

# DIFFERENTIAL PATTERNS OF HBV RNA AND HBcrAg LEVELS IN A LARGE EUROPEAN CROSS-SECTIONAL STUDY OF UNTREATED PATIENTS WITH CHRONIC HEPATITIS DELTA

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## Introduction/Summary

○ Serum HBV RNA and HBcrAg levels have been proposed as useful biomarkers in the management of HBV patients, however their role in chronic hepatitis Delta (CHD) is currently unknown.

## Study Design

○ Consecutive untreated CHD patients were enrolled in a cross-sectional study in three EU centers.

## Methods

- Clinical and virological characteristics were collected.
- Serum HBV RNA and HBcrAg levels were quantified by an automated real-time investigational assay (Cobas® 6800, Roche Diagnostics, Pleasanton, Ca, USA) and by LUMIPULSE® G HBcrAg assay (Fujirebio Europe), respectively.
- In a subset of patients (n=18), intrahepatic analyses were performed.

## Results

○ Overall, 240 HDV patients were enrolled, whose characteristics are shown in **Table 1**

**Table 1. Demographic, clinical and virological features of the 240 CHD patients enrolled**

Variables	Overall (n=240)
Age, years	46 (20-78)
Males	144 (62%)
European origin	170 (71%)
BMI, Kg/m <sup>2</sup>	24 (17-44)
Cirrhosis	126 (53%)
CPT- A	101 (80%)
Esophageal varices <sup>°</sup>	46 (47%)
LSM, kPa <sup>§</sup>	10.4 (3.4-74.6)
ALT, U/L	70 (15-889)
ALT>ULN	193 (80%)
AST, U/L	63 (17-380)
GGT, U/L	49 (8-491)
PLT, 10 <sup>3</sup> /mm <sup>3</sup>	140 (29-369)
On NUC treatment	137 (57%)
HBsAg, log <sub>10</sub> IU/mL	3.8 (0.3-4.6)
HBeAg positive	28 (12%)
HBV DNA detectable	74 (31%)
HBV DNA log <sub>10</sub> IU/mL*	1.8 (1.0-8.1)
HDV genotype 1 <sup>@</sup>	84 (95%)
HDV RNA, log <sub>10</sub> IU/mL	4.9 (0.8-9.6)

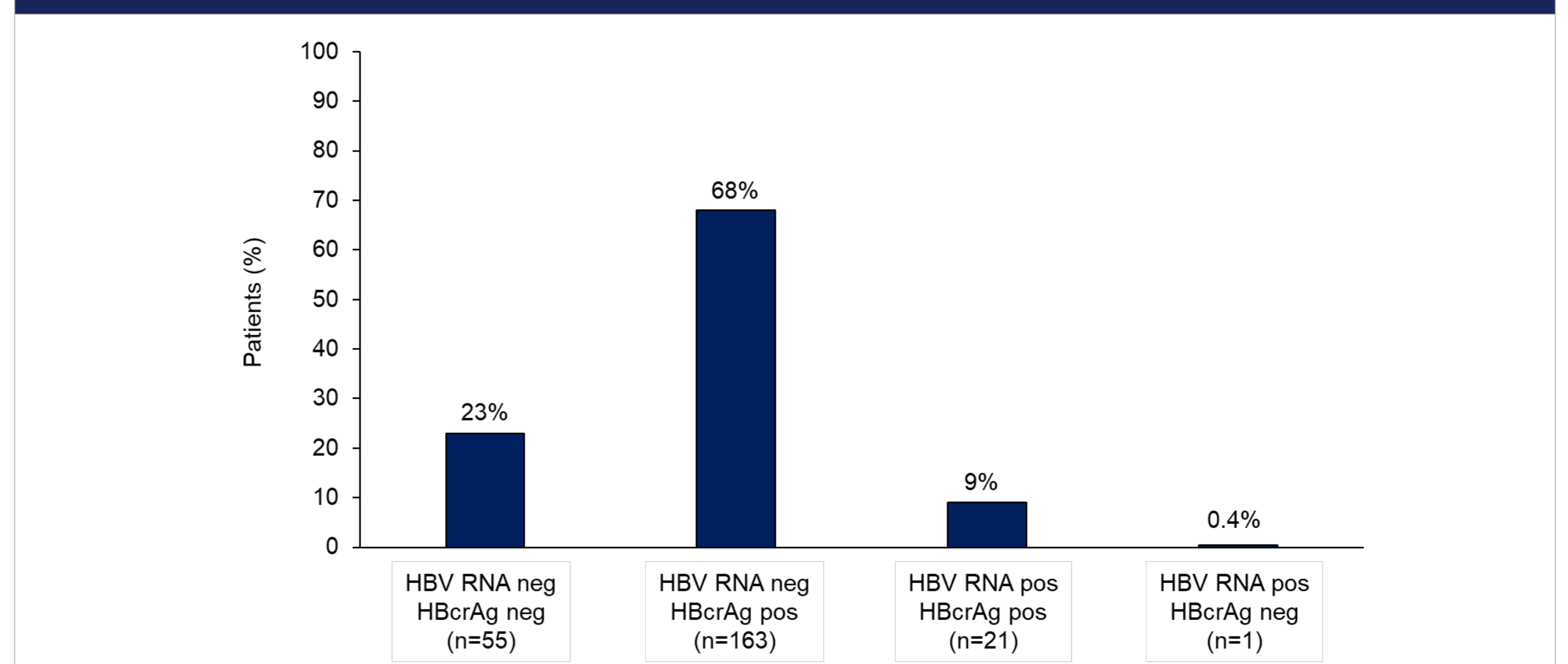
Values are expressed as number (percentage), median (range); available in 98 (78%) out of 126 patients with cirrhosis, § available in 184 (77%) patients; @available in 88 (37%) patients; HDV-1 n=84, HDV-5 n=2, HDV-7 n=2; \*in 74 patients with detectable HBV DNA.

