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ORIGINAL ARTICLE

Mortality in Greenlanders with chronic hepatitis B virus infection

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Abstract

In-depth reviewing of all medical records and clinical databases concluded a 7-year shorter lifespan among Greenlanders infected with hepatitis B virus (HBV) compared with non-infected. Mortality did not associate with liver disease or any other specific disease entity. A possible mechanism for the reduced lifespan is subclinical inflammation that may be augmented by chronic viral infection. We hypothesized that chronic HBV infection contributes to this process causing a reduced life span. We added measurement of two markers of inflammation to the 10-year follow-up on our study of HBV among 50- through 69-years-old subjects in Greenland. The markers were YKL40 related to liver disease and hsCRP as a global marker of inflammation. Survival was evaluated using Cox regression with time until death entered as dependent variable and age, sex, smoking, alcohol intake, BMI, the presence of HBsAg and one marker of inflammation as explanatory variables. Forty-eight percent of participants with chronic HBV infection were alive after 10 years compared with 65% of participants without infection ($p = 0.003$). Survival associated with age ($p < 0.001$), BMI ($p = 0.003$) and both YKL40 and hsCRP (both, $p < 0.001$). Harboring HBV influenced 10-year survival in the Cox regression after adjusting for age, sex, BMI, smoking, alcohol intake and inflammation. In conclusion, chronic low-grade inflammation and being infected with HBV were independent markers of mortality in otherwise healthy subjects. Thus, the 7-year shorter lifespan among Greenlanders with chronic HBV infection seems related to the long-lasting infection. Our findings call for caution in perceiving a chronic infection as benign.

KEYWORDS

chronic infection, Greenland, Hepatitis B virus, inflamm-ageing, mortality

1 | BACKGROUND

Hepatitis B virus infection was previously reported to be a benign disease among Greenlanders with more than 90% in phase-3 with HBeAg-negative chronic HBV infection.^{1,2} Due to this belief, vaccination was not introduced until 2010 in Greenland despite the fact

that chronic HBV infection was common. However, intriguing results came from an in-depth reading of medical records, radiological scans and descriptions, pathology reports, the laboratory information management system (BCC), the National Registry of Pathology, and the Death Registry for the participants in a population-based study among Greenlanders.³ This recent analysis reported an approximately

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7-year shorter lifespan among HBV-infected Greenlanders compared with non-infected individuals. Furthermore, there was no direct relation to liver disease or any other disease entity, but the profoundly reduced lifespan is important to HBV-infected populations.

East Greenland Inuit is burdened by Progressive Greenland Familial Cholestasis (Byler disease) caused by a mutation in APT8B1 (FIC1).^{4,5} Heterozygosity for the disease is common and could influence lifespan in this population.

Another possible mechanism for the reduced lifespan is sub-clinical inflammation. A range of diseases arise with age in association with inflammation, and smoking and adiposity contribute to low-grade persistent inflammation.⁶ Inflamm-aging is based on increasing dysregulation of the innate immune system with persistent inflammatory response. This response may be augmented by chronic viral infection being a likely environmental stressor of the immune system.^{7,8} Hence, we hypothesized that chronic HBV infection may contribute to this process causing a reduced life span.

This led us to evaluate the influence of the FIC1 mutation and markers of inflammation between 86 HBV-infected and 346 non-infected participants in our population-based clinical study.

1.1 | Methods

The present report extends our population-based clinical study on HBV infection among Inuit in Greenland,¹ with mortality analyses illustrated in Figure 1.³

In brief, we included men and women born 1928 through 1948, living in the capital Nuuk in West Greenland or in rural Ammassalik district in East Greenland. Information on lifestyle patterns was obtained by an interview-based questionnaire as described in detail previously.^{9,10} Participants were born in Greenland with at least one

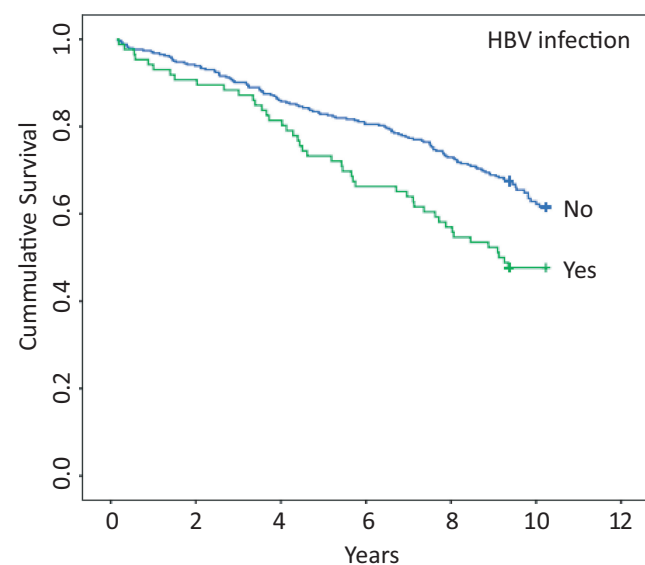


FIGURE 1 Kaplan-Meier plot of 10-year survival among Greenlanders with and without chronic HBV infection

parent born in Greenland. We measured height and weight in indoor clothing and calculated body mass index (BMI, kg/m²).¹¹

