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TRICARBOXYLIC ACID METABOLITES PREDICT METABOLIC COMORBIDITIES AND DEATH IN AGING PWH

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BACKGROUND

- Macrophage/monocyte activation contributes to the pathogenesis of age-related comorbidities in people with HIV (PWH). Upon activation, macrophages undergo a metabolic shift, similar to the Warburg effect, by increasing glycolysis, reducing oxidative phosphorylation and accumulating tricarboxylic acid (TCA) cycle metabolites including citrate and succinate.[1]
- These TCA cycle metabolites are actively transported out of mitochondria and may promote disease by generating reactive oxygen species (ROS) and/or engaging pro-inflammatory pathways that include hypoxia inducible factor (HIF)-1α, GLUT-1 and succinate receptor1 (SUCR1).[2-6]
- We hypothesized that this metabolic shift contributes to prevalent and incident age-related comorbidities in PWH.

METHODS

- HAILO is a multicenter, prospective, observational study of 1,035 PWH aged ≥40 yrs, who initiated ART by randomized allocation in ACTG trials.
- Plasma citrate and succinate concentrations were assayed by liquid chromatography/mass spectrometry (LC-QTOF-MS/MS) from frozen samples of **971 participants; collected at entry, in the fasting state**.
- Participants were followed every 24 weeks, at which time targeted intercurrent clinical events were captured including:
  - **Cardiovascular disease (CVD):** myocardial infarction, coronary revascularization, congestive heart failure or cerebrovascular event.
  - **Diabetes:** fasting or random plasma glucose ≥126 or ≥ 200 mg/dL, respectively, or hemoglobin A1c ≥ 6.5%.
  - **Hypertension (HTN):** BP ≥ 140/90 on ≥ 2 readings, OR receipt of antihypertensive treatment.
  - **Chronic Kidney Disease (CKD)** (at entry & every 48 wks): by eGFR<60 ml/min/1.73 m^2 for >3 mos using the CKD EPI equation.
  - **Frailty** (at entry & every 48 wks) using the following criteria:
    a) weakness, by grip strength; **b) slowness**, by 4-meter walk;
    c) weight loss >10 lbs; **d) reduced activity** (by SF-36 questionnaire);
    e) exhaustion by CES-D.
    as: **Not Frail**=0 criteria; **Pre-Frail**=1-2 criteria; **Frail**=≥3 criteria

Prevalent outcomes were present upon entry to HAILO, and examined by multivariable logistic regression. **Incident outcomes** occurred during follow-up among participants who were **without these conditions at entry**, and were examined by Cox proportional hazards regression. TCA metabolites were log-2 transformed to accommodate non-linear associations. All models were adjusted for age, sex, race/ethnicity; models for CKD diagnosis also were adjusted for exposure to tenofovir disoproxil fumarate.

Higher fasting plasma **citrate** concentrations are associated with prevalent **CKD, HTN & frailty,** incident **frailty** and increased **mortality.** Higher **succinate** concentrations are associated with incident **frailty & diabetes.** These associations may identify metabolic pathways that contribute to the pathogenesis of age-related comorbidities in PWH.

RESULTS

Participants at Entry	N=971
Age, yrs; *med, IQR*	51 (46,56)
Male; *n,%*	783 (81%)
Race/Ethnicity; *n,%*	
White-not Hispanic	480 (49%)
Black-not Hispanic	291 (30%)
Hispanic *regardless of race*	200 (21%)
Viral load ≤ 50 copies/mL; *n,%*	891 (91%)
CD4+ T-cell count, per μL; *med, IQR*	617 (447, 822)
Nadir T-CD4+ count, per μL; *med, IQR*	194 (59, 304)
ART duration, yrs; *med, IQR*	7.7 (4.3, 11.9)
Smoking History; *n,%*	
Current	383 (41%)
Past	316 (33%)
Never	246 (26%)
Citrate, μg/ml; *mean, std*	10.05 (+/-3.81)
Succinate, μg/ml; *mean, std*	0.91 (+/-0.78)
Follow up Duration, yrs; *med, IQR*	4.6 (4.6, 4.8)

