Background and Aims: Chronic hepatitis B virus (HBV) infection is one of the major risk factors for hepatocellular carcinoma (HCC) development. The major mechanism of HBV-induced hepatocarcinogenesis is an indirect pathway through the process of inflammation and fibrosis, but a direct oncogenic effect of HBV also contributes. It remains still unknown the impact of direct carcinogenic effect of HBV.

Method: This study included consecutive patients diagnosed as chronic HBV infection with normal alanine aminotransferase (ALT) levels and without evidence of cirrhosis at a tertiary referral hospital in Korea. Study participants were classified according to the presence of HBeAg, serum HBV DNA levels, and antiviral treatment: HBeAg-positive chronic infection (HBeAg-positive and HBV DNA $>20,000$ IU/ml), untreated HBeAg-negative chronic infection (HBeAg-negative and HBV DNA $<2,000$ IU/ml without antiviral treatment), or treated HBeAg-negative chronic infection (HBeAg-negative and HBV DNA $<2,000$ IU/ml with antiviral treatment). Primary endpoint was an HCC development. Cox proportional hazard model and inverse-probability weighting (IPW) were utilized to adjust baseline characteristics.

Results: A total of 1,197 patients were included: 373 HBeAg-positive, 308 untreated HBeAg-negative, and 516 treated HBeAg-negative chronic infection. Age and baseline liver function were significantly more favorable for HBeAg-positive group than HBeAg-negative groups. In multivariate analyses to adjust confounding factors, HBeAg-positive group showed significantly higher risks of HCC than both untreated HBeAg-negative group (adjusted hazard ratio [aHR] = 7.93, 95% confidential interval [CI] = 2.87–21.91, $p < 0.001$) and treated HBeAg-negative group (aHR = 8.51, 95%CI = 3.32–21.5, $p < 0.001$). After balancing baseline characteristics with IPW, HBV, HBeAg-positive group consistently showed significantly higher risks of HCC than both untreated (HR = 4.44, 95%CI = 2.22–8.88, log-rank $p < 0.001$) and treated HBeAg-negative group (HR = 3.03, 95%CI = 2.14–4.25, log-rank $p < 0.001$). These results might suggest the considerable impact of direct oncogenic effect of HBV in HCC development.

Conclusion: Even with normal ALT level, HBeAg-positive chronic infection phase had 4.4–7.9-fold and 3.0–8.5-fold higher risk of HCC than untreated and treated HBeAg-negative chronic infection, respectively. These results might suggest the considerable impact of direct oncogenic effect of HBV in HCC development.
Background and Aims: Recently, PAGE-B score has been developed to predict the risk of hepatocellular carcinoma (HCC) in Caucasian patients with chronic hepatitis B (CHB). We aimed to validate PAGE-B scores in Asian patients with CHB and suggested modified PAGE-B scores to potentiate the predictive performance.

Method: From 2007 to 2017, we examined 2,844 Asian patients with CHB receiving entecavir/tenofovir therapy. We assessed the performances of PAGE-B and three conventional risk prediction models (CU-HCC, GAG-HCC, and REACH-B) for HCC development. A modified PAGE-B score (mPAGE-B) was developed (derivation set from three centers, n = 1,896) based on multivariable Cox models. Bootstrap for internal validation and external validation (validation set from one center, n = 948) were performed.

Results: The 5-year cumulative HCC incidence rates were 5.6% and 5.0% in the derivation and validation datasets, respectively. In the derivation dataset, age, gender, serum albumin levels, and platelet counts were independently associated with HCC. The mPAGE-B score was developed based on age, gender, platelet counts, and albumin levels (time-dependent area under receiver operating characteristic curves [AUROC] = 0.81, 0.80 after bootstrap validation). In the validation set, the original PAGE-B showed similar AUROCs to CU-HCC, GAG-HCC, and REACH-B at 5 years (0.73 vs 0.67, 0.69, and 0.68 respectively; all p > 0.05), whereas the AUROCs of mPAGE-B at 5 years were significantly higher than those of the PAGE-B and the other three models (0.82, all p < 0.001). HCC incidence rates within 5 years of antiviral therapy initiation in CHB patients were significantly lower compared with rates beyond year 5.

Conclusion: Although PAGE-B is applicable in Asian CHB patients receiving entecavir/tenofovir therapy, mPAGE-B scores including additional albumin levels showed better predictive performance than the original PAGE-B score.

