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MAJOR ARTICLE

Mid–Upper Arm Circumference Is a Strong Predictor of Mortality Among Ugandan Adults With HIV-Associated Cryptococcal Meningitis: A Prospective Cohort Study

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Background. Mortality among adults diagnosed with HIV-associated cryptococcal meningitis remains high (24%–40%). We hypothesized that nutritional state, as measured by mid–upper arm circumference (MUAC), is a potentially modifiable risk factor for mortality.

Methods. Ugandan adults hospitalized with HIV-associated cryptococcal meningitis had MUAC measurements performed at baseline. We compared MUAC measurements with baseline clinical and demographic variables and investigated associations with survival using Cox regression.

Results. Of 433 participants enrolled, 41% were female, the median CD4 T-cell count (interquartile range [IQR]) was 15 (6–41) cells/μL, and 37% were antiretroviral therapy naïve. The median MUAC (IQR) was 24 (22–26) cm, the median weight (IQR) was 53 (50–60) kg, and MUAC correlated with weight (Pearson $r = 0.6$; $P < .001$). Overall, 46% (200/433) died during the 18-week follow-up. Participants in the lowest MUAC quartile (≤22 cm) had the highest mortality: 39% (46/118) at 2 weeks and 62% (73/118) at 18 weeks. A baseline MUAC ≤22 cm was associated with an 82% increased risk of 18-week mortality as compared with participants with an MUAC >22 cm (unadjusted hazard ratio, 1.82; 95% CI, 1.36–2.42; $P < .001$). Following adjustment for antiretroviral therapy status, CD4 count, hemoglobin, amphotericin dose, and tuberculosis status, the adjusted hazard ratio was 1.84 (95% CI, 1.27–2.65; $P < .001$). As a continuous variable, 18-week mortality was reduced by 10% for every 1-cm increase in MUAC. CSF Th17 immune responses were positively associated with MUAC quartile.

Conclusions. MUAC measurement is a simple bedside tool that can identify adults with HIV-associated cryptococcal meningitis at high risk for mortality for whom an enhanced bundle of care, including nutritional supplementation, should be further investigated.

Keywords. cryptococcal meningitis; HIV; malnutrition; mid–upper arm circumference; mortality.

Despite advances in the treatment of HIV-associated cryptococcal meningitis, mortality remains high, accounting for almost 20% of AIDS-related deaths [1]. Ten-week mortality among adults diagnosed with HIV-associated cryptococcal meningitis is 24%–40% even in the context of clinical trials [2, 3]. Risk factors for mortality are well described and include Glasgow Coma Scale score <15 [4], anemia [5], acute kidney injury [6], hyponatremia [7], tuberculosis (TB) coinfection [8, 9], and cytomegalovirus (CMV) viremia [10]. Lack of cryptococcal antigen screening and late presentation to care are also contributors to cryptococcal meningitis mortality [11]. Poor nutritional status as measured by weight, body mass index, or mid–upper arm circumference (MUAC) has been shown to be independently associated with increased 2-month mortality in adults with HIV [12]. Notably, in individuals with HIV-associated TB disease, there is a 9% reduction in the relative risk in mortality when MUAC is ≥18.5 cm, compared with those with an MUAC <18.5 cm [13].

MUAC is a quick, simple, and affordable anthropometric measurement, developed in the 1960s to diagnose malnutrition in children [14]. Its application has subsequently been validated

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for use in adults [15]. Studies in adults have shown a robust correlation between MUAC and body mass index (weight kg/height m^2) [14, 16]. The use of MUAC as a simple-to-conduct bedside measurement may serve as a potentially valuable indicator of nutritional status in critically ill adults, who are unable to stand for weight and height measurements. There are, however, no established standardized MUAC cutoffs for detecting malnourishment in adults [17]. As a result, MUAC measurements have not been used to date as a prognostic tool among hospitalized adults with advanced HIV disease, who may benefit from nutritional support. We sought to understand the value of MUAC measurements in identifying adults with HIV-associated cryptococcal meningitis at increased risk for both early (2-week) and late (18-week) mortality. In this nested cohort study, we aimed to (i) describe the range of MUAC measurements in hospitalized adults with HIV-associated cryptococcal meningitis, (ii) investigate an association between MUAC measurement and all-cause mortality over time, and (iii) investigate for differential CSF cytokine responses stratified by MUAC group.

