Semi-quantitative Cryptococcal Antigen Testing & Mortality in HIV-related Cryptococcal Meningitis

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BACKGROUND

- Elevated baseline cryptococcal antigen (CrAg) titers in blood and CSF are associated with mortality in individuals with HIV-associated cryptococcal meningitis (HIV-CM)[1-2].
- Quantifying CrAg levels at the point of diagnosis could inform risk stratification and care pathways and thereby reduce mortality; however, current methods (CrAg LFA serial dilutions and quantitative fungal cultures) are not feasible for routine use in resource-limited clinical contexts.
- The CrAgSQ (IMMY, Norman, OK, USA) is a one-step, dip-stick assay yielding both a qualitative and semi-quantitative (SQ) score within 10 minutes in blood and CSF.
- CrAgSQ has a high diagnostic accuracy when compared to IMMY CrAg LFA[3-5], and yields CrAgSQ scores associated with clinical outcomes[3], however previous studies have not definitively evaluated the prognostic accuracy of CrAgSQ in individuals with HIV-CM.

METHODS

- We evaluated the prognostic accuracy of CrAgSQ retrospectively in a large cohort of adult participants (≥18 years) with first-episode HIV-CM enrolled onto the AMBITION-cm Phase 3 randomized clinical trial for HIV-CM in Botswana, Zimbabwe, Malawi, Uganda and South Africa; and followed prospectively to 10-weeks.
- Frozen pretreatment CSF and/or plasma were thawed and tested using CrAgSQ as per the manufacturer's instructions yielding scores of 0 to 5+.
- We examined associations between CrAgSQ scores and linked baseline variables including quantitative fungal culture (QFC) and mortality at 2- and 10-weeks using GraphPad Prism *version* 10.2.0.

RESULTS

- Pre-treatment CSF and/or plasma were stored for 796/810 enrolled AMBITION-cm trial participants. 756 CSF and 745 plasma were evaluated.
- Of the 796, 61% were male, median age was 37 years (IQR 32-43), and median CD4 count was 27 cells/μL (IQR 10-58).
- Overall mortality was 13% by 2 weeks, and 27% by 10 weeks.
- In plasma, 0.13% (1/745) were SQ negative, 4.03% (30/745) had an SQ score of 1, 3.49% (26/745) 2, 83.62% (623/745) 3, and 8.72% (65/745) 4.

The risk of mortality increased with increasing plasma CrAg SQ scores. This could help to stratify patients that require more intensive management of cryptococcal meningitis

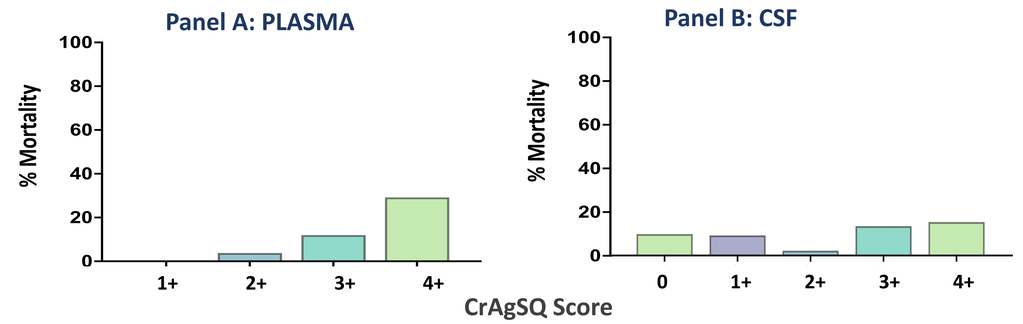


Figure 1. Depicts baseline CrAgSQ scores (x-axis) in plasma (**Panel A**) and CSF (**Panel B**) for the proportion of individuals who died within 2-weeks of initiating antifungal therapy (y-axis). **Mortality risk increased with increasing plasma SQ score (Panel A) (p for trend <0.001),** plasma SQ score could potentially identify individuals who are at risk of dying within 2-weeks.

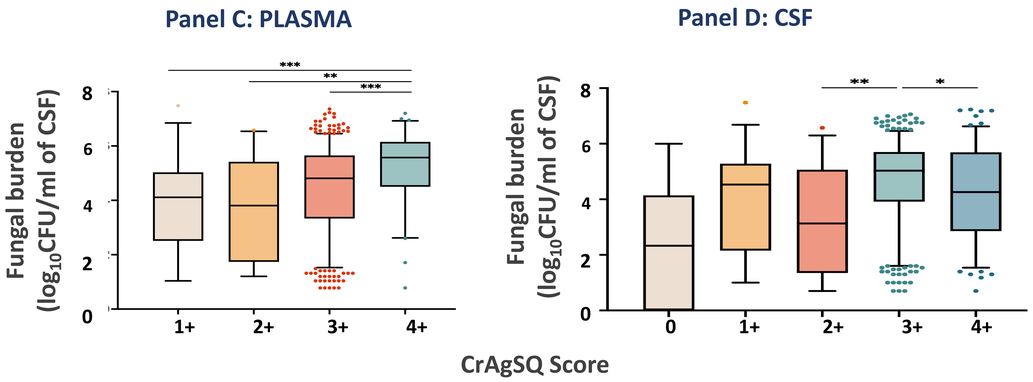


Figure 2. Baseline CSF cryptococcal burden determined by quantitative fungal culture (QFC) (i.e. colony forming units (CFU) per ml of CSF). Log_{10} QFC depicted as medians and interquartile ranges (IQR), are shown on the y-axis for each CrAgSQ score obtained in **Panel C**: plasma (n=745) or **Panel D**: CSF (n=756) on the x-axis. **SQ scores increase with increasing fungal burden.** Kruskal-wallis (plasma: test statistic=26.99, p<0.00001 CSF: test statistic= 37, p<0.00001). SQ scores can potentially be used to estimate baseline fungal burden.

RESULTS Cont.

- In CSF, 1.32% (10/756) were negative, 7.01% (53/756) had an SQ score of 1, 5.69% (43/756) 2, 63.76% (482/756) 3, and 22.22% (168/756) 4.
- CrAg Q scores in plasma and CSF positively correlated with each other (Table 1) and with fungal burdens (Figure 2) p<0.0001.
- Increasing CrAgSQ scores in plasma were strongly associated with increasing mortality risk at 2-weeks (Figure 1 Panel A). Mortality was 0% (0/22) in those with plasma SQ score of 1, 4.4% (1/23) with plasma SQ score of 2, 13.9% (75/540) with plasma SQ score of 3, and 34.55% (19/55) with plasma SQ score of 4 (p for trend <0.001).

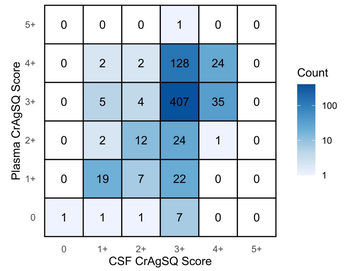


Table 1. Contingency table summarizing SQ results obtained in individuals with paired Plasma- and CSF (n=705) The numbers in each cell of the table are the counts. **Plasma- and CSF- SQ scores were related; Pearson's r=0.4429, (95%CI 0.3815-0.5003) p<0.0001**. One sample type could potentially be used to determine SQ score.

CONCLUSIONS

- Plasma CrAgSQ is a promising prognostic tool for 2-week mortality risk in patients with HIV-CM, making it a viable option for the point of care in resource limited settings.
- Further research is warranted to establish how the test could be used to stratify management in individuals presenting with HIV-associated CM at the point of care.

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ADDITIONAL INFORMATION

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