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MAJOR ARTICLE

Baseline Serum C-Reactive Protein Level Predicts Mortality in Cryptococcal Meningitis

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Background. C-reactive protein (CRP) is an acute phase protein produced by the liver in response to systemic inflammation. CRP is a helpful surrogate biomarker used for following the progression and resolution of infection. We aimed to determine the association of baseline CRP level and the temporal change in CRP over time with cryptococcal meningitis outcome.

Methods. We reviewed 168 prospectively enrolled HIV-infected Ugandans with confirmed first-episode cryptococcal meningitis. Baseline plasma CRP collected within 5 days of meningitis diagnosis was categorized into quartiles. We compared baseline CRP with 18-week survival using time-to-event analysis.

Results. Of 168 participants, the baseline first quartile of serum CRP was <29.0 mg/L, second quartile 29.0–49.5 mg/L, third quartile 49.6–83.6 mg/L, and fourth quartile >83.6 mg/L. Baseline CD4 count, HIV viral load, and cerebrospinal fluid results did not differ by CRP quartile. Participants with CRP >49.5 mg/L more likely presented with Glasgow Coma Scale (GCS) <15 ($P = .03$). The 18-week mortality rate was 55% (46/84) in the highest 2 quartile CRP groups (>49.5 mg/L), 41% (17/42) in the mid-range CRP group (29.0–49.5 mg/L), and 14% (6/42) in the low-CRP group (<29.0 mg/L; $P < .001$). After adjustment for possible confounding factors including GCS <15, CRP remained significantly associated with mortality (adjusted hazard ratio, 1.084 per 10 mg/L; 95% CI, 1.031–1.139; $P = .0016$).

Conclusions. Higher baseline CRP is associated with increased mortality in HIV-infected individuals with first-episode cryptococcal meningitis. CRP could be a surrogate marker for undiagnosed coinfections or may reflect immune dysregulation, leading to worse outcomes in persons with advanced AIDS and concomitant cryptococcal meningitis.

Keywords. C-reactive protein; cryptococcal meningitis; *Cryptococcus*; mortality.

Cryptococcal meningitis remains a significant cause of morbidity and mortality in HIV-infected individuals worldwide [1]. Access to antiretroviral therapy (ART), cryptococcal antigen (CrAg) screening with preemptive therapy, and optimization of ART are the major strategies to reduce mortality [2, 3]. Despite those strategies, mortality is still unacceptably high, with 1-year mortality up to 70% in low-income countries [1]. Multiple studies have demonstrated a variety of clinical factors for poor outcomes in cryptococcal meningitis, including altered mental status, low baseline weight, high opening pressure, cerebrospinal fluid (CSF) with low white blood cell count, protein, glucose, high CrAg titer, and high fungal burden [4–6]. However, there is no well-described serologic marker that potentially predicts clinical outcome.

C-reactive protein (CRP) is an acute-phase protein that is commonly used as a surrogate marker for inflammation and infection [7]. Elevated interleukin-6 (IL-6) in the setting of systemic inflammation stimulates the production of CRP from the liver [8]. CRP is a useful biomarker to detect, follow, and predict the outcome in both systemic and localized bacterial infections, mainly bloodstream infection, bacterial pneumonia, and bacterial meningitis [9–13]. CRP can also be used to detect systemic fungal infections, but no clear data have demonstrated an association between cryptococcal meningitis clinical outcome and elevated CRP [14–16]. The primary goal of this study was to examine the association between baseline CRP level and cryptococcal meningitis mortality in HIV-infected individuals. The secondary objective was to determine the change in CRP over time from cryptococcal diagnosis to eventual outcome.

METHODS

Study Design and Participants

We conducted a cohort study among 168 HIV-infected Ugandans with confirmed first-episode cryptococcal

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meningitis at Mulago Hospital in Kampala, Uganda, who had plasma CRP level collected from August 2013 through August 2014. Our study is a substudy of the Adjunctive Sertraline for the Treatment of Cryptococcal Meningitis (ASTRO-CM) trial (Clinical Trials: NCT01802385) [17].