METHODS

We conducted a prospective cohort study of Ugandan adults diagnosed with HIV-associated cryptococcal meningitis, nested within the ASTRO-CM (Adjunctive Sertraline for the Treatment of Cryptococcal Meningitis) randomized clinical trial [18, 19]. ASTRO-CM participants were living with HIV, age ≥18 years, with confirmed index cryptococcal meningitis, defined by a positive cerebrospinal fluid (CSF) cryptococcal antigen (CrAg). Participants were recruited from Mulago National Referral Hospital and Mbarara Regional Referral Hospital between March 2015 and May 2017. All participants received standard-of-care cryptococcal meningitis treatment (10–14 days of intravenous amphotericin B deoxycholate 0.7–1 mg/kg and 800–1200 mg of oral fluconazole) and were randomized to additionally receive adjunctive sertraline or matching placebo for 14 weeks. Participants were followed for 18 weeks post–cryptococcal meningitis diagnosis; 2-week (early) and 18-week (late) mortality were the primary outcomes of interest. Sertraline had no clinical benefit on 2- or 18-week mortality in cryptococcal meningitis [18].

MUAC Measurements

MUAC measurements were performed at baseline (time of cryptococcal meningitis diagnosis). MUAC was measured using a standardized protocol with measurement of the left arm positioned at a right angle, midway between the tip of the shoulder and the tip of the elbow, using a standard measuring tape, by a trained study nurse.

TB Diagnoses and Definitions

TB diagnostics (Sputum Xpert MTB/Rif [Cepheid, Sunnyvale, CA, USA], chest radiography, abdominal ultrasound scan) were employed at physician discretion at any time during the study period based on clinical syndrome. TB disease was defined as microbiologically confirmed or clinically suspected TB (empirical treatment). Participants who had received antituberculous therapy >14 days before cryptococcal meningitis diagnosis were classified as having previously treated TB, while those who received TB therapy within 14 days on either side of cryptococcal meningitis diagnosis were classified as having prevalent TB disease. Participants started on TB therapy >14 days after cryptococcal meningitis diagnosis were classified as having incident TB disease.

CSF Cytokine Analysis

We hypothesized that malnutrition may be associated with impaired immune responses within our cohort. In an exploratory analysis, to investigate whether nutritional status—as measured by MUAC—was associated with a differential cytokine immune response, baseline CSF cytokine and chemokine concentrations were measured for 317 participants. Baseline CSF samples were centrifuged, and supernatant was collected and stored at −80°C for subsequent measurement with available stored CSF for analysis. CSF cytokines were measured using the Human Luminex Discovery Assay (R&D systems, Minneapolis, MN, USA), employing multi-analyte profiling to quantify levels of 43 cytokines and chemokines.

Patient Consent and Ethics

All participants (or a surrogate in cases of mental incapacity) provided written informed consent for inclusion in the ASTRO-CM trial. In cases of surrogate consent, re-consent from the participant was taken when capacity was regained. Approval for the ASTRO-CM trial was obtained from the Mulago Research Ethics Committee, the University of Minnesota institutional review board, the Uganda National Council for Science and Technology, and the Uganda National Drug Authority.

Statistical Analyses

MUAC at baseline (at the time of cryptococcal meningitis diagnosis) was the primary exposure of interest. To assess the effect of MUAC values, participants were classified into MUAC groups: quartile 1 (MUAC ≤22 cm), quartiles 2 and 3 combined (MUAC >22 to 26 cm), and quartile 4 (MUAC >26 cm). Baseline demographics, clinical characteristics, laboratory parameters, amphotericin B deoxycholate dose, and laboratory adverse events were summarized across MUAC quartiles as counts and percentages for categorical data and as medians (with interquartile ranges) for continuous data. Chi-square tests or Kruskal-Wallis tests, as appropriate, were used to compare those in the lowest MUAC quartile (MUAC ≤22 cm) with those in quartiles 2 and above. We also assessed differences in CSF cytokine/chemokine levels comparing quartile 1 with quartiles 2 and above using a linear regression analysis.

Table 1. Baseline Characteristics and Clinical Outcomes by Mid–Upper Arm Circumference Group in Persons With HIV and Cryptococcal Meningitis

