Hepatic Fibrosis Determined with MRE Significantly Predicts Cognitive Impairment

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BACKGROUND

- ✓ Neurocognitive impairments (NCI) affect 20–50% of people living with HIV (PLWH), even after long-term viral suppression.(Saloner, 2017) Liver disease is a major cause of morbidity and mortality in PLWH (Ganesian, 2018) and has been associated with NCI, even in the absence of viral hepatitis.(Ciccarelli, 2019) Co-infection with HCV is associated with greater risk for NCI.(Barokar, 2019)
- ✓ Ciccarelli et al. (2014; 2019) reported associations between indirect measures of liver fibrosis, such as FIB-4, and NCI in PLWH. However, studies using more sensitive markers of liver fibrosis are needed. Magnetic resonance elastography (MRE) is currently the most accurate non-invasive measure of liver fibrosis.
- ✓ Substance use and HIV transmission are closely related and share many risk behaviors.(Welch, 2000) Substance use may worsen liver disease and NCI outcomes through impairment of the immune system (Baum, 2009), and lower adherence to anti-retroviral medications (DiLorenzo, 2011)
- ✓ In those with liver disease, NCI is also mediated by reduced clearance of toxins and shunting of nitrogenous neurotoxins from the gut to the brain. (Watanabe, 2000)
- ✓ The purpose of this study was to examine the association between liver fibrosis and NCI among people living with HIV, HCV, HIV/HCV co-infection, or uninfected participants from the Miami Adult Studies on HIV (MASH) cohort.

METHODS

- ✓ Cross-sectional analysis of baseline data from the ongoing MASH cohort.
- ✓ Demographics were self-reported. Anthropometries measured by staff.
- ✓ HIV, viral load, CD4 count, Hepatitis C, and lack of hepatitis B infection were documented from medical charts.
- ✓ NCI was determined with the Mini Mental State Examination (MMSE), using a cutoff of ≤ 24. The Centers for Epidemiological Studies – Depression (CES-D) scale was used to assess depressive symptoms.
- ✓ Plasma neurofilament light chain protein (NFL), a novel marker of neuronal injury,(Yilmaz, 2017) was examined in 40 participants.
- ✓ Liver fibrosis indicative of liver disease was determined as liver stiffness (LS) via MRE. LS ≥ 2.5 kPa is consistent with the presence of inflammation or fibrosis. LS ≥ 2.9 kPa is consistent with fibrosis stage 1 or higher.
- ✓ Substance use was self-reported. Alcohol consumption was assessed with the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C).
- ✓ All statistics performed in SAS Studio 3.8.

RESULTS

Table 1: Characteristics of MASH Cohort

Variable	HIV mono-infected (N=211)	HIV/HCV coinfected (N=76)	HCV mono-infected (N=74)	Uninfected (N=265)	P-value
Age (years)[a]	54 (49,58)	54 (50,58)	58 (52,62)	55 (51,60)	0.0002
Sex (Male) (%)	57.4	55.3	64.9	52.1	0.244
Ethnicity (%)					0.002
Black non-Hispanic	67.3	50.0	54.1	63.0	
White non-Hispanic	6.2	1.8	2.1	2.6	
Hispanic	24.2	34.2	27.0	30.6	
BMI ≥ 30 kg/m^2 (%)	39.3	31.6	39.2	44.5	0.216
HIV VL < 50 copies/mL (%)	77.3	71.8			0.350
CD4 (cells/μL)[a]	545 (328,751)	602 (376,827)			0.250
On ART (%)	99.1	97.4			0.286
Tobacco (%)	40.8	47.4	32.4	38.1	0.276
Hazardous drinking (%)	28.0	21.1	44.6	36.6	0.004
Cocaine (%)	52.1	39.5	51.4	50.2	0.286
Opioid misuse (%)	21.8	26.3	33.8	15.1	0.022
Liver stiffness ≥2.9 kPa[b] (%)	10.4	36.8	27.0	7.9	<0.001
CES-D ≥ 16 (%)	36.5	39.5	50.0	35.1	0.124

[a] Continuous variables reported as median (IQR)
[b] LS ≥ 2.9 kPa is consistent with fibrosis stage 1 or higher

- ✓ LS was negatively correlated with MMSE scores (rho=–0.11, p=0.008) and directly correlated with NFL (rho=0.46, p=0.017).
- ✓ LS ≥ 2.9 kPa was more prevalent in HCV+ not virally suppressed than those virally suppressed (56.9% vs 29.2%, p=0.002).

Figure 1: Frequency of NCI by Study Group:

- ✓ HIV mono-infected group had a higher NCI frequency than the uninfected group (P=0.009).
- ✓ No significant difference between any other study group for NCI frequency.

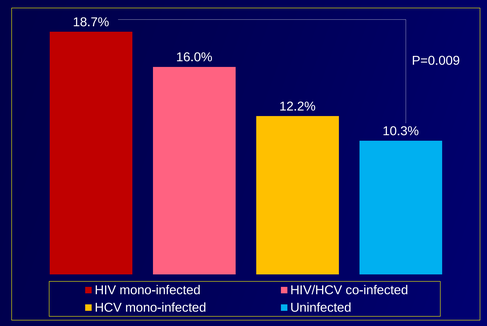


Figure 2: Frequency of NCI by LS:

- ✓ The presence of hepatic inflammation or fibrosis was significantly associated with higher frequency of NCI.

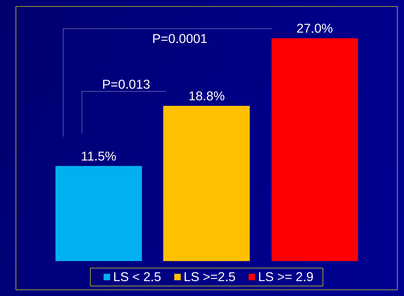


Table 2: Univariate and Multivariable Logistic Regressions for MMSE ≥ 24

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Group				
HIV mono	2.01	1.82–3.40	1.93*	1.01–3.47
HCV mono	1.21	0.54–2.70	0.65	0.25–1.67
HIV/HCV	1.67	0.80–3.47	1.31	0.56–3.09
Uninfected (ref)	-	-	-	-
BMI	0.99	0.96–1.03	-	-
LS ≥ 2.9 kPa	2.75***	1.61–4.70	2.49**	1.29–4.80
Tobacco	0.51**	0.30–0.84	0.50*	0.29–0.87
Hazardous drinking	0.81	0.49–1.33	-	-
Cocaine	0.83	0.53–1.31	-	-
Rx opioid misuse	0.54	0.23–1.31	-	-
Heroin/fentanyl	1.21	0.59–2.49	-	-
CES-D > 16	1.87**	1.18–2.95	2.11**	1.26–3.53

[a] Multivariable regression model also adjusts for age, education, and race/ethnicity.

*P<0.05; **P<0.01; ***P<0.001

CONCLUSION

Our findings indicate that liver fibrosis is significantly associated with NCI, regardless of HIV or HCV infection, potentially due to liver-brain shunting of toxic metabolites. These findings are particularly relevant for PLWH due to high rates of NCI and liver disease. Strategies to prevent liver disease and NCI in this population are needed.

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