Figure 1: Kaplan-Meier Curves

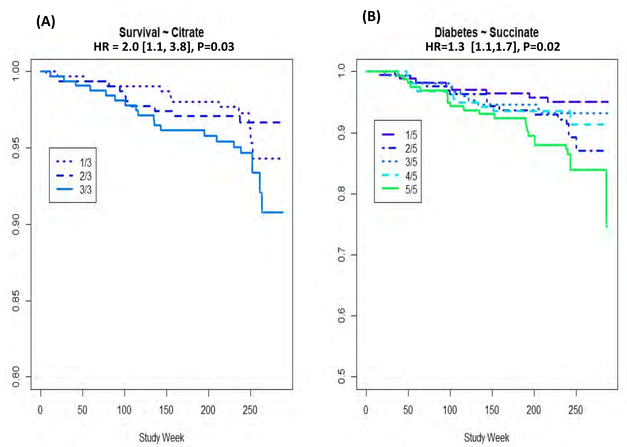


Figure 1: Kaplan Meier Plots of survival **(A)** or incident diabetes **(B)**, associated with plasma citrate concentrations, divided in tertiles (from lowest=1, to highest= 3), or succinate concentrations, in quintiles & similarly ranked. HR estimates by Cox proportional hazards regression were adjusted for age, sex & race/ethnicity and expressed per each 2–fold increase in the metabolite's plasma concentration.

	Prevalent Outcomes		Incident Outcomes	
	Total	n (%)	At Risk	n
Mortality	971	-	971	40
CVD	971	64 (6.6%)	907	61
Diabetes	971	112 (11.5%)	859	66
HTN	971	370 (38.1%)	601	70
CKD	934	42 (4.5%)	892	53
Frailty	967	62 (6.4%)	533*	18

*excludes Pre-Frail & Frail

Figure 2A

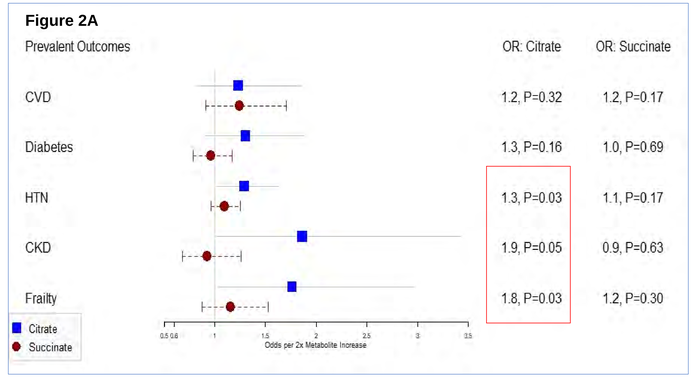


Figure 2B

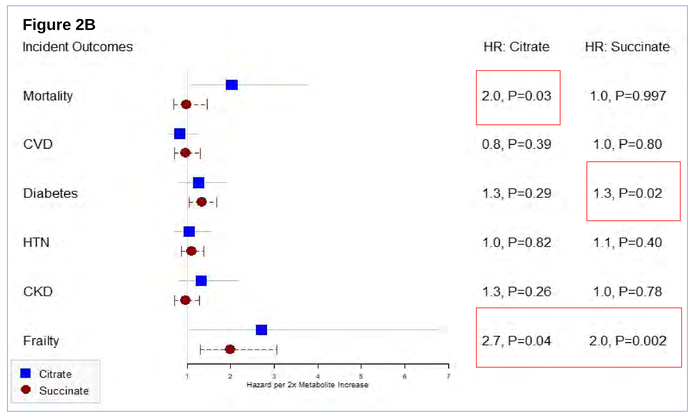


Figure 2: Odds Ratios (OR) **(2A)** or Hazard Ratios (HR) **(2B)** for prevalent or incident outcomes, respectively, and their 95% Confidence Intervals associated with a 2-fold increase in plasma citrate or succinate concentrations.

CONCLUSIONS

In people with HIV on ART:

- Higher plasma citrate concentrations are associated with prevalent: CKD, hypertension and frailty; incident frailty; and increased mortality.
- Higher plasma succinate concentrations are associated with both incident frailty and diabetes.

These associations may identify metabolic pathways that contribute to the pathogenesis of age-related comorbidities[1-6].

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