Characteristics	No.	Overall No. (%) or Median [IQR]	No.	MUAC ≤ 22 cm No. (%) or Median [IQR]	No.	22 < MUAC ≤ 26 cm No. (%) or Median [IQR]	No.	MUAC > 26 cm No. (%) or Median [IQR]	*P* Value[a]
Demographics and baseline clinical and laboratory covariates									
Age, y	433	35 [29–40]	118	34 [29–39]	214	35 [29–40]	101	36 [30–44]	.27
Female	433	176 (41)	118	51 (43)	214	79 (37)	101	46 (46)	.51
MUAC, cm	433	24 [22–26]	118	21 [20–22]	214	24 [23–25]	101	28 [27–30]	<.001
Weight, kg	418	53 [50–60]	114	47 [43–52]	209	53 [50–60]	95	61 [58–68]	<.001
Glasgow Coma Scale <15	433	189 (44)	118	47 (40)	214	93 (44)	101	49 (49)	.33
Seizure	432	63 (15)	118	18 (15)	213	28 (13)	101	17 (17)	.81
ART experienced	433	269 (62)	118	74 (63)	214	135 (63)	101	60 (59)	.88
ART[b] duration, mo	241	6.4 [1–35]	62	5.4 [1–25]	123	6.9 [1–35]	56	4.1 [1–40]	.99
CD4 count, cells/μL	410	15 [6–41]	111	15 [6–32]	200	14 [6–45]	99	19 [7–43]	.17
Hemoglobin, g/dL	399	11.4 [9.9–12.9]	111	10.5 [9.0–12.0]	199	11.5 [10.0–13.1]	89	12.2 [10.7–14.0]	<.001
Cerebrospinal fluid parameters									
Opening pressure, mmH_2O	387	270 [180–390]	108	250 [174–375]	187	265 [180–380]	92	305 [200–448]	.28
Cryptococcus, log_{10} CFU/mL	389	4.8 [3.5–5.6]	108	4.8 [3.3–5.6]	191	4.8 [3.7–5.6]	90	4.6 [3.4–5.8]	>.99
White cells/μL	419	<5 [<5–45]	112	<5 [<5–35]	210	<5 [<5–60]	97	<5 [<5–<5]	.18

Abbreviations: ART, antiretroviral therapy; CFU, colony-forming units; IQR, interquartile range; MUAC, mid–upper arm circumference; QCC, quantitative cryptococcal culture; TB, tuberculosis.

[a]*P* values determined by chi-square or Wilcoxon, comparing Q1 (MUAC ≤22 cm) with groups 2 to 4.

[b]Among those on ART.

All-cause mortality at 2 and 18 weeks was the primary outcome of interest. Univariate and adjusted Cox proportional hazards models assessed the impact of MUAC with 2 different types of models: a hazard ratio (HR) comparing those in the lowest quartile (MUAC ≤22 cm) with those in quartiles 2 and above and a hazard ratio for MUAC as a continuous measurement. Adjusted models considered the impact of baseline CD4 cell count, ART status, hemoglobin, amphotericin B deoxycholate dose, and time-updated indicators for TB status. Secondary outcomes included a serious adverse event and specific grade ≥3 laboratory adverse events.

RESULTS

Baseline Characteristics

Between March 9, 2015, and May 29, 2017, we recruited 460 adults with HIV-associated cryptococcal meningitis into the ASTRO-CM trial. Overall, 433 participants had a baseline MUAC measurement, 331 from Mulago hospital and 102 from Mbarara hospital. MUAC measurements were normally distributed across the cohort, with a median MUAC (interquartile range [IQR]) of 24 (22–26) cm (Supplementary Figure 1). Among study participants, 27% (118/433) were in the lowest quartile 1 (median MUAC, 21 cm), 50% (214/433) were distributed across quartiles 2 and 3 combined (median MUAC, 24 cm), and 23% (101/433) were in the highest quartile 4 (median MUAC, 28 cm) (Table 1). Baseline weight (by scale or estimated) was available for 96% (418/433) of the cohort, with a median weight (IQR) of 53 (50–60) kg. There was a strong correlation between MUAC measurement and weight (Pearson correlation $r = 0.63$; $P < .001$) (Supplementary Figure 2).

Baseline demographic variables were similar across MUAC groups (Table 1). At baseline, the median age (IQR) was 35 (29–40) years, 41% (176/433) were female, the median CD4 T-cell count (IQR) was 15 (6–41) cells/μL, and 37% (164/433) were ART naïve. There were no statistically significant differences for age, sex, CD4 T-cell count, or ART status between those in lowest quartile (MUAC ≤22 cm) and all others. At baseline, 44% (189/433) of participants had a Glasgow Coma Scale score <15, and 15% (63/432) had self-reported seizures, with no statistically significant difference in Glasgow Coma Scale score or seizures across MUAC groups. The baseline hemoglobin level was lowest in quartile 1 (median [IQR], 10.5 [9.0–12.0] g/dL) compared with quartiles 2 and 3 (median [IQR], 11.5 [10.0–13.1] g/dL) and the highest quartile (median [IQR], 12.2 [10.7–14.0] g/dL; $P < .001$).

