**LETTER TO THE EDITOR**

**The gamma-glutamyl transpeptidase to platelet ratio (GPR) shows poor correlation with transient elastography measurements of liver fibrosis in HIV-positive patients with chronic hepatitis B in West Africa**

**Reply to:** The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa [1]

**Authors**

Alexander J Stockdale1; Richard Odame Phillips2,3; Anna Maria Geretti; - HEPIK Study Group.

1Institute of Infection & Global Health, University of Liverpool, Liverpool, United Kingdom (UK); 2Department of Medicine, Kwame Nkrumah University of Science & Technology and 3Komfo Anokye Teaching Hospital, Kumasi, Ghana

**Corresponding author:**

Dr Alexander J Stockdale MBChB MRCP

Institute of Infection & Global Health

University of Liverpool, 8 West Derby Street L69 7BE, United Kingdom

+44 151 795 9665; [A.Stockdale@liverpool.ac.uk](mailto:A.Stockdale@liverpool.ac.uk)

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**Reply to:** The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa.[1]

Lemoine *et al.*’s excellent article from the Gambia reported on non-invasive markers of liver fibrosis in patients with chronic hepatitis B virus (HBV) infection.[1] They propose a novel biomarker - the gamma-glutamyl transpeptidase (GGT) to platelet ratio (GPR) - as a routinely available test that could identify patients with fibrosis or cirrhosis in resource-limited settings, thereby informing prognosis and guiding monitoring. Notably, the study excluded patients with conditions that might predispose to altered GGT or platelet counts, including pregnancy, significant alcohol consumption, use of antiviral therapy, acute malaria, and hepatitis C, hepatitis delta or HIV co-infection. In their letter, Boyd and colleagues subsequently reported that in a French HBV/HIV co-infected cohort, GPR showed reasonable performance for identifying significant liver fibrosis.[2]

HBV and HIV are highly co-endemic in West Africa and chronic liver disease is an emerging threat to the long-term health of HIV-positive patients in this region.[3] Since 2010, we have been following a prospective cohort of patients attending the HIV clinic at the Komfo Anokye Teaching Hospital in Kumasi, Ghana, where prevalence of HBV co-infection is 14% (95% confidence interval 12.4-15.8%).[4] To date, 122 patients have undergone laboratory investigations paired with a valid measurement of liver fibrosis by transient elastography (TE) (Fibroscan® F402, Echosens, Paris). Here we report on the performance of the GPR and AST to platelet ratio index (APRI) in this cohort, in relation to TE measurements as a reference standard. Interpretive cut-offs were 7.6 kPa [F3: advanced fibrosis] and 9.4 kPa [F4: cirrhosis], as previously determined for HBV/HIV co-infection.[4]

For the purpose of the analysis, we excluded patients with pregnancy (n=2), significant alcohol consumption (n=1), acute malaria (n=2), and detectable HCV RNA (n=0) or HDV RNA (n=1). In order to reflect the currently predominant profile of HIV-positive patients across sub-Saharan Africa, we only included patients established on antiretroviral therapy (ART) with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus efavirenz (n=89) or nevirapine (n=11), and excluded those not receiving ART (n=6) or receiving protease inhibitors (n=10).

The 100 patients (67% female) were median 44 years old (interquartile range 38-48), had received ART for median 7.2 years (5.0-9.0), and had a CD4 count of median 572 cells/mm3 (361-711); 78% showed plasma HIV-1 RNA suppression (<40 copies/ml). Median AST, GGT and platelet counts were 32 U/L (25-39), 60 U/L (44-81) and 165 x 109/L (118-225), respectively. TE measurements were median 4.6 kPa (3.8-6.2). Of 100 patients, 18% and 7% were classified as having advanced fibrosis and cirrhosis, respectively. Factors significantly associated with TE measurements were GGT (r=0.33, p=0.001), AST (r=0.34, p=0.001), CD4 count (r= -0.21, p=0.033), APRI (r=0.24, p=0.014), GPR (r=0.29, p=0.004) (Spearman’s rho) and male gender (p=0.013, Mann-Whitney) (Figure 1); there was no correlation with duration of ART (p=0.99) or age (p=0.76).

**Table 1.** Performance of gamma-glutamyl transpeptidase to platelet ratio (GPR) and AST to platelet ratio index (APRI) compared to transient elastography (TE) as reference standard for the diagnosis of advanced fibrosis and cirrhosis in HBV/HIV co-infected patients in West Africaa

|  |  |  |
| --- | --- | --- |
|  | Advanced fibrosis  (TE threshold 7.6 kPa) | Cirrhosis  (TE threshold 9.4 kPa) |
| **GPR** |  |  |
| AUROC (95% CI) | 0.73 (0.61 – 0.85) | 0.71 (0.55 - 0.86) |
| Cut-off values | 0.54 | 0.72 |
| Sensitivity (%) | 61 | 57 |
| Specificity (%) | 72 | 79 |
| Correctly classified (%) | 66 | 77 |
| PPV (%) | 32 | 17 |
| NPV (%) | 89 | 96 |
| Positive LR | 2.2 | 2.7 |
| Negative LR | 0.5 | 0.5 |
|  |  |  |
| **APRI** |  |  |
| AUROC (95% CI) | 0.62 (0.46 – 0.78) | 0.59 (0.32 – 0.85) |
| Cut off values | 0.57 | 0.70 |
| Sensitivity (%) | 67 | 57 |
| Specificity (%) | 63 | 74 |
| Correctly classified (%) | 64 | 73 |
| PPV (%) | 29 | 14 |
| NPV (%) | 90 | 96 |
| Positive LR | 1.8 | 2.2 |
| Negative LR | 0.5 | 0.6 |
|  |  |  |
| **APRI (WHO threshold)b** |  |  |
| Cut off values | - | 2.0 |
| Sensitivity (%) | - | 0 |
| Specificity (%) |  | 99 |
| Correctly classified (%) | - | 92 |
| PPV/NPV (%) | - | 0 |
| NPV (%) |  | 93 |
| Positive LR | - | 0 |
| Negative LR |  | 1.0 |

aBased on histologically-defined interpretive cut-offs for patients with HIV/HBV co-infection as previously described.[4]; bAs recommended in the “Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (March 2015)”.[3] AUROC= area under receiver operating curve; PPV = positive predictive value; NPV = negative predictive value; LR= likelihood ratio; WHO = World Health Organisation.

GPR and APRI had good negative predictive values for excluding cirrhosis (96%) and to a lesser extent advanced fibrosis (89% and 90% respectively) (Table 1). Overall diagnostic performance was poor for identifying advanced fibrosis and cirrhosis however, with positive predictive values of 32% and 17% for GPR, and 29% and 14% for APRI. GPR had a better diagnostic performance than APRI for advanced fibrosis but not for cirrhosis (p=0.029 and 0.13 respectively, DeLong). It is important to note that the APRI threshold for the diagnosis of cirrhosis (>2.0) recommended by the World Health Organisation was unsuitable in this population, such that none of the seven patients with cirrhosis were correctly identified.[3]

The non-invasive and routinely available biomarkers GPR and APRI cannot be recommended for the diagnosis of advanced fibrosis and cirrhosis in HIV/HBV co-infected population established on ART in West Africa, due to insufficient positive predictive value.

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**Competing interests**

The authors declare no competing interests.

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**Figure 1: Association between APRI and GPR scores and TE measurements**



[FIGURE1.TIFF]

APRI= AST to platelet ratio index, GPR= GGT to platelet ratio. Bivariate correlations determined using Spearman’s rho. Linear association is represented by straight line.

**References**

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