Inflammasome Activation and Hemophagocytic Lymphohistiocytosis Associate with Mortality in HIV-TB

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BACKGROUND

- We hypothesized that, among inpatients with HIV, high disseminated *Mycobacterium tuberculosis* load is associated with inflammasome activation resulting in hyperinflammation along the secondary hemophagocytic lymphohistiocytosis (HLH) spectrum and this predicts early mortality.

METHODS

- We analysed clinical data and frozen samples from a prospective observational cohort study of inpatient adults (≥18 years) with microbiologically confirmed HIV-associated tuberculosis in Khayelitsha Hospital, Cape Town.
- We measured blood biomarkers including ferritin, caspase-1, soluble interleukin-2 receptor, and triglycerides.
- *Mtb* load was derived from modelling co-variance of multiple TB detection assays applied to urine and blood.
- Several published criteria, including HScore, HLH2004, ACR/MAS and MALS scores, were used to estimate prevalence of HLH after multiple imputation of missing observations.
- Spearman rank correlation was used to assess relationships between biomarkers. Survival analysis with relative mortality risk was assessed by Cox-proportional hazards modelling.

RESULTS

- 355 participants with microbiologically confirmed HIV-TB and a valid ferritin concentration were included.
- Ferritin > 3 000 ugl/l in 131/355 (37%).
- Ferritin > 10 000 ug/l in 50/355 (14%).
- Prevalence estimates of HLH are shown in **Figure 1** using 5 published scores or modification thereof. Range was 18–50%
- *Mtb* load and caspase-1 correlated with ferritin **(Figure 2)** and those who met HLH criteria by any of the scores had higher *Mtb* load (data not shown).
- Fulfilling HLH criteria was associated with higher mortality (MALS OR 4.1 p<0.001, HScore169 OR 2.0 p<0.001, HScore151 OR 2.1 p<0.001, HLH-2004 OR 1.9 p=0.004, ACR-MAS OR 2.3 p<0.001)
- *Mtb* load correlated with caspase-1 (R=0.43, p<0.001); caspase-1 and ferritin were also co-variate (R=0.57, p<0.001) **(Figure 2).**
- Caspase-1 was higher in those who died compared to survivors and controls with HIV but not TB **(Figure 3 and 4)**.

A high proportion of inpatients with HIV-TB have hyperferritinemia, and fulfill criteria for secondary HLH and this predicts mortality

Table 1: Baseline characteristics

	Total (n = 355)	Died (n = 79)	Survived (n = 276)	P-value
Age, years	36 (32-43)	39 (33-47)	35 (31-42)	<0.001
Female sex	189 (53%)	41 (52%)	148 (54%)	0.8
CD4 cell count, cells/µl	57 (22-117)	36 (14-88)	61 (24-132)	0.004
Creatinine, µmol/l	78 (60-119)	108 (68-197)	77 (59-106)	<0.001
Ferritin, µgl/l	3 092 (1 122-6 581)	5 661 (1 907-10 931)	2 492 (853-5 101)	<0.001
Caspase-1*, pg/mL	194 (112-315)	301 (177-439)	175 (106-275)	<0.001