Plasma CRP Measurement

Plasma CRP was measured on-site with a point-of-care Piccolo MetLyte Plus CRP Reagent Disc (Abaxis, Union City, CA, USA). The baseline CRP result was defined as the first CRP result from a specimen drawn within 5 days of cryptococcal meningitis diagnosis. Follow-up plasma CRP was obtained on the subsequent study visits within 14 days of diagnosis.

Outcome Measurement

Baseline demographic data and clinical outcomes were prospectively collected. We categorized baseline plasma CRP levels into 4 groups by quartiles. We assessed the percent change in CRP between baseline plasma CRP and the most recent follow-up plasma CRP through day 14 using a ±20% difference as a threshold to define a clinically significant change in CRP from baseline, with 20% being >3-fold greater than the coefficient of variation of the assay. We compared baseline plasma CRP as well as percent change in CRP with 18-week survival after enrollment.

Statistical Analysis

Baseline characteristics were compared using chi-square or Kruskal-Wallis tests, while log-rank testing compared 18-week all-cause mortality using a time-to-event model. We used Cox regression to adjust for possible confounders associated with 18-week mortality including age, male sex, Glasgow Coma Scale score <15, baseline CSF white cell count <5, ART status, and receiving antibiotic therapy within 14 days of enrollment. We conducted all analyses using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline Demographic Data

The median age of the 168 participants (interquartile range [IQR]) was 35 (30–40) years. Fifty-four percent were men. The median CD4 T-cell count (IQR) was 19 (8–41) cells/μL. Baseline plasma CRP ranged from 0.7 mg/L to 201.0 mg/L. The first quartile of baseline plasma CRP was <29.0 mg/L, the second quartile was 29.0–49.5 mg/L, the third quartile was 49.6–83.6 mg/L, and the fourth quartile was >83.6 mg/L. Baseline characteristics stratified by quartile are shown in Table 1.

Associations With Baseline Plasma CRP

There was no difference in baseline HIV parameters, electrolytes, absolute neutrophil count, CSF microscopy, or protein result between quartile groups. The incidence of tuberculosis (TB) after enrollment was 19% (23/146). There was no difference in median baseline CRP in the TB group vs the non-TB group ($P = .58$). A GCS score <15 on presentation was found in 43% (36/84) of the third and fourth quartile groups compared with 36% (15/42) of the second quartile group and only 19% (8/42) of the first quartile group ($P = .03$). The percentage of patients who received antibiotic therapy within 14 days of enrollment was 31% (13/42) of the first quartile group compared with 57.1% (24/42) of the second quartile group and 58.3% (49/84) of the third and fourth quartile groups ($P = .001$).

Timing of ART and Baseline Plasma CRP

Median baseline CRP for the patients who were on ART before enrollment (IQR) was 56.3 (34.7–88.9) mg/L, and in the non-ART group it was 45.0 (27.8–72.0) mg/dL ($P = .03$). Within the ART group, participants who were on ART for <30 days had a median baseline CRP (IQR) of 77.0 (46.0–111.8) mg/L, which was significantly higher than the median baseline CRP of participants who were on ART for >30 days (48.8 [31.0–83.2] mg/L; $P = .05$).

Baseline Plasma CRP and Clinical Outcome

The 18-week mortality rate was 14% (6/42) in the first CRP quartile group (<29.0 mg/L), 41% (17/42) in the second quartile group (29.0–49.5 mg/L), 56% (24/43) in the third quartile group (49.6–83.6 mg/L), and 54% (22/41) in the fourth quartile group (>83.6 mg/L; log-rank $P < .001$). As a continuous variable, CRP also remained associated with risk (hazard ratio, 1.086 per 10 mg/L unit increase; 95% CI, 1.039–1.136; $P = .0004$) (Figure 1). After adjusting for age, sex, Glasgow Coma Scale score <15, baseline CSF white cell count <5, ART status, and receiving antibiotic therapy within 14 days of enrollment, CRP remained significantly associated with mortality (adjusted hazard ratio, 1.084 per 10 mg/L; 95% CI, 1.031–1.139; $P = .0016$) (Table 2). Focusing on the third and fourth quartile groups, receiving antibiotic therapy within 14 days of enrollment was not associated with mortality (adjusted hazard ratio, 1.578; 95% CI, 0.647–3.850; $P = .32$).