Primary Outcome Analysis

We examined 18-week mortality by baseline MUAC and MUAC as a continuous variable. Overall all-cause mortality was 27% (116/433) at 2 weeks and 46% (200/433) at 18 weeks. Mortality by 2 weeks was 39% in quartile 1, 24% in quartiles 2 and 3 combined, and 19% in quartile 4 ($P = .001$) (Table 2). By 18 weeks, mortality was 62% in quartile 1, 44% in quartiles 2 and 3 combined, and 32% in quartile 4 ($P < .001$). Having a baseline MUAC measurement ≤22 cm was associated with an increased risk of mortality at 18 weeks (unadjusted hazard ratio [aHR], 1.82; 95% CI, 1.36–2.42; $P < .001$; aHR, 1.84; 95% CI, 1.27–2.45; $P = .001$) (Figure 1; Supplementary Table 1). When we analyzed MUAC as a continuous variable, we found a 10% lower risk of 18-week mortality per 1-cm increase in MUAC (unadjusted HR, 0.90 per cm increase in

MUAC; 95% CI, 0.85–0.94; $P < .001$). After adjusting for baseline CD4 T-cell count, ART status, hemoglobin, amphotericin B deoxycholate dose per MUAC cm, and time-updated TB coinfection status, the adjusted Hazard Ratio was 0.86 per cm increase in MUAC; 95% CI 0.80–0.93; $P < .001$ (Supplementary Table 1). Other risk factors for 18-week mortality are detailed in Supplementary Table 3.

Amphotericin Dosing and Adverse Effects

Given that amphotericin B deoxycholate is weight based, we evaluated the dose administered to study participants by both weight and MUAC group (Table 3). Participants in the lowest MUAC quartile received a higher dose of amphotericin B deoxycholate per kg of weight (median dose, 1 mg/kg; 95% CI, 0.9–1.1), compared with the amphotericin B deoxycholate dose received in quartiles 2 and 3 (median dose, 0.9 mg/kg; 95% CI, 0.8–1.0) and the highest quartile (median dose, 0.8 mg/kg; 95% CI, 0.7–0.9; $P < .001$). Similarly, the amphotericin B deoxycholate dose received per MUAC cm was also higher in the lowest MUAC quartile (median dose, 2.3 mg/MUAC cm; 95% CI, 2.3–2.4), compared with quartiles 2 and 3 (median dose, 2.1 mg/MUAC cm; 95% CI, 1.7–1.9) and the highest quartile (median dose, 1.8 mg/MUAC cm; 95% CI, 1.7–1.9; $P < .001$).

Due to the known toxicities of amphotericin B deoxycholate, we routinely evaluated the frequency of grade ≥3 laboratory adverse events (Table 3). We found a higher percentage of grade ≥3 hemoglobin adverse events in the lowest quartile (33%), compared with quartiles 2 and 3 (25%) and the highest quartile (15%; $P = .02$). There was no statistically significant difference in the frequency of acute kidney injury, hypokalemia, or hyponatremia across MUAC groups.

Table 2. Mortality in Cryptococcal Meningitis by Mid–Upper Arm Circumference

Time Period	Overall	MUAC ≤ 22 cm	22 < MUAC ≤ 26 cm	MUAC > 26 cm	*P* Value[a]
No.	433	118	214	101	…
2-week mortality	116 (27)	46 (39)	51 (24)	19 (19)	.001
18-week mortality	200 (46)	73 (62)	95 (44)	32 (32)	<.001

Data are presented as No. (%).

Abbreviation: MUAC, mid–upper arm circumference.

[a]*P* values determined by chi-square.

Tuberculosis Diagnosis

We examined TB diagnoses among study participants over the 18-week study follow-up period (Figure 2). At baseline, prevalent TB was observed in 6.8% of participants in the lowest quartile, 6.1% in those in quartiles 2 and 3, and 8.9% in the highest