Background and Aims: The natural history of chronic hepatitis B (CHB) is characterized by different dynamic phases which are not necessary sequential. Antiviral therapy is recommended only in patients with chronic hepatitis (CH) or cirrhosis, whereas patients with chronic infection (CI) should be periodically monitored. However, a reliable identification of CHB patients requiring treatment could be challenging when hepatitis is in a biochemical remission simulating a CI profile. We assessed the added value of hepatitis B core-related antigen (HBcrAg) and anti-hepatitis B core antibody class IgC (anti-HBc IgC) levels for the discrimination between the different CHB phases.

Method: Serum samples of 132 CHB patients (13 CH-HBeAg+, 64 CH-HBeAg- 21 low viremic CI-HBeAg- [fluctuating HBV DNA between 2000 and 20,000 IU/mL] and 34 true CI-HBeAg- [HBV DNA persistently <2,000 IU/mL] and 97 HBsAg-/anti-HBc+ subjects (51 occult HBV infection [OBI]+ and 46 OBI-) were analyzed. HBsAg, HBeAg, HBcrAg and anti-HBc IgG level were assessed by CLEA (Lumipulse®), Fujirebio, Japan). Biomarkers levels were reported in logIU/mL, logU/mL and Log cut-off index (COI), respectively. OBI+ was defined according to consensus statements.

Results: Mean HBsAg, HBcrAg and anti-HBc IgG levels were different among CHB phases (one-way ANOVA, p < 0.001), with higher values in CH-HBeAg+ (4.47 ± 0.79 log IU/mL, 6.9 ± 0.3 log U/mL and 4.07 ± 0.69 logCOI, respectively) and lower in true CI-HBeAg- (2.25 ± 1.26 log IU/mL, 2.2 ± 0.4 log U/mL and 3.29 ± 0.52 logCOI, respectively). We observed a correlation between HBV DNA and HBsAg (r = 0.642, p < 0.001), HBeAg (r = 0.875, p < 0.001) and anti-HBc IgG (r = 0.515, p < 0.001). Area under the curve (AUC) for the discrimination between low viremic and true CI-HBeAg- was 0.736 for HBsAg, 0.749 for HBcrAg and 0.648 for anti-HBc IgG; a higher accuracy (AUC = 0.812) was obtained combining HBcrAg and anti-HBc IgG. Among HBsAg-/anti-HBc+ subjects, anti-HBc IgG levels were different between OBI+ and OBI- (1.16 ± 0.60 vs. 0.78 ± 0.64 logCOI, p = 0.004) with AUC = 0.671.

Conclusion: The combination of HBcrAg and anti-HBc IgG levels may improve the correct identification of true CI-HBeAg- patients (HBV DNA persistently <2,000 IU/ml) that do not require antiviral therapy. Anti-HBc IgG is the only circulating HBV marker detectable and quantifiable in HBsAg- subjects with previous HBV exposure and may help clinicians to predict HBV reactivation in OBI+ subjects undergoing pharmacological immunosuppression.

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Pan-genotypic loop-mediated isothermal amplification assay for HBV: a simple, rapid and affordable point-of-care test to semi-quantify HBV DNA

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Background and Aims: To achieve the global elimination of HBV, it is essential to scale up antiviral therapy through decentralized services in low- and middle-income countries (LMIC). However, the access to nucleic acid amplification test to quantify HBV DNA, a key marker to determine treatment eligibility, is limited and non-affordable in LMIC. Loop-mediated isothermal amplification assay (LAMP) is a simple, rapid and inexpensive technique to efficiently amplify DNA at a constant temperature. We designed a pan-genotypic LAMP assay to semi-quantify HBV viral load (VL) and evaluated its performance.

Method: Pan-genotypic primers sets were designed on conserved HBV gene regions using the LAMP Explorer software. The ability of LAMP to discriminate two clinically important HBV DNA levels (2,000 and 200,000 IU/mL), determined by the reference PCR assay (Roche COBAS®), was evaluated using well-characterized plasma samples from 240 French blood donors with positive HBV DNA (genotype A (n = 67), B (31), C (37), D (45), E (51) and F (9)) and 50 HBV-negative controls. HBV DNA was extracted from plasma using a simple