Change in Plasma CRP and Clinical Outcome

The percent change from baseline to the most recent follow-up CRP result through day 14 was calculated. The median time difference between baseline CRP and follow-up CRP (IQR) was 4 (3–5) days. A total of 84 participants with baseline plasma CRP >32 mg/L had at least 1 follow-up plasma CRP result available. Of these, 43% (36/84) had a 20% increase in follow-up plasma CRP from baseline, 25% (21/84) had a 20% decrease, and 32% (27/84) had no clinically significant change in CRP. There was no difference in 18-week mortality within these 3 groups ($P = .10$).

Table 1. Baseline Demographics by Baseline CRP

CRP Groups	No.	CRP < 29.0	CRP 29.0–49.5	CRP > 49.5	*P* Value
Participants, No.	168	42	42	84	
Median age [IQR], y	168	36 [31–44]	35 [30–40]	35 [30–40]	.31
Male sex, No. (%)	168	17 (40.5)	28 (66.7)	47 (56)	.05
Median weight, kg [IQR]	149	52.5 [50–58]	50 [45.5–55]	50 [46–60]	.47
Receiving TB therapy at baseline, No. (%)	168	5 (11.9)	3 (7.1)	16 (19.0)	.17
Receiving antibiotic therapy within 14 d of enrollment, No. (%)	168	13 (31.0)	24 (57.1)	49 (58.3)	.01
Glasgow Coma Scale score <15, No. (%)	168	8 (19.0)	15 (35.7)	36 (42.9)	.03
Antiretroviral therapy			Median [IQR] or No. (%)		
Currently on ART, No.	168	16 (38.1)	22 (52.4)	46 (54.8)	.20
Months on ART,[a] mo	84	7.9 [2.1–29.2]	7.4 [1.0–29.8]	2.7 [0.6–20.9]	.66
Days on ART[a]					.82
≤14 d	15	2 (12.5)	3 (13.6)	10 (21.7)	
15–30 d	8	0 (0.0)	2 (9.1)	6 (13.0)	
31–90 d	16	4 (25.0)	4 (18.2)	8 (17.4)	
91–180 d	5	1 (6.3)	2 (9.1)	2 (4.3)	
>180 d	40	9 (56.3)	11 (50.0)	20 (43.5)	
Baseline blood results			Median [IQR]		
CD4+, cells/μL	160	23 [11–40]	28 [8–52]	14 [6–39]	.28
Sodium, mmol/L	137	130 [125–133]	129 [126–132]	128 [125–130]	.26
Potassium, mmol/L	164	4.2 [3.7–4.6]	4.1 [3.7–4.4]	4.1 [3.5–4.6]	.67
Absolute neutrophil count, kcells/μL	157	1.6 [0.9–2.1]	1.8 [1.2–2.4]	2.0 [1.3–3.5]	.06
Baseline CSF results			Median [IQR] or No. (%)		
Culture *Cryptococcus*, $\log_{10}$ CFU/mL	168	4.9 [3.2–5.3]	4.7 [2.4–5.4]	4.6 [3.2–5.2]	.76
Sterile CSF culture, n	168	2 (4.8)	4 (9.5)	7 (8.3)	.69
Opening pressure, mmH_2O	151	250 [170–340]	220 [165–335]	255 [190–424]	.45
Opening pressure >250 mmH_2O, No.	151	18 (48.6)	18 (43.9)	37 (50.7)	.78
White cell count, cells/μL	162	<5 [<5–20]	<5 [<5–70]	<5 [<5–30]	.39
White cell count >5 cells/μL, No.	162	12 (28.6)	15 (38.5)	22 (27.2)	.43
Protein, mg/dL	156	44 [23–80]	47 [21–136]	50 [27–94]	.79

CRP groups based on first plasma CRP result between days 0 and 5. Quartiles 3 and 4 are grouped together due to similar clinical outcomes. *P* values were calculated by Kruskal-Wallis test for medians; chi-square test for proportions.

Abbreviations: ART, antiretroviral therapy; CRP, C-reactive protein; CFU, colony-forming unit; CSF, cerebrospinal fluid; IQR, interquartile range; TB, tuberculosis.

[a]Among those on ART at cryptococcal meningitis diagnosis.