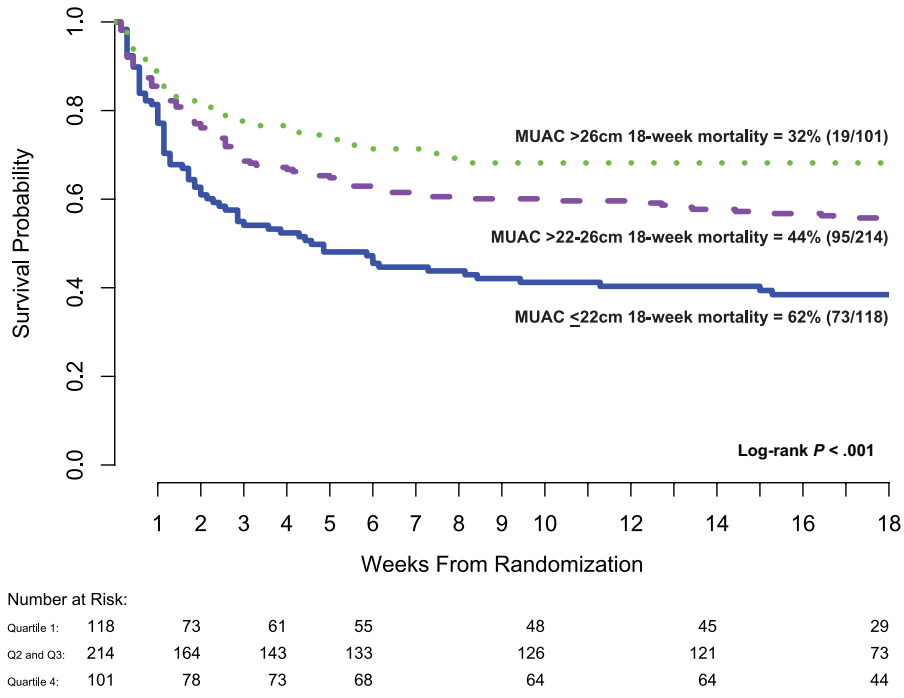

Figure 1. Eighteen-week mortality by mid–upper arm circumference group in persons with HIV and cryptococcal meningitis. In comparing the mortality for MUAC ≤22 cm vs MUAC >22 cm, the hazard ratio was 1.82 (95% CI, 1.36–2.42; $P < .001$). When adjusted for CD4 T-cell count, antiretroviral therapy status, baseline hemoglobin, amphotericin B deoxycholate dose per MUAC cm, and time-updated tuberculosis status, the adjusted hazard ratio was 1.84 (95% CI, 1.27–2.65; $P < .001$). Abbreviation: MUAC, mid–upper arm circumference.

Table 3. Amphotericin Treatment Dose and Adverse Events by Mid–Upper Arm Circumference Group Through 18 Weeks

	MUAC ≤ 22 cm	22< MUAC ≤ 26 cm	MUAC >26 cm	*P* Value
Amphotericin B dose, mg/kg				
No.	114	208	93	…
Max dose, mg/kg	1.9	1.3	1.1	…
Median [IQR] dose, mg/kg	1.0 [0.9–1.1]	0.9 [0.8–1.0]	0.8 [0.7–0.9]	<.001
Min dose, mg/kg	0.7	0.7	0.5	…
Amphotericin B dose, mg/MUAC cm				
No.	118	213	99	…
Max dose, mg/MUAC cm	3.6	2.3	2.0	…
Median [IQR] dose, mg/MUAC cm	2.3 [2.3–2.4]	2.1 [2.0–2.1]	1.8 [1.7–1.9]	<.001
Min dose, mg/MUAC cm	1.5	1.3	1.1	…
Serious adverse events, No. (%)	14 (12)	25 (12)	6 (6)	.54
Grade ≥3 lab adverse event,[a] No. (%)				
Hemoglobin <9 g/dL	39 (33)	54 (25)	15 (15)	.02
Creatinine >1.8 upper limit normal	19 (16)	35 (16)	16 (16)	.98
Sodium <125 mmol/L	43 (36)	90 (42)	40 (40)	.36
Potassium <2.5 mmol/L	21 (18)	33 (15)	17 (17)	.63

P value determined by Kruskal-Wallis test of distribution comparing the lowest quartile (MUAC ≤22 cm) with quartiles 2 to 4.

Abbreviations: IQR, interquartile range; MUAC, mid–upper arm circumference.

[a]Lab adverse events of grade ≥3 by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2017, was used to determine grading of lab adverse events.

