Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load

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Table of contents

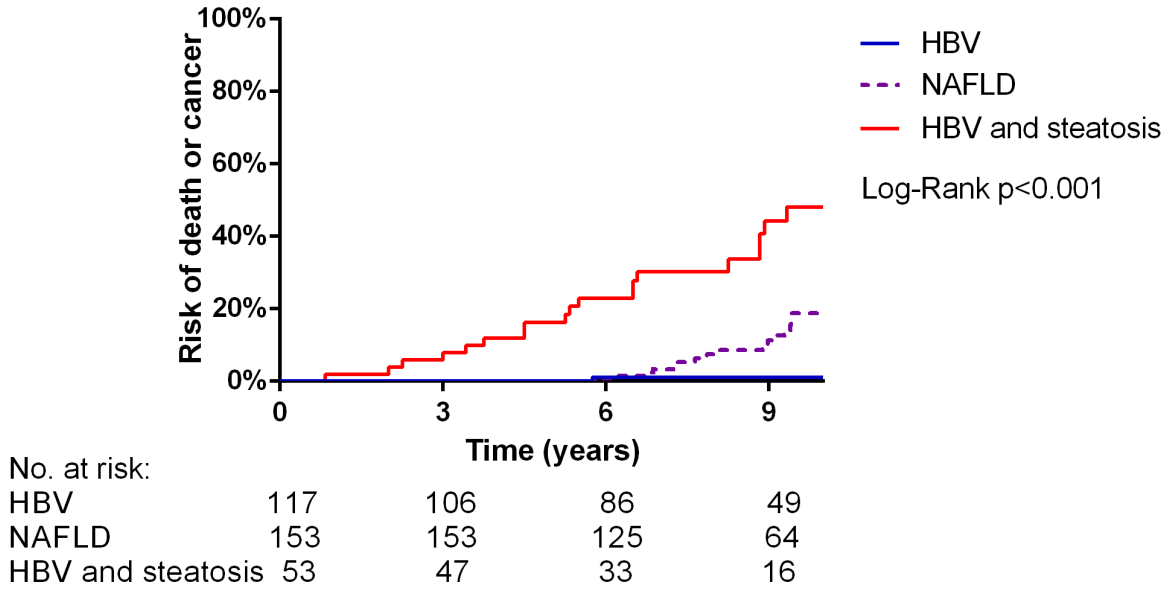

Fig S1. Cumulative rates of mortality and cancer (primary composite outcome) according to the status of liver steatosis in patients with CHB compared to historic cohort of patients with NAFLD (HBV-hepatitis B virus, CHB-chronic hepatitis B, NAFLD-nonalcoholic fatty liver disease).

Table S1. Factors associated with composite outcome of mortality and cancer in CHB patients: univariate analysis

Variable	p value
Gender–male	0.461
Age	<0.001
BMI	0.382
Positive HTN diagnosis	<0.001
Positive DM2 diagnosis	<0.001
Hemoglobin A1C	<0.001
Total cholesterol	0.017
Triglycerides	0.319
Creatinine	0.304
Hemoglobin	0.010
Platelets	0.062
INR	0.544
Albumin	<0.001
Bilirubin	0.547
Alpha feto protein	<0.001
AST	0.018
ALT	0.333
ALKP	<0.001
GGT	<0.001
HBeAg positivity	0.370
HDV Antibody positivity	0.092
Longer HBV duration	<0.001
Baseline liver steatosis	<0.001
HBV VL > 2000 IU/ml	0.001
APRI score	<0.001
FIB-4 score	<0.001

HTN = hypertension, DM2 = type 2 diabetes mellitus, BMI = Body mass index, APRI = AST to Platelets ratio index, FIB4 = fibrosis 4 score, HBV DNA lower limit of detection 1.3 log IU/ml (20 IU/ml)

Table S2A. Major clinical outcomes of study population during the follow-up period according to advanced fibrosis in patients who underwent liver biopsy

	Advanced fibrosis (N = 27)	**No advanced fibrosis (N = 143)**	**P Value**
Length of follow up (months) (range)	8.09 (0.95 – 14.04)	7.94 (0.94 – 14.04)	0.822
Composite outcome of all-cause mortality and cancer % (N)	29.62% (8)	10.48% (15)	0.010
All-cause mortality % (N)	18.51% (5)	7.69% (11)	0.084
Hepatocellular carcinoma % (N)	7.41% (2)	4.19% (6)	0.477
Extra-hepatic malignancies % (N)	11.11% (3)	4.19% (6)	0.141

Table S2B. Major clinical outcomes of study population during the follow-up period according to APRI score in patients that underwent liver biopsy

	APRI > 1.5 (N = 16)	**APRI < 1.5 (N = 154)**	**P Value**
Length of follow up (years) (range)	8.13 (0.95 – 14.04)	7.40 (1.01 – 12.01)	0.353
Composite outcome of all-cause mortality and cancer % (N)	31.25% (5)	11.68% (18)	0.033
All-cause mortality % (N)	25% (4)	7.79% (12)	0.041
Hepatocellular carcinoma % (N)	18.75% (3)	3.24% (5)	0.010
Extra-hepatic malignancies % (N)	0% (0)	5.84% (9)	0.323

