Predictive Value of C-Reactive Protein for Hospitalization and Mortality among People with Advanced HIV Disease in Uganda Receiving the WHO-Recommended Package of Care

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BACKGROUND

- People with advanced HIV disease (AHD, CD4 ≤200 cells/μL) remain at high risk for opportunistic infections (OIs), hospitalization, and death, despite access to ART.[1,2] Predictors of adverse outcomes in this vulnerable population are needed.
- C-reactive protein (CRP), a biomarker for inflammation and infection, is associated with common OIs and decreases following appropriate treatment.[3-5] The role of CRP within the framework of the WHO-recommended package of care for people with AHD remains unclear.
- We evaluated baseline serum CRP as a predictor of OIs, hospitalization, and death among a cohort of outpatients with AHD in Uganda, where the WHO-recommended package of care is widely implemented.

METHODS

- We analyzed data from 785 participants in the ENCORE trial (NCT05085171), a cluster-randomized trial of point-of-care CD4 testing and enhanced screening and prophylaxis for AHD. Participants were adults who presented to a participating clinic in Kampala and Wakiso, Uganda with CD4 ≤200 cells/μL between May 2022 and February 2024.
- TB status at enrollment was categorized into four levels – confirmed TB, probable TB, symptomatic AHD, and no TB – using TB diagnostic results, TB treatment, and clinical symptom data within 30 days of trial enrollment.
- The primary outcome was 30-day hospitalization or death.
- Secondary outcomes included the 30-day incidence of OIs, hospitalization, or death.
- We used relative risks, cumulative incidence curves, and Cox regression to assess CRP's predictive value. ROC curves compared models with and without CRP.

RESULTS

Table 1. Baseline Characteristics by Baseline CRP Group

Baseline Factor	CRP <10 mg/L (N=459, 59%)	CRP ≥10 mg/L (N=326, 41%)	p-value
Age, years	33 (28–40)	34 (30–40)	0.087
Female Sex	257 (56%)	138 (42%)	**<0.001**
Weight, kg	56 (50–63)	53 (47–59)	**<0.001**
CD4 Count, cells/μL	103 (56–154)	61 (28–199)	**<0.001**
ART Naïve Status	225 (49%)	217 (67%)	**<0.001**

Summary Statistics presented as N (%) or Median (IQR)

Table 2. Outcomes by Baseline CRP Group

Outcome	CRP <10 mg/L (N=459, 59%)	CRP ≥10 mg/L (N=326, 41%)	Risk Ratio (95% CI)	p-value
Hospitalization or Death	11 (2.4%)	33 (10%)	4.2 (2.2–8.2)	**<0.001**
Hospitalization	9 (2.0%)	20 (6.1%)	3.1 (1.4–6.8)	**0.002**
Death	3 (0.7%)	18 (5.5%)	8.5 (2.5–28)	**<0.001**
Incident OIs	123 (27%)	175 (54%)	2.0 (1.7–2.4)	**<0.001**

Each 2-fold increase in serum CRP is associated with a 30% increased hazard of 30-day hospitalization or mortality in people with advanced HIV disease. The addition of serum CRP testing may be valuable to risk-stratify patients with advanced HIV disease, especially in lower-resource settings.

RESULTS

Figure 1. Participants with baseline CRP ≥10 mg/L had a higher 30-day incidence of hospitalization or death compared to those with CRP <10 mg/L.

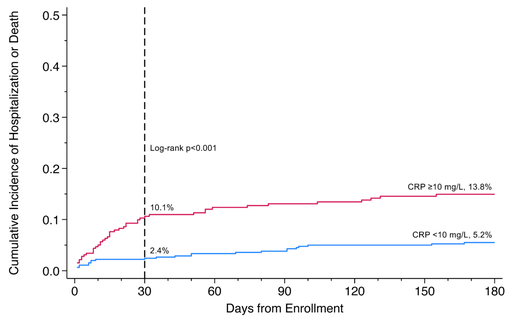


Figure 2. Participants with probable TB or symptomatic AHD had higher 180-day incidence of hospitalization or death than those with confirmed TB.

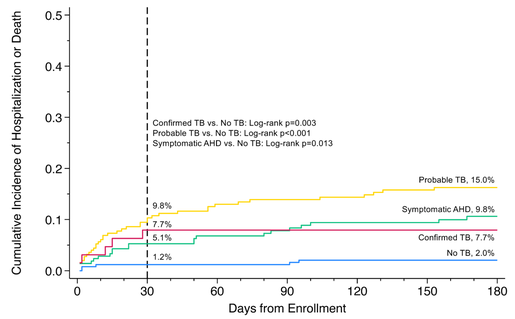


Figure 3. Among participants with baseline CRP ≥10 mg/L, 30-day incidence of hospitalization or death varied by ART status, with ART-naïve people at higher risk.

