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Persistently detectable serum HBV DNA and pgRNA is associated with subsequent hepatocellular carcinoma development in chronic hepatitis B patients receiving chronic NRTI treatment

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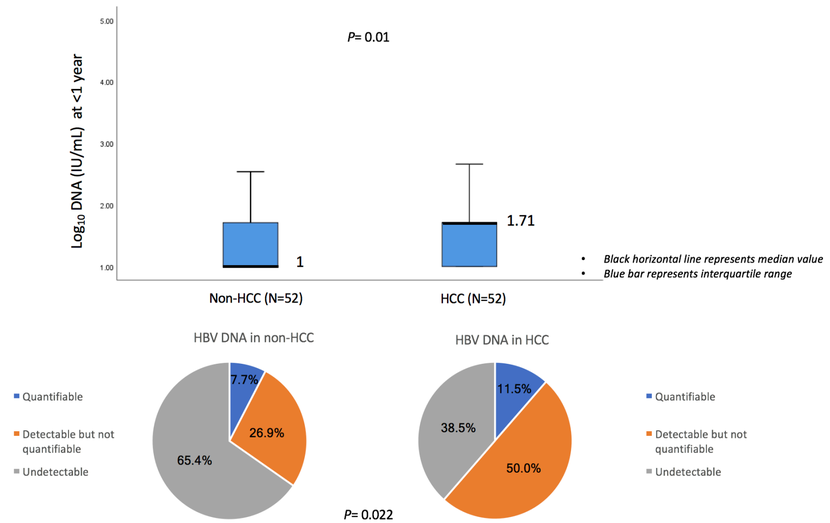
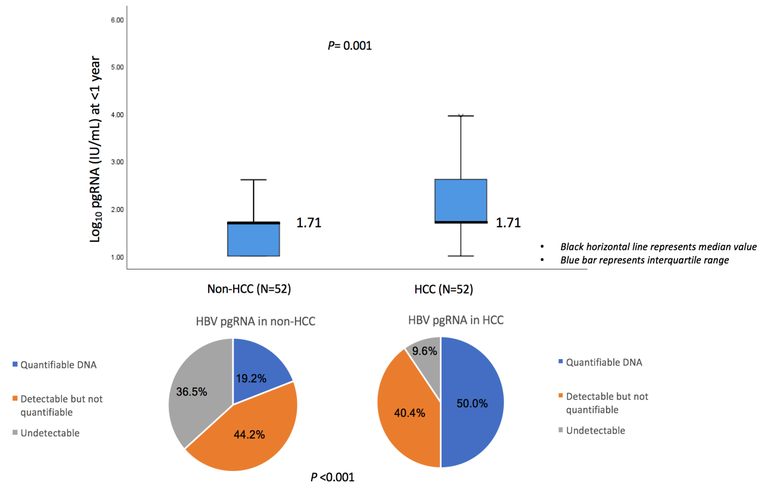
Introduction: In patients with chronic hepatitis B (CHB) infection, the risk of liver-related complications, in particular hepatocellular carcinoma (HCC), is not completely eliminated. We aimed to assess whether residual hepatitis B virus (HBV) viraemia is associated with HCC development.

Methods: This is a case-control study of 104 CHB patients [52 HCC and 52 non-HCC (matched with age, gender, cirrhosis and treatment duration)] on ≥3 years entecavir (ETV) with unquantifiable HBV DNA by Cobas Taqman assay v2.0 (Roche Diagnostics; lower limit of quantification [LLOQ] 20 IU/mL). Serial sera within 1, 1-2, and >2 years prior to HCC diagnosis or last follow-up (LFU) were retrieved for detection of HBV DNA and pre-genomic (pg) RNA using a highly sensitive semi-quantitative RT-PCR assay with lower limit of detection (LLOD) of 10 IU/mL and LLOQ of 51.5 IU/mL respectively.

Results:
Among the 104 patients,
- 80.8% male, median age 61.2 years old, 38.5% cirrhosis, median duration of ETV 45.5 months
- 38.5% and 9.6% HCC patients had undetectable serum DNA and pgRNA, respectively; compared to 65.4% and 36.5% in non-HCC patients; P=0.005 & 0.001 respectively at the time of HCC diagnosis/ LFU
- No significant differences were observed for qHBsAg levels between HCC and non-HCC patients over 3 time points

	HCC (N=52)	Non-HCC (N=52)	P value
Age	61.2 (56.9 – 66.6)	61.2 (56.9 – 66.5)	1.00
Gender (male)	42 (80.8%)	42 (80.8%)	1.00
Duration on NRTI till HCC diagnosis or last FU (months)	44.0 (26.1 – 57.1)	46.8 (32.1 – 65.7)	0.259
Presence of cirrhosis at baseline	20 (38.5%)	20 (38.5%)	1.00
Serum HBV DNA level at >2 years before HCC (log_{10} IU/mL)	1.71 (0.7 – 3.71)	1.73 (0 – 1.73)	0.028
Serum HBV pgRNA level at >2 years before HCC (log_{10} IU/mL)	2.5 (1.71 – 4.47)	1.73 (1.73 – 2.44)	0.005
Serum qHBsAg level at >2 years before HCC (log_{10} mIU/mL)	2.9 (2.5 – 3.2)	2.7 (2.4 – 3)	0.167





Results…continued
- Detectable viral nucleic acids (HBV DNA and/or pgRNA) was associated with a higher 2-year risk of HCC development (HR 2.604, 95%CI 1.151-5.891; P=0.022)
- Poorly-differentiated HCC or presence of lymphovascular permeation tended to have lower serum pgRNA around the time of HCC diagnosis

Conclusion: More than 50% CHB patients on ETV with HBV DNA <LLOQ by standard assay had persistent viraemia as determined by a more sensitive assay. Detectable HBV DNA and/or pgRNA was associated with HCC development. More potent viral suppression is required to further reduce the risk of HCC.

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