Table S2C. Major clinical outcomes of study population during the follow-up period according to FIB-4 score in patients that underwent liver biopsy

	FIB-4 > 2.67 (N = 18)	**FIB-4 < 2.67 (N = 152)**	**P Value**
Length of follow up (years) (range)	8.10 (0.95 – 14.04)	7.78 (1.01 – 12.08)	0.671
Composite outcome of all-cause mortality and cancer % (N)	38.88% (7)	10.52% (16)	0.001
All-cause mortality % (N)	33.33% (6)	6.57% (10)	0.010
Hepatocellular carcinoma % (N)	16.66% (3)	3.28% (5)	0.010
Extra-hepatic malignancies % (N)	0% (0)	5.92% (9)	0.279

Table S3. Major clinical outcomes during the follow-up period according to baseline liver steatosis status for patients that were treated with anti-viral therapy during follow-up

	Liver steatosis (N =71)	**No liver steatosis (N =138)**	**P Value**
Length of follow up (months) (range)	91.21 (3.4 – 168.5)	82.08 (3.4 – 166.6)	0.090
Composite outcome of all-cause mortality and cancer % (N)	36.61% (26)	6.52% (9)	<0.001
All-cause mortality % (N)	21.12% (15)	2.17% (3)	<0.001
Malignancy (all types) % (N)	29.57% (21)	4.34% (6)	<0.001
Hepatocellular carcinoma % (N)	16.90% (12)	2.89% (4)	<0.001
Extra-hepatic malignancies % (N)	12.67% (9)	1.45% (2)	0.001

Table S4. Multivariate analysis: Predictors of the composite endpoint of all-cause mortality and cancer

	HR	95% CI	p value
Baseline liver steatosis	4.96	1.84 – 13.33	0.002
HBV VL > 2000 IU/ml	1.33	0.72 – 3.42	0.541
Initiation of anti-viral therapy	1.91	0.95 – 3.78	0.063
Age	1.03	1.01 – 1.05	0.003
Albumin	0.21	0.09 – 0.43	0.010
BMI	0.97	0.91 – 1.04	0.397
Type 2 DM	1.05	0.64 – 2.03	0.881

DM – Diabetes mellitus, VL-viral load, HBV DNA lower limit of detection 1.3 log IU/ml (20 IU/ml)

Table S5. Multivariate analysis: Predictors of the composite endpoint of all-cause mortality and cancer

	HR	95% CI	p value
Baseline liver steatosis	4.44	1.72 – 11.45	0.001
HBV VL > 2000 IU/ml	1.44	0.57 – 3.61	0.434
APRI score	0.79	0.58 – 1.08	0.143
FIB-4 score	1.24	1.09 – 1.41	0.010
Albumin	0.35	0.17 – 0.71	0.010
BMI	1.22	0.69 – 3.31	0.454
Type 2 DM	1.34	0.71 – 2.53	0.361

DM – Diabetes mellitus, VL-viral load, HBV DNA lower limit of detection 1.3 log IU/ml (20 IU/ml)

Table S6. Multivariate analysis: Predictors of the composite endpoint of all-cause mortality and HCC

	HR	95% CI	p value
Baseline liver steatosis	4.29	1.18 – 15.61	0.029
HBV VL > 2000 IU/ml	1.77	0.53 – 5.87	0.349
Alpha feto protein	1.03	1.02 – 1.04	<0.001
Type 2 DM	2.56	1.22 – 5.74	0.013
BMI	0.94	0.85 – 1.03	0.158

DM – Diabetes mellitus, VL-viral load, HBV DNA lower limit of detection 1.3 log IU/ml (20 IU/ml)

Table S7. Predictors of the composite endpoint of all-cause mortality and cancer in patients with NAFLD and CHB: univariate and multivariate analysis

	Univariate		**Multivariate**	
	p value	**HR**	**95% CI**	**p value**
CHB and LS*	**<0.001**	**21.15**	**4.90 – 90.09**	**<0.001**
NAFLD*	**<0.001**	**4.08**	**0.92 – 18.08**	**0.071**
Gender–male	0.382			
Age (per year)	**<0.001**	**1.07**	**1.05 – 1.11**	**<0.001**
BMI	0.022			
Positive HTN diagnosis	<0.001			
Positive DM2 diagnosis	0.074			
Hemoglobin A1C	0.012			
Total cholesterol	0.943			
Triglycerides	0.268			
Creatinine	0.559			
Platelets	0.050			
INR	0.178			
Albumin	0.010			
Bilirubin	0.641			
Alpha feto protein	0.031			
AST	0.051			
ALT	0.949			
Alkaline phosphatase	0.451			
GGT	0.124			

*Compared to CHB without liver steatosis

CHB – chronic hepatitis B, NAFLD – nonalcoholic fatty liver disease, HTN - hypertension, DM2 - type 2 diabetes mellitus, BMI = Body mass index