CHD: chronic hepatitis Delta; BMI: body mass index; CPT: Child Pugh Turcotte score; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement; ALT: Alanine aminotransferase; ULN: Upper limit of normal; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transferase; PLT: platelets; NUC: Nucleos(t)ide analogue

## Results (Continued)

- HBV RNA levels were associated with male sex and detectable HBV DNA, while HBcrAg positivity correlated with higher HBsAg levels.
- By combining these biomarkers, 3 categories were identified: 23% double negative (HBV RNA neg/HBcrAg neg), 9% double positive (HBV RNA pos/HBcrAg pos) and 68% negative for HBV RNA/positive for HBcrAg (**Figure 1**). Double positive patients were younger, non-European, with elevated ALT and HDV RNA levels and detectable HBV DNA (**Table 2**).
- Intrahepatic HDV RNA and HBV RNA were positive in most samples, while intrahepatic levels of covalently closed circular (ccc) DNA were low.

**Figure 1. Distribution of the 240 CHD patients according to HBV RNA and HBcrAg status**



**Table 2. Clinical, virological and demographic features of the 240<sup>#</sup> untreated CHD patients according to HBV RNA/HBcrAg patterns**

Variables	HBV RNA neg HBcrAg neg (n=55)	HBV RNA neg HBcrAg pos (n=163)	HBV RNA pos HBcrAg pos (n=21)	p value
Age, years	48 (23-64)	47 (20-78)	36 (20-56)	<b>0.005</b>
Males	30 (55%)	96 (59%)	17 (81%)	0.10
European origin	36 (66%)	126 (77%)	7 (33%)	<b>0.0001</b>
BMI, kg/m <sup>2</sup>	25 (19-37)	24 (17-44)	25 (18-31)	0.12
Cirrhosis	30 (55%)	88 (54%)	7 (33%)	0.19
LSM, kPa <sup>§</sup>	8.4 (4.1-66.0)	10.9 (3.4-57.4)	8.5 (5.0-35.0)	0.39
AST, IU/L	64 (23-380)	64 (17-374)	53 (32-186)	0.36
ALT, U/L	51 (17-743)	78 (15-889)	62 (26-171)	0.10
ALT>ULN	37 (67%)	135 (83%)	19 (91%)	<b>0.02</b>
GGT, IU/L	57 (13-491)	49 (8-362)	42 (16-469)	0.70
PLT, 10 <sup>3</sup> x mm <sup>3</sup>	131 (41-369)	145 (29-316)	140 (84-307)	0.36
On NUC therapy	30 (55%)	99 (61%)	7 (33%)	0.05
HBsAg, log <sub>10</sub> IU/mL	3.4 (0.3-4.4)	3.8 (2.0-4.6)	3.9 (2.8-4.3)	<b>0.001*</b>
HBeAg positive	0	16 (10%)	11 (52%)	<b>&lt;0.0001</b>
HBV DNA detectable	13 (24%)	45 (28%)	15 (71%)	<b>0.0001</b>
HBV DNA, log <sub>10</sub> IU/mL <sup>§</sup>	1.5 (1.1-2.4)	1.9 (1.0-3.5)	3.5 (1.0-8.1)	<b>0.001</b>
HDV genotype 1 <sup>@</sup>	20 (100%)	55 (97%)	9 (82%)	0.17
HDV RNA, log <sub>10</sub> IU/mL	3.9 (1.1-8.2)	4.9 (0.8-9.0)	6.4 (1.0-9.6)	<b>&lt;0.001</b>

Categorical variables were compared using the  $\chi^2$  or the Fisher's exact tests; continuous variables were compared using the Student t-test, the Mann-Whitney U-test or the Kruskal-Wallis test, when appropriate.

Values are expressed as number (percentage), median (range)

#The only HBV RNA positive/HBcrAg negative patient was not included in the table.

@available in 20 (36%), 57 (35%) and 11 (52%) patients, respectively; § in 74 patients with detectable HBV DNA.

\*HBV RNA neg/HBcrAg neg vs. HBV RNA neg/HBcrAg pos: p=0.0002; HBV RNA neg/HBcrAg pos vs. HBV RNA pos/HBcrAg pos: p=0.01; HBV RNA neg/HBcrAg pos vs. HBV RNA pos/HBcrAg pos: p=0.68

CHD: chronic hepatitis Delta; BMI: body mass index; CPT: Child Pugh Turcotte score; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ULN: Upper limit of normal; GGT: Gamma glutamyl transferase; PLT: platelets; NUC: Nucleos(t)ide analogue

## Conclusion

- In untreated CHD patients, HBV RNA and HBcrAg showed a divergent pattern: most patients had undetectable HBV RNA but quantifiable HBcrAg in the absence of HBeAg.
- Additional studies aimed to unravel the molecular mechanisms underlying these findings are warranted.

## References

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