DISCUSSION

Our study found that increasing baseline plasma CRP positively correlates with 18-week mortality, especially in the third and fourth quartile groups (CRP >49.5 mg/L) among cryptococcal meningitis patients. This remained significant after adjusting for other possible confounders. Based on our multivariate analysis, CRP appeared to be more predictive of mortality than GCS score <15 and lack of CSF pleocytosis (<5 white cells/μL). Mortality was prominent during the first 2 weeks of the amphotericin B deoxycholate induction therapy. Unlike other infections, CRP during the first 2 weeks of cryptococcal meningitis therapy initially rises rather than decreases [18]. The potential explanation was the systemic inflammation induced by intensive antifungal therapy. Interestingly, our study found that the direction of follow-up CRP tended to be scattered and difficult to predict. The change in CRP within the first 2 weeks was not able to predict 18-week mortality; however, this finding was limited by short time interval between baseline and follow-up CRP and loss to follow-up.

Several hypotheses explain the association of elevated baseline CRP and mortality in cryptococcal meningitis. First, elevated CRP may reflect immune dysregulation. Cell-mediated immunity plays a critical role in the host immune response to cryptococcal infection. In the normal host response, type 1 helper T cells (Th1) with protective cytokines activate macrophages to eliminate the phagocytic *Cryptococcus* [19–22]. On the other hand, increase of counter-regulatory cytokines from type 2 helper T cells (Th2) in HIV-infected individuals leads to uncontrolled cryptococcal infection [23–25]. Dysregulation of Th1 and Th2 leads to severe disease and poor outcomes [20, 26, 27]. We also observed that patients with higher plasma CRP presented more often with altered mental status. Previous studies have shown that low Glasgow Coma Scale score reflects high severity of disease and unfavorable outcome [28, 29].

Second, CRP is a sensitive marker of infection [8]. Undiagnosed coinfection is another potential factor that drives the elevation of CRP. We found that the high CRP group had significantly higher prevalence of antibiotic therapy within the first 14 days from enrollment. This indirectly indicated that the

