CLINICAL RELEVANCE OF CRAG SEMIQUANTITATIVE SCORES IN CRAG-POSITIVE AIDS PATIENTS IN VIETNAM

Thu T. Nguyen[*1], Sruthi Venugopalan[*1], Khanh H. Dang[2], Phuong L. Trinh[2], Heera N. Sambath[1], Matthew T. Burke[1], Vo Trieu Ly[3], H Rogier van Doorn[2], Vu Quoc Dat[3], Thuy Le[1]. *Authors contributed equally

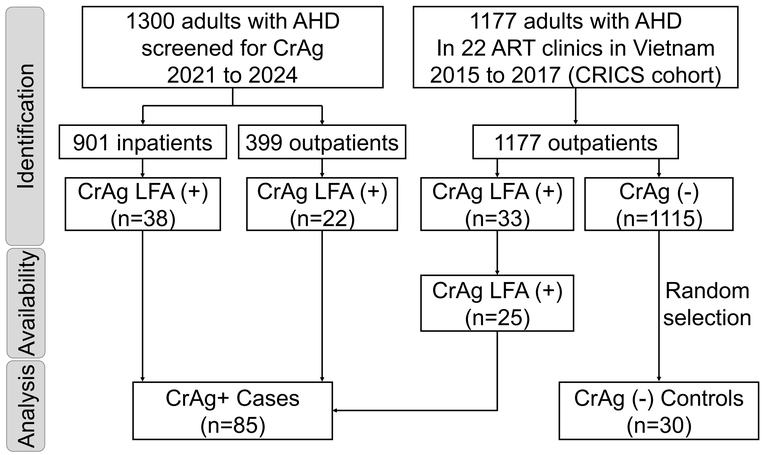
[1] Duke University School of Medicine, Durham, North Carolina, USA, [2] Oxford University Clinical Research Unit in Vietnam, Ho Chi Minh, Vietnam, [3]Hanoi Medical University, Hanoi, Vietnam, [4] Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam

BACKGROUND

- Cryptococcal meningitis (CM) is a major cause of morbidity and mortality in patients with **advanced HIV disease (AHD, CD4 ≤100, WHO stage III/IV).**
- High cryptococcal antigen (CrAg) titer is associated with higher mortality in patients with fulminant CM as well as in asymptomatic CrAg-positive people in Africa. However, these associations have not been investigated in in people with AHD in Southeast Asia.
- **Objective:** We evaluate the diagnostic performance of the CrAg semiquantitative (CrAg SQ) LFA newly developed by IMMY and determine the association of CrAg SQ scores with CrAg titers and mortality in cohorts of inpatient and outpatients with ADH who were CrAg positive in Vietnam.

METHODS

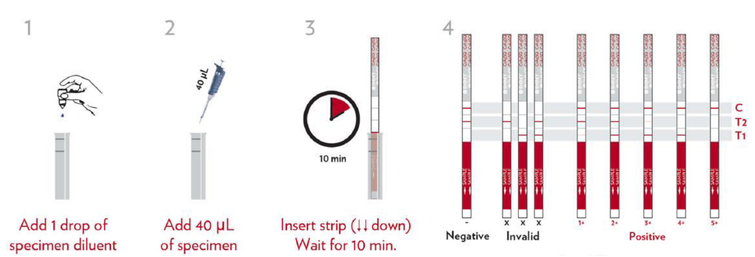
Figure 1. Study population



CrAg: Cryptococcal antigenemia, ADH: advanced disease HIV.

Figure 2. CrAg SQ LFA procedure and scoring.

Samples were diluted 1:1 with sample diluent. CrAg SQ scores were derived from line intensity patterns as follows: T1<T2=1+, T1=T2=2+, T1>T2=3+; only T1=4+; and only T2 and C=negative.



- CrAg SQ LFA has a 98% sensitivity and 97% specificity compared to the standard CrAg LFA.
- CrAg SQ scores are highly correlated to CrAg titers
- Mortality increases by 35% with every one unit increase in CrAg SQ score and increases by 50% with a CrAg SQ score > 3+

RESULTS

- Of 901 inpatient and 1576 outpatients with AHD who underwent CrAg screening, **3.8% (93/2477) were CrAg positive**. Samples were available for 85 CrAg positive cases (38 inpatients, 47 outpatients), and 30 CrAg negative outpatients were randomly selected as controls.
- 83.5% were men. Median age: 34 (IQR: 29-43). Median CD4: 22 (IQR: 8-46).
- Mortality of all CrAg positive patients over 12 months was 28/85 (32.9%), higher in inpatients 42.1% (16/38, 95% CI: 26.7% - 59.1%) than outpatient 25.5% (12/47, 95% CI: 14.4% - 40.6%).