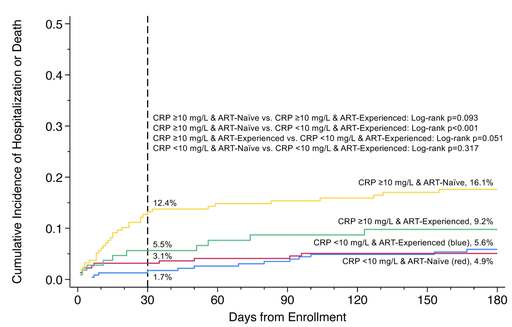
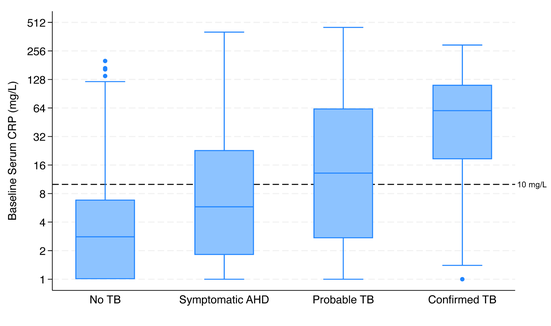


Figure 4. Baseline CRP increased as the certainty of TB diagnosis increased. Participants with CRP ≥10 mg/L: 12% (no TB), 37% (symptomatic AHD), 55% (probable TB), 86% (confirmed TB).



RESULTS

Table 3. Predictors of 30-Day Hospitalization or Death among People with AHD

	Unadjusted Models		Adjusted Model	
Baseline Factor	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Serum CRP ≥10 mg/L	4.33 (2.19–8.57)	**<0.001**		
Serum CRP per 2-fold change	1.40 (1.24–1.59)	**<0.001**	1.31 (1.15–1.50)	**<0.001**
CD4 per 10 cells/μL	0.88 (0.82–0.93)	**<0.001**	0.92 (0.86–0.98)	**0.011**
ART-Naïve Status	2.70 (1.34–5.47)	**0.003**	1.76 (0.86–3.61)	0.120
Weight per 10 kg	0.64 (0.47–0.89)	**0.005**	0.78 (0.56–1.10)	0.160
Age per 5 years	1.08 (0.93–1.25)	0.290		
Female Sex	0.81 (0.45–1.48)	0.499		

Table 4. Model Performance

Model	ROC AUC (95% CI)	DeLong's p-value
Adjusted Model excluding CRP	0.73 (0.66–0.80)	**0.009**
Adjusted Model including CRP	0.80 (0.74–0.85)	

DISCUSSION

- Baseline serum CRP levels ≥10 mg/L predicted the occurrence of OIs, hospitalization, and death within 30 days in a cohort of 785 Ugandan outpatients with AHD receiving WHO-recommended OI screening and prophylaxis. Inclusion of CRP improved the discriminatory ability of models beyond traditional factors such as CD4 count, ART status, and weight, suggesting that CRP could serve as a valuable prognostic biomarker.
- No participants with both confirmed TB and low CRP experienced hospitalization or death, highlighting the effectiveness of TB treatment. Participants with probable TB or symptomatic AHD had higher rates of hospitalization or death, indicating the need for improved TB diagnostics.
- If point-of-care serum CRP testing is both effective and cost-effective, CRP testing could be a valuable tool to prioritize rapid, intensive evaluation for the 40% of patients with CRP ≥10 mg/L. This approach could be especially beneficial in settings with limited access to comprehensive diagnostics, allowing for a more targeted allocation of healthcare resources to reduce AIDS-related deaths.

ACKNOWLEDGEMENTS

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REFERENCES

1. Advanced HIV disease (AHD). Accessed July 27, 2023. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/advanced-hiv-disease
2. Rajasingham R, Govender NP, Jordan A, et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. *Lancet Infect Dis*. 2022;22(12):1748-1755. doi:10.1016/S1473-3099(22)00499-6
3. Lawn SD, Wiktor S, Coulibaly D, Ackah AN, Lal RB. Serum C-reactive protein and detection of tuberculosis in persons co-infected with the human immunodeficiency virus. *Trans R Soc Trop Med Hyg*. 2001;95(1):41-42. doi:10.1016/s0035-9203(01)90328-1
4. Skipper CP, Kirumira P, Dai B, et al. Baseline C-reactive Protein as a Risk Factor for Cryptococcal Meningitis and Death in HIV-associated Cryptococcal Antigenemia With CrAg Titer as an Effect Modifier. *Open Forum Infect Dis*. 2024;11(8):ofae392. doi:10.1093/ofid/ofae392
5. Azam K, Khosa C, Viegas S, et al. Reduction of blood C-reactive protein concentration complements the resolution of sputum bacillary load in patients on anti-tuberculosis therapy. *Front Immunol*. 2022;13:1005692. doi:10.3389/fimmu.2022.1005692