cause of death could have provided relevant insights into the pathophysiological dynamics in fragile patients. At the same time, the availability of other relevant information (such as socio-economic level, literacy, occupation, etc.) could have given

Table 4
Univariate analysis for TB diagnosis.

	OR	CI	
BMI <b24.9 kg/m^2	2.55	1.14–5.72	*
Hb <11 mg/dl	3.01	1.36–6.63	*
CD4 < 350 cells/mm^3	2.45	1.15–5.22	*
HS-CRP >20 mg/l	6.68	3.87–11.52	*
Undetectable HIV viral load	0.82	0.35–1.90	

BMI, body mass index; CI, confidence interval; Hb; HS-CRP, high-sensitivity C-reactive protein; OR, odds ratio.* p<0.05

informative results about survival and other determinants of poor health outcomes.

In conclusion, many studies have investigated the possible role of CRP in TB diagnosis (Ciccacci et al., 2019a; Lawn et al., 2013a; Schleicher et al., 2005; Skogmar et al., 2015; Wilson et al., 2011), however the real use of the test is still under investigation. The results of the present study seem to suggest the efficacy of HS-CRP in TB diagnosis, as already known, but also its prognostic value regarding short-term survival in malnourished HIV-positive patients. In our opinion, this represents an important finding, as HS-CRP could provide additional information to the clinical evaluation and help in identifying those patients in need of special attention because of suspected TB or a high risk of short-term mortality.

The double role that HS-CRP could play, i.e. TB diagnosis and determining the short-term prognosis, is valuable for further studies to assess the real utility of its use in clinical practice.

The results of this study indicate that it is important for the HIV programme to strengthen follow-up for nutritional status of HIV-positive and TB co-infected patients. Interventions to improve the nutritional status of TB/HIV co-infected patients should be initiated as soon as possible to avert deaths among these patients.

Moreover, the association of poor nutritional status, high level of HS-CRP, and mortality in TB-negative patients may suggest the presence of other comorbidities that could have been associated with mortality. Whereas TB-infected patients received TB treatment, with a possible reduction in mortality (even if with malnutrition or elevated HS-CRP), TB-negative patients with these two signs could have been misdiagnosed. In our opinion, this result is one of the most original findings of the present study, as it could have important consequences for the operative point of view. According to these results, the introduction of HS-CRP testing in HIV-positive patients could help in identifying those in need of special attention due to a high risk of mortality in the next 6 months.

In conclusion, this study showed two major results: as expected, HS-CRP was of good value in diagnosing TB in HIV-positive patients, and in addition, it was strongly related to early mortality in the next 6 months in HIV-positive patients both with and without TB co-infection.

Conflict of interest

All authors declare that they have no conflict of interest.

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