*n = 269

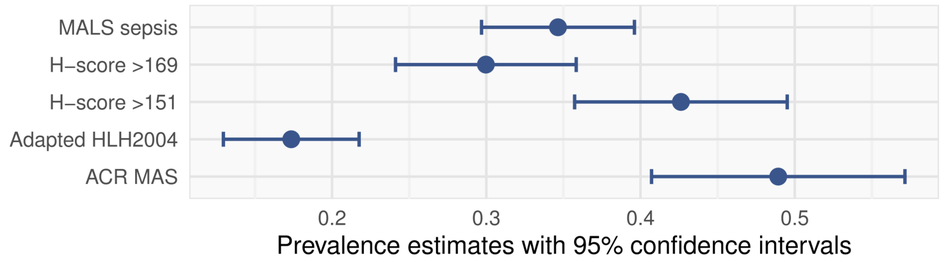


Figure 1: Prevalence of secondary HLH by range of published scores

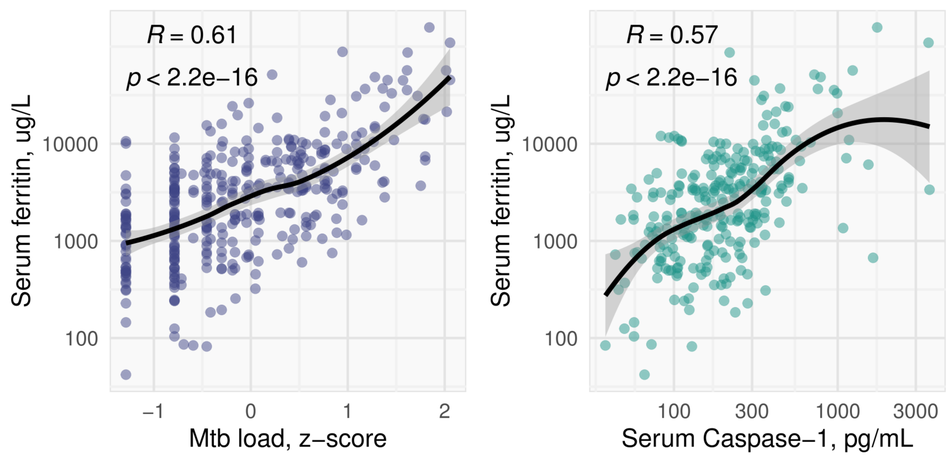


Figure 2: Scatterplot and Spearman correlation of ferritin with *Mtb* load *(left)* and caspase-1 (*right*)

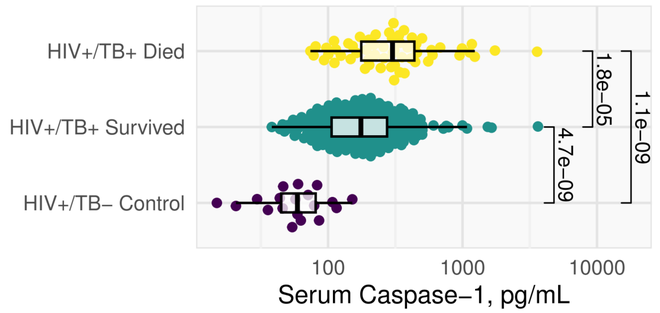


Figure 3: Caspase-1 concentration in HIV controls vs HIV-associated TB survivors vs those who died by week 12

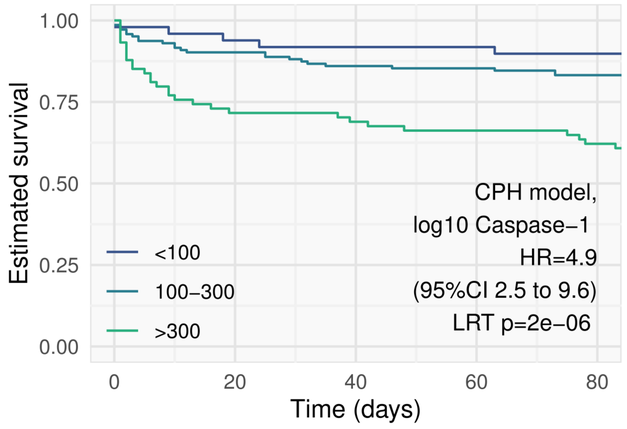


Figure 4: Survival analysis by caspase-1 stratum

CONCLUSIONS

- The prevalence of secondary HLH is high in patients admitted with HIV-associated tuberculosis.
- Secondary HLH and inflammasome activation are associated with 12-week mortality, suggesting a prominent role for innate immune activation in pathogenesis and outcome. *Mtb* load correlated with markers of secondary HLH and inflammasome activation.

ADDITIONAL KEY INFORMATION

- We have no conflicts of interest to disclose; this work was supported by Wellcome

PLAIN LANGUAGE SUMMARY

Many patients admitted to hospital with HIV-associated TB die despite appropriate treatment. We report activation of innate immune recognition pathways associated with disseminated TB load and predictive of these deaths.