Table 1. CrAg SQ performance compared to CrAg LFA as the reference standard

CrAg SQ	CrAg LFA	
	Positive (n = 85)	Negative (n = 30)
Positive	83 (TP)	0 (FP)
Negative	2 (FN)	30 (FP)
Sensitivity	97.6% (95% CI: 90.9% – 99.6%)	
Specificity	96.9% (95% CI: 82.0% - 99.8%)	

Notes: TP =True Positive, FN = False Negative FN, TN = True Negative, FP = False Positive.

Figure 3. Association between CrAg SQ scores and CrAg titers.

Pearson's correlation coefficient, $r = 0.89$ (95% CI: 0.88 - 0.92), $P < 0.001$.

CrAg SQ score	Median CrAg Titer (IQR)
1+	1:5 (1:5 - 1:8)
2+	1:56 (1:40 - 1:134)
3+	1:5,042 (1:320 - 1:40,342)
4+	1:114,104 (1:7,131 - 1:322,737)

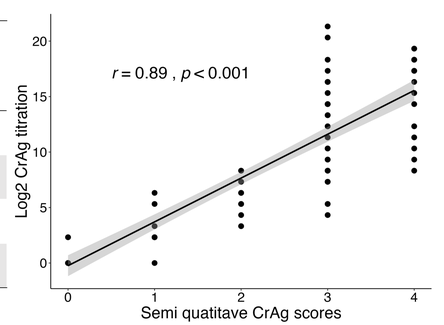
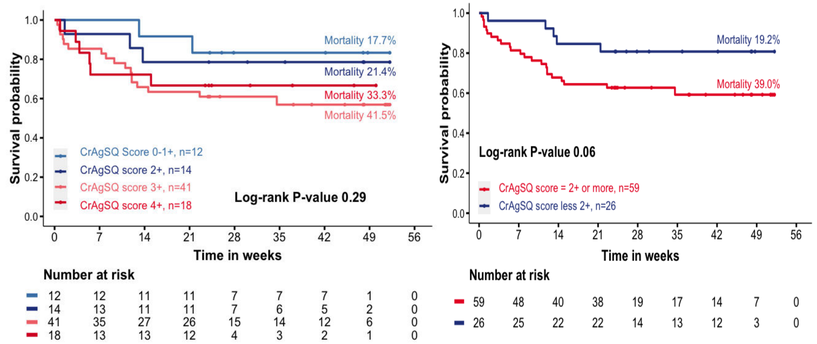


Table 2. Risk factors for mortality over 12 months

Characteristics	Univariate effect HR (95% CI)	P	Multivariate effect HR (95% CI)	P
CrAg SQ score, by +1 increase	1.38 (0.92 – 2.07)	.12	1.35 (0.89-2.06)	.16
Age, by +10 years	0.88 (0.60 – 1.28)	.49	0.92 (0.61 – 1.38)	.68
CD4, by +10 cells	0.95 (0.82 – 1.11)	.53	0.96 (0.82 – 1.12)	.61
Gender (male)	0.63 (0.26 – 1.56)	.32	0.60 (0.24 – 1.50)	.27

Notes: Summary statistics for Tables 2 and 3 are median (IQR) for continuous variables and % for binary variable

Figure 4. Survival estimates by CrAg SQ scores



CONCLUSIONS

- The CrAg SQ LFA demonstrates excellent sensitivity and specificity compared to the CrAg LFA reference standard.
- CrAg SQ scores are highly correlated with CrAg titers.
- For every one unit increase in CrAg SQ score, the odds of mortality increases by 35%. CrAg SQ score greater than 3+ is associated with an estimated 50% increase in mortality; however, a larger sample size is needed to demonstrate statistically significant risk of mortality.

ACKNOWLEDGEMENTS

We thank all patients who participated in this study, collaborators, and the CDC Foundation and the NIH for funding this research.

Author contact: Thu Nguyen, MSc
Email: thu.t.nguyen@duke.edu