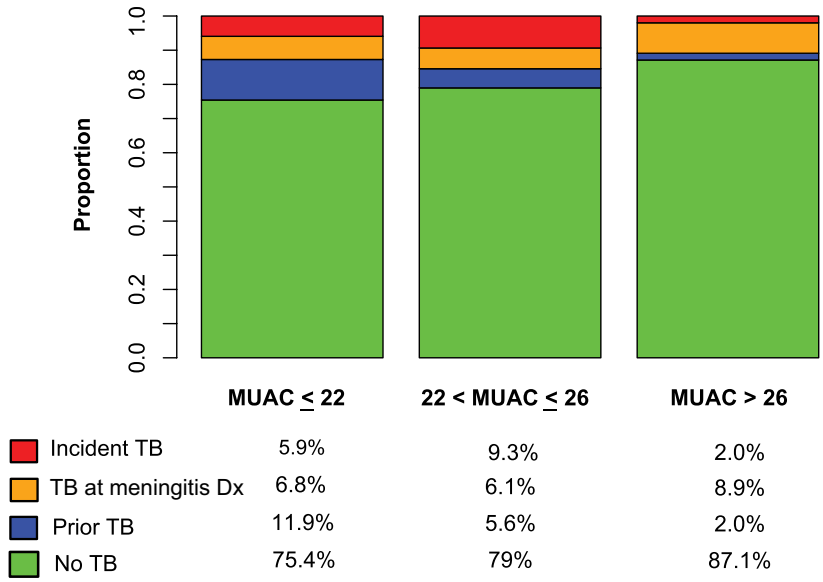

Figure 2. Final tuberculosis diagnosis by mid–upper arm circumference group in persons with HIV and cryptococcal meningitis. Tuberculosis status throughout the follow-up study period. Prior TB disease was defined as having received TB therapy >14 days before cryptococcal meningitis diagnosis. TB at meningitis diagnosis (prevalent TB) was defined as those who received TB therapy within 14 days of cryptococcal meningitis diagnosis. Incident TB was defined as those who received TB therapy >14 days after cryptococcal meningitis diagnosis. The distribution of TB classification was not significantly different for those in the lowest MUAC quartile compared with those in quartile 2 or above ($P = .05$). Abbreviations: MUAC, mid–upper arm circumference; TB, tuberculosis.

quartile. At the end of the 18-week follow-up period, 80% (346/433) had no diagnosis of TB, while 6% (28/433) had a prior history of TB at baseline, 9% (30/433) had prevalent TB, and 9% (29/433) had experienced incident TB disease. The distribution of TB classifications was marginally different for those in the lowest MUAC quartile compared with those in other groups ($P = .05$).

CSF Cytokine Analysis

In assessing potential differences in CSF immune response that could account for survival differences to generate hypotheses, we found >2-fold lower mean concentrations of T helper cell 17 (Th17) cytokines of interleukin (IL)-17 ($P = .02$) and IL-25 ($P = .02$) as well as tumor necrosis factor (TNF)–related apoptosis–induced ligand (TRAIL; $P < .01$) among those with

MUAC ≤22 cm as compared with MUAC >26 cm. There were also marginal differences in Granzyme B ($P = .05$), IL-12 ($P = .05$), and transforming growth factor–α (TGF-α; $P = .05$) (Supplementary Table 2).

DISCUSSION

Our study demonstrates that among adults with HIV-associated cryptococcal meningitis, an MUAC ≤22 cm at baseline is strongly associated with increased mortality. For every 1-cm increase in MUAC, participants had a ∼10% decrease in risk of death at 18 weeks. Participants with an MUAC ≤22 cm had an 84% increased hazard of 18-week mortality compared with those with an MUAC >22 cm. Our data also suggest that participants with a baseline MUAC ≤22 cm were more likely to experience grade ≥3 anemia. An MUAC ≤22 cm at the time of cryptococcal meningitis diagnosis represents a potentially modifiable risk factor to improve survival outcomes in adults with advanced HIV disease and cryptococcal meningitis.

Our study is consistent with previously published data that demonstrate that nutritional status is an important predictor of mortality in HIV disease [9], and specifically in cryptococcal meningitis. Jarvis et al. have previously shown that body weight >50 kg was independently associated with 40% lower odds of 10-week mortality among individuals with cryptococcal meningitis [20, 21]. However, we know that in our clinical context, it is difficult to obtain weight measurements consistently, given the level of critical illness and frailty. Clinicians often estimate weight, which has clinical implications for risk stratification and, more tangibly, medication dosing. Our research contributes to the expanding body of evidence supporting the strong correlation between MUAC and weight [14, 16]. Given the good concordance between MUAC and weight, we suggest that MUAC could be used either alongside, or instead of, weight or body mass index measurements.

We previously reported that TB coinfection in adults with HIV-associated cryptococcal meningitis is associated with increased risk of death by 18 weeks [9, 22]. Data from our current cohort demonstrate that 7% of people with an MUAC ≤22 cm had prevalent TB at cryptococcal diagnosis and 6% had incident TB disease diagnosed during follow-up. Given the high early mortality in individuals with an MUAC ≤22 cm and loss of follow-up opportunities to undergo TB diagnosis, we postulate that this an underestimate of the true TB coinfection burden. While we observed a possible statistical difference in TB diagnoses between those in the lowest MUAC quartile compared with those in quartile 2 and above ($P = .05$), we hypothesize that undiagnosed TB coinfection may have contributed to the increased mortality observed in those with an MUAC ≤22 cm. Indeed, as demonstrated by Gupta et al. in a meta-analysis of autopsy studies of people with HIV, ∼50% of TB diagnoses remain undiagnosed and untreated at the time of in-hospital death [23].