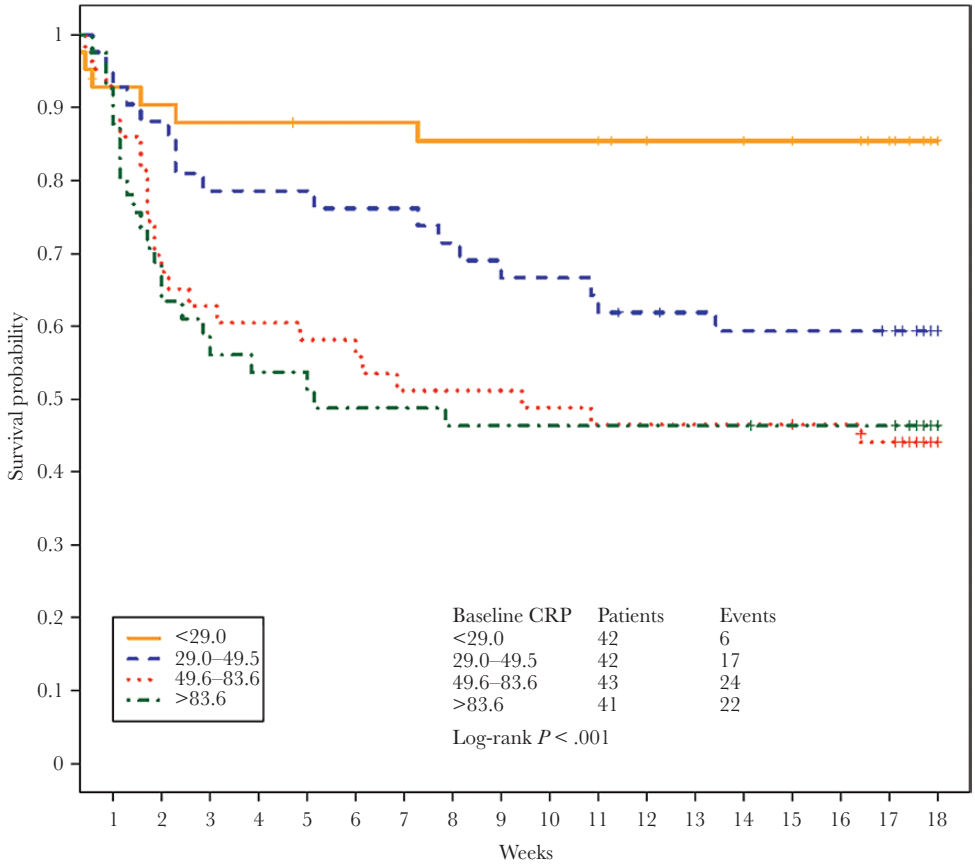

Figure 1. Kaplan-Meier plot of cumulative survival stratified by baseline plasma CRP quartiles. Eighteen-week survival in the low-CRP group (<29 mg/L) was 86% (36/42), which was significantly higher than the 59% survival in the mid-CRP group (29–49.5 mg/L) and 44% survival in the highest 2 quartiles (>49.5 mg/L; $P < .001$). Abbreviation: CRP, C-reactive protein.

clinical suspicion for coinfection was higher than in the low CRP group. The majority of participants in our study had a baseline CD4 T-cell count <50 cells/μL. Even though we did not see the relationship between CRP level and TB status, patients who develop cryptococcal meningitis are more likely to have other opportunistic infections [30, 31]. Given the degree of immune suppression, undiagnosed infections could be a cause of high mortality.

Table 2. Hazard Ratios for 18-Week Mortality From Cox Regression Model

	Multivariate Analysis	
Variable	Hazard Ratio (95% CI)	*P* Value
Plasma CRP, per 10 mg/L	1.084 (1.031–1.139)	.003
Age, per 10 y	1.130 (0.847–1.508)	.41
Male sex	1.078 (0.654–1.777)	.77
Glasgow Coma Scale score <15	1.587 (0.945–2.666)	.08
CSF white cell count <5 cells/μL	1.388 (0.786–2.449)	.25
Currently on HIV therapy	1.192 (0.713–1.991)	.50
Receiving antibiotic therapy within 14 d	1.160 (0.695–1.935)	.57
TB diagnosis at baseline or within 14 d	1.495 (0.821–2.720)	.19

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; TB, tuberculosis.

Another explanation is systemic inflammation from immune reconstitution inflammatory syndrome (IRIS). We found that the median baseline CRP in participants who initiated ART within a month was significantly higher than that of participants who were on ART for a longer period. Shorter duration of ART before developing cryptococcal meningitis has been linked to poor outcomes [32]. In other words, an unmasked IRIS likely augments the risk of death in preexisting subclinical cryptococcal meningitis. This finding suggests that CRP could be a marker for unmasked IRIS, which leads to high mortality. Furthermore, CRP >32 mg/L is known to be a surrogate marker for paradoxical IRIS after treatment initiation [33].

There are some limitations. Our study includes a prospective analysis of a subgroup in a clinical trial, limiting our ability to differentiate causation from association. We conducted this study in HIV-infected Ugandans; therefore, the results may not be generalizable to other immunocompromised or transplant populations. We hypothesized several explanations for the elevated CRP, including undiagnosed concurrent bacterial or mycobacterial infections, immune dysregulation, or IRIS. However, in reality, elevated CRP likely has heterogeneous and multifactorial etiologies in this sick population, precluding a singular

approach to management of these patients. Nevertheless, our study demonstrates that CRP can contribute to prognostication that a poor outcome is more likely, suggesting that further research is warranted to determine if elevated CRP is a modifiable risk factor. Evaluation of change in CRP over time was limited by small sample size with repeat testing.

To our knowledge, this is the first study to describe the relationship between plasma CRP level and mortality of HIV-infected individuals with cryptococcal meningitis. A bundle of discovered prognostic clinical and biomarker factors could lead to a comprehensive scoring system to predict outcomes of cryptococcal meningitis in the future. Elevated CRP should prompt additional diagnostic evaluations in persons with advanced AIDS. Additionally, this could potentially lead to tailor-made adjunctive therapies or individualized interventions in the poor prognostic group.

In conclusion, elevated baseline CRP reflects high mortality and poor outcome. This finding suggests that baseline plasma CRP could be a promising prognostic biomarker in cryptococcal meningitis. Additional clinical studies investigating the long-term trends of other inflammatory biomarkers in the future would be helpful.

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