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AST-to-Platelet Ratio Index Increases Significantly 3 Years Prior to Liver-Related Death in HIV-Hepatitis-Coinfected Men

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Abstract

The utility of longitudinal AST-to-platelet ratio index (APRI), a surrogate for hepatic fibrosis, is unknown. We compared APRI up to 9 years before liver-related death among 57 cases of viral hepatitis-infected men (91% HIV+) to matched controls. APRI was stable among controls but among cases increased 4.6%/year from 9 to 3 years pre-death (p=0.10) and 30%/year during the 3 years pre-death (p<0.001). Thus, rapid APRI increase may predict impending liver-related death in HIV-viral hepatitis coinfection.

Liver disease, primarily due to hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection, is a leading cause of non-AIDS mortality among people living with HIV[1]. Identifying patients at highest risk of adverse outcomes is critical to reducing liver-related events in this population. The aspartate aminotransferase-to-platelet-ratio index (APRI), a noninvasive surrogate for liver fibrosis, utilizes routinely-obtained serum markers and is especially useful when alternative non-invasive options are unavailable[2]. Studies validating APRI have primarily been cross-sectional[3–5]. We performed a nested case-control study in the Multicenter AIDS Cohort Study (MACS) to determine whether APRI changes are

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associated with liver-related death in viral hepatitis-infected men with or without HIV infection.

The MACS is an ongoing cohort study of HIV-infected and -uninfected men who have sex with men (MSM) with cohort details described elsewhere[6, 7]. Men with chronic HCV or HBV followed between January 1, 1984 and December 31, 2010 were eligible. Cases were participants who experienced liver-related death during follow-up and had stored serum available at specified timepoints before death. Liver-related deaths were determined from death certificates with primary or contributing International Classification of Diseases, 9th Revision, diagnosis codes for HBV, HCV, viral hepatitis, hepatic failure, chronic hepatitis, cirrhosis, liver failure, chronic liver disease, hepatocellular carcinoma, hepatic coma, or hepatorenal syndrome. Randomly selected HCV- or HBV-infected controls were matched 1:1 to cases by age, HIV, HBV and HCV status, and race. APRI was calculated at years 9,6,3,2, and 1 prior to death for cases, and at visits matched by calendar year for controls. HCV, HBV, and HIV status were defined at the visit closest to death for cases and the calendar-matched visit for controls.

We used a paired t-test to compare natural-log-transformed (ln)APRI by case status. We evaluated APRI changes using multilevel linear regression models with ln(APRI) as the dependent variable and included random effects to account for clustering within each case-control pair. Time interval was categorized from 9 to >3 years and 3 to 1 years before death based on graphical exploration indicating a precipitous APRI increase 3 years before death. Coefficients were exponentiated to produce relative APRI differences. The model included HIV status, race, age, CD4 count, and use of HBV medication. Analyses were performed using Stata 12.1 (College Station, TX).

Most of the 57 cases were HIV-infected (91%) and white (88%), with a median age of 44 years [interquartile range (IQR) 37,51]. Chronic HBV was more common than HCV, as expected in MSM (38 versus 23 men, including 4 HBV/HCV/HIV-coinfected). Among HIV-infected cases and controls, median CD4 counts were 206 (IQR 109,342) and 431 (IQR 315,679), respectively ($p<0.001$). Only 33% and 38% of HIV-infected cases and controls, respectively, were on combination antiretroviral therapy (ART) at the visit closest to death (or calendar year-matched visit for controls)($p=0.61$). For deaths after 2001, these numbers increased to 62% and 78%($p=0.33$). There were no differences in ART use by case/control status at any timepoint. Forty-seven percent of liver-related deaths occurred before 1996. Among those with chronic HBV, 26% of cases and 28% of controls received an anti-HBV medication. Two HCV-infected cases and no HCV-infected controls received HCV treatment.