Given the considerable toxicity associated with IV amphotericin B deoxycholate, particularly with courses exceeding 7 days, we hypothesized that the observed increased mortality among individuals with an MUAC ≤22 cm may be in part attributable to amphotericin B deoxycholate toxicity. In fact, in our adjusted mortality models, accounting for amphotericin dose per MUAC cm and hemoglobin levels, the statistical significance of 2-week mortality was no longer sustained. We observed that individuals with an MUAC ≤22 cm had lower hemoglobin levels at baseline, received higher doses of amphotericin B deoxycholate, and had significantly more grade ≥3 laboratory adverse events due to anemia. Baseline anemia is a well-established risk factor for increased mortality at 10 weeks [5, 24]. Significant declines in hemoglobin (2.3–4.2 g/dL) have been reported by day 14 of amphotericin B deoxycholate therapy [5, 24]. Given that individuals with an MUAC ≤22 cm were more likely to have baseline anemia and receive higher doses per kg and MUAC cm of amphotericin B deoxycholate, development of worsening anemia over the 2 weeks of antifungal therapy may have contributed to the early 2-week mortality observed in our study. Our findings provide additional support for recent publications advocating for the use of shorter durations of amphotericin B deoxycholate [3] or use of single-dose liposomal amphotericin B [2].

In HIV-associated cryptococcal meningitis, the presence of a CSF inflammatory response has been shown to be correlated with a more rapid fungal clearance and improved survival [25]. We sought to understand if malnutrition influences the immune response, potentially contributing to the increased overall mortality in those with an MUAC ≤22 cm. Through our exploratory cytokine analyses, we have demonstrated statistically significantly lower levels of CSF IL-17A and IL-25 at baseline among those with an MUAC ≤22 cm as compared with those with a baseline MUAC >22 cm. IL-17A and IL-25, cytokines belonging to the IL-17 family of cytokines, are produced by T helper 17 (Th17) cells and Th2 cells, respectively [26]. While IL-17A typically elicits a proinflammatory response, the effects of IL-25 can vary, exhibiting either a synergistic inflammatory or anti-inflammatory effect [26]. IL-17 production has been found to exhibit antifungal immunity [27]. In cryptococcal infection, stimulation of Th17 cells leads to an increased production of IL-17 and is associated with a faster rate of fungal clearance and improved survival [25]. Hence, we postulate that malnutrition plays a key role in dampening the inflammatory response associated with CSF cryptococcal clearance and survival.

Based on our study findings, there are several key interventions that can be implemented to help decrease mortality in individuals with HIV-associated cryptococcal meningitis. First, we recommend that MUAC be systematically measured for all hospitalized adults diagnosed with HIV-associated cryptococcal meningitis, as it may provide surrogate information on

a patient's weight and nutritional status, factors that may not be obtained otherwise. Second, food-based nutritional supplementation has recently been shown to significantly improve survival in adults with microbiologically confirmed pulmonary tuberculosis (TB) [28]. We recommend that nutritional supplementation be further investigated for individuals with advanced HIV diseases presenting with opportunistic infections, including cryptococcal meningitis, especially if they present with an MUAC ≤22 cm. Lastly, we recommend early enhanced TB screening and treatment for hospitalized patients diagnosed with advanced HIV and cryptococcal meningitis.

Our study has several limitations. One critical limitation was the lack of TB diagnostic capacity at the time of the study, with the majority of TB diagnoses being clinical [22]. Therefore, while we conducted a time-updated multivariate analysis with adjustment for TB disease, we recognize that due to suboptimal TB diagnostics, undiagnosed TB may still be acting as a partial confounder of the observed association between MUAC measurement and death. This may have been compounded by an element of immortal time bias, in that those in the lowest MUAC quartile were most likely to die before TB could be diagnosed. As this is a retrospective analysis of prospective data collection, another potential limitation is confounding due to unmeasured variables.

CONCLUSIONS

MUAC is a cost-effective and readily accessible bedside tool that can be used to identify persons with cryptococcal meningitis at increased risk of both early (2-week) and late (18-week) mortality. Implementation of an enhanced bundle of care that includes nutritional assessment, optimized TB screening, and nutritional supplementation should be considered. Food-based nutritional supplementation as a potential therapeutic intervention to improve survival outcomes in advanced HIV disease and cryptococcal meningitis warrants further investigation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. 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;** 22:1748–55.
2. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. N Engl J Med **2022;** 386:1109–20.
3. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med **2018;** 378: 1004–17.
4. Lofgren S, Hullsiek KH, Morawski BM, et al. Differences in immunologic factors among patients presenting with altered mental status during cryptococcal meningitis. J Infect Dis **2017;** 215:693–7.
5. Tugume L, Morawski BM, Abassi M, et al. Prognostic implications of baseline anaemia and changes in haemoglobin concentrations with amphotericin B therapy for cryptococcal meningitis. HIV Med **2017;** 18:13–20.
6. Schutz C, Boulware DR, Huppler-Hullsiek K, et al. Acute kidney injury and urinary biomarkers in human immunodeficiency virus-associated cryptococcal meningitis. Open Forum Infect Dis **2017;** 4:XXX–XX.
7. Tugume L, Fieberg A, Ssebambulidde K, et al. Association of hyponatremia on mortality in cryptococcal meningitis: a prospective cohort. Open Forum Infect Dis **2022;** 9:XXX–XX.
8. Rutakingirwa MK, Kiiza TK, Rhein J. False negative' CSF cryptococcal antigen with clinical meningitis: case reports and review of literature. Med Mycol Case Rep **2020;** 29:29–31.
9. Cresswell FV, Ellis J, Kagimu E, et al. Standardized urine-based tuberculosis (TB) screening with TB-lipoarabinomannan and Xpert MTB/RIF ultra in Ugandan adults with advanced human immunodeficiency virus disease and suspected meningitis. Open Forum Infect Dis **2020;** 7:XXX–XX.
10. Skipper C, Schleiss MR, Bangdiwala AS, et al. Cytomegalovirus viremia associated with increased mortality in cryptococcal meningitis in Sub-Saharan Africa. Clin Infect Dis **2020;** 71:525–31.
11. Levin AE, Bangdiwala AS, Nalintya E, et al. Outpatient cryptococcal antigen screening is associated with favorable baseline characteristics and improved survival in persons with cryptococcal meningitis in Uganda. Clin Infect Dis **2022;** 76: e759–65.
12. Gupta-Wright A, Fielding K, Wilson D, et al. Tuberculosis in hospitalized patients with human immunodeficiency virus: clinical characteristics, mortality, and implications from the rapid urine-based screening for tuberculosis to reduce AIDS related mortality in hospitalized patients in Africa. Clin Infect Dis **2020;** 71:2618–26.
13. Bayowa JR, Kalyango JN, Baluku JB, et al. Mortality rate and associated factors among patients co-infected with drug resistant tuberculosis/HIV at Mulago National Referral Hospital, Uganda, a retrospective cohort study. PLOS Glob Public Health **2023;** 3:e0001020.
14. Thorup L, Hamann SA, Kallestrup P, et al. Mid-upper arm circumference as an indicator of underweight in adults: a cross-sectional study from Nepal. BMC Public Health **2020;** 20:1187.
15. Tang AM, Chung M, Dong KR, et al. Determining a global mid-upper arm circumference cut-off to assess underweight in adults (men and non-pregnant women). Public Health Nutr **2020;** 23:3104–13.
16. Das A, Saimala G, Reddy N, et al. Mid-upper arm circumference as a substitute of the body mass index for assessment of nutritional status among adult and adolescent females: learning from an impoverished Indian state. Public Health **2020;** 179:68–75.
17. Maalouf-Manasseh Z, Remancus S, Milner E, et al. Global mid-upper arm circumference cut-offs for adults: a call to action. Public Health Nutr **2020;** 23: 3114–5.
18. Rhein J, Huppler Hullsiek K, Tugume L, et al. Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial. Lancet Infect Dis **2019;** 19:843–51.
19. Rhein J, Morawski BM, Hullsiek KH, et al. Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. Lancet Infect Dis **2016;** 16:809–18.
20. Anekthananon T, Manosuthi W, Chetchotisakd P, et al. Predictors of poor clinical outcome of cryptococcal meningitis in HIV-infected patients. Int J STD AIDS **2011;** 22:665–70.

21. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. Clin Infect Dis **2014;** 58:736–45.
22. Rutakingirwa MK, Cresswell FV, Kwizera R, et al. Tuberculosis in HIV-associated cryptococcal meningitis is associated with an increased risk of death. J Clin Med **2020;** 9:781.
23. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS **2015;** 29:1987–2002.
24. Bicanic T, Bottomley C, Loyse A, et al. Toxicity of amphotericin B deoxycholate-based induction therapy in patients with HIV-associated cryptococcal meningitis. Antimicrob Agents Chemother **2015;** 59:7224–31.
25. Jarvis JN, Meintjes G, Bicanic T, et al. Cerebrospinal fluid cytokine profiles predict risk of early mortality and immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis. PLoS Pathog **2015;** 11: e1004754.
26. Yuan Q, Peng N, Xiao F, et al. New insights into the function of interleukin-25 in disease pathogenesis. Biomark Res **2023;** 11:36.
27. Sparber F, LeibundGut-Landmann S. Interleukin-17 in antifungal immunity. Pathogens **2019;** 8:54.
28. Bhargava A, Bhargava M, Meher A, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India. Lancet Glob Health **2023;** 11:e1402–11.