The proportion of cases with APRI>1.5 (consistent with cirrhosis) steadily rose during follow-up from 31% to 75% while remaining stable among controls (6% to 9%) (Supplemental Figure 1). Mean APRI, which was higher in cases than controls at all timepoints, was stable among controls but increased among cases, particularly in the 3 years preceding death (Table, Supplemental Figure 2). Among cases, the adjusted APRI increased 4.6%/year between 9 and 3 years before death ($p=0.10$ compared to no change) and 30%/year within 3 years of death ($p<0.001$). The annual APRI change among cases was

significantly higher in the 3 to 1 year interval compared to the 9 to >3 year interval (p=0.01). On multivariable analysis, lower CD4 counts were also independently associated with significantly higher APRI. Compared to CD4 counts ≥500 cells/mm^3, CD4 counts of 300–499 cells/mm^3 and <300 cells/mm^3 were associated with 36% (p=0.005) and 51% (p<0.001) higher APRI, respectively.

Since HIV and/or ART can affect both platelets and AST, we evaluated whether APRI changes were primarily driven by either of these values. The mean platelet count (in APRI denominator) was lower in cases than controls and declined at each timepoint. Conversely, mean AST (in APRI numerator) was higher in cases than controls and increased longitudinally supporting that APRI changes were driven by both these parameters.

In summary, APRI was consistently higher and increased more rapidly in men who died a liver-related death over the 9 years before death. This increase was most precipitous in the 3 years preceding death, likely reflecting the rapid reduction in hepatic function observed in cirrhosis once decompensation occurs. These data are consistent with a study demonstrating that baseline APRI predicted 3-year liver morality in a cohort of HCV-monoinfected and HIV/HCV-coinfected individuals[8] and another study showing that baseline APRI predicted liver complications in a cohort of HIV-monoinfected and HIV/HCV-coinfected patients followed for a median of 4.6 years[9]. Additionally, lower CD4 counts were associated with higher APRI, regardless of case status. This is consistent with a prior cross-sectional analysis in which we found an independent association of lower CD4 count and higher APRI in the MACS[10]. Studies in other HIV cohorts have similarly found an inverse association of CD4 count and fibrosis stage[11–14].

Unique features of our study include the prospective design, APRI testing at discrete timepoints pre-death, use of liver-related death as the outcome, and inclusion of matched controls. We recognize that the relatively small sample limited our ability to control for all potential factors associated with liver-related mortality, that death certificates have limitations, and that the all-male cohort limits generalization to women. These data suggest that increasing APRI, especially when the baseline APRI is elevated, heralds the onset of an adverse liver-related outcome in HIV-viral hepatitis coinfection and underscores the urgency of aggressive treatments in this population. Further examination in large prospectively-followed cohorts is needed to determine specific APRI values and trajectories with the highest predictive value for liver-related death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table.

APRI by timepoint and adjusted annual percent change in APRI

	Cases		Controls			
Time point	**Mean APRI (SD)**		**Median APRI (SD)**		**% Difference in APRI Cases vs Controls (195% CI)[2,3]**	**p-value**
9 years pre-death[1]	1.57 (1.52)		0.75 (0.51)		61% (12% to 131%)	0.01
6 years pre-death	1.78 (1.98)		1.06 (1.29)		88% (40% to 153%)	<0.001
3 yearspre-death	2.24 (1.83)		1.08 (1.45)		121% (53% to 219%)	<0.001
2 years pre-death	4.11 (5.54)		1.09 (2.01)		195% (117% to 300%)	<0.001
1 year pre-death	4.77 (4.95)		0.89 (0.77)		293% (172% to 469%)	<0.001
	Annual % Change in APRI (95% CI)[2,3]	**p-value[4]**	**Annual % Change in APRI (95% CI)[2,3]**	**p-value[4]**	**% Difference in Annual Change Cases vs Controls (95% CI)[2,3]**	**p-value**
9 to 3 years pre-death	4.6% (−0.9% to 10%)	0.10	−0.8% (−6.0% to 4.7%)	0.78	5.4% (−1.8% to 13%)	0.16
3 to 1 year pre-death	30% (13% to 50%)	<0.001	−2.4% (−16% to 13%)	0.75	33% (8.6% to 64%)	0.004

[1] References=controls at calendar-matched time points

[2] Adjusted for age, CD4 count, HIV serostatus, race, and HBV treatment

[3] Outcomes are ln-transformed; results are back-transformed to produce estimated relative differences in APRI.

[4] p-value refers to comparison to reference of no change in APRI over time