Laboratory analyses included markers of HBV (HBsAg, anti-HBs, HBeAg, anti-HBe, HBV-DNA, HBV-DNA genotype, pre-core mutation, anti-HBc (total)),¹ FIC1⁵ and vitamin D (25OH(D)),¹⁰ and the inflammatory markers high sensitive CRP (hsCRP) and YKL40.¹² All data on disease occurrence and vital statistics were collected from registries as detailed in a recent comprehensive report.³

Age was split into equal year-intervals, smoking by present smoking status, alcohol by intake below or above 7 units per week, and vitamin D into groups of <50, 50–100, 100+ nmol/L. BMI was grouped according to Inuit standards.¹¹ Elevated CRP was set at 10 mg/L and YKL40 at 200 ng/ml delineating the upper quartile group.

The study was conducted according to the guidelines laid down by the Declaration of Helsinki. Ethical approval by the Commission for Scientific Research in Greenland was obtained (J. no. 505–31) with supplementary approval for hepatitis diagnostics (J. no. 505–99) and for registry follow-up (2016–20), and the Board for Prevention and Health in Greenland approved and supported access to health data (3 November 2016). All participants gave informed written consent for the clinical study in Danish or Greenlandic by participant choice.

1.2 | Statistical analysis

Data were described using medians and quartiles and comparisons were performed using Chi-squared test for comparison of fractions, Mann-Whitney test for comparison of medians, and Spearman's rho for testing correlations. Kaplan-Meier plots were used to depict survival by separate groups. Linear regression analysis was performed entering the two markers of inflammation as dependent variable and the following entered as explanatory variables: age, sex, smoking, alcohol intake, BMI and the presence of HBsAg. Cox regression analysis was used with survival time entered as dependent variable and the following explanatory variables: age, sex, smoking, alcohol intake, BMI, the presence of HBsAg and one marker of inflammation at a time leading to two separate analyses. Effect modification on death was tested using markers of inflammation as an interaction term. BMI and markers of inflammation were entered after logarithmic transformation.

2 | RESULTS

Participant characteristics are provided in Table 1. Forty-eight percent of participants with chronic HBV infection were alive after 10 years compared with 65% of participants without infection ($p = 0.003$). Survival also associated with age ($p < 0.001$), BMI ($p = 0.003$) and the two markers of inflammation, hsCRP and YKL40 (both, $p < 0.001$). Thus, hsCRP was >10 in 10.9% and YKL40 was >200 in 28.7% of participants. Nearly one-third were alcohol abstainers and had a slightly higher mortality compared with ever

TABLE 1 Baseline characteristics of the Inuit in the clinical, population-based study in West and East Greenland with 10-year follow-up

	All	Lost to follow-up	10-year follow-up		<i>p</i> [*]
	n		Alive	Diseased	
All	434	2	266	166	
Gender					
Men	229		141	88	NS
Women	205	2	125	78	
Age					
<i>n</i> , <60 years	259	1	183	75	<0.001
<i>n</i> , 60+ years	175	1	83	91	
Smoking					
Yes	328	2	194	132	NS
No	105		71	34	
Missing	1		1		
Alcohol					
Never	129		70	59	0.04
Ever	297	2	191	104	
Missing	8		5	3	
Main meal local^a					
3 days or less	102	1	63	38	NS
4 days or more	325	1	200	124	
Missing	7		3	4	
Place of living					
East Greenland	284	1	169	114	NS
West Greenland	150	1	97	52	
BMI groups					
<18.5	26		13	13	0.003
18.5–27	250	1	144	105	
>27	128		95	33	
Missing	30	1	14	15	
Vitamin D					
<50	51		25	26	0.07
50–100	305	2	188	115	
100+	72		50	22	
Missing	6		3	3	
FIC1^b					
Heterozygous	33		12	21	NS
Wildtype	250	1	102	147	
Missing	1	1			
Chronic HBV					
Yes	86		41	45	0.003
No	346		225	121	
Missing	2				
hsCRP					
<10	383		246	137	<0.001
10+	47		18	29	
Missing	4	2	2		

TABLE 1 (Continued)

	All	Lost to follow-up	10-year follow-up		<i>p</i> [*]
	n		Alive	Diseased	
YKL40					
<200	308	1	212	95	<0.001
200+	124	1	52	71	
Missing	2		2		

^aLocal food items are mainly marine mammals and fish

^bOnly East Greenlanders were tested for the FIC1 mutation

*NS: $p > 0.1$.

drinkers. There was no difference when subdividing in three groups by alcohol intake ($p = 0.10$). Smoking was frequent with 76% of participants being smokers with equal numbers in 10-year survivors and non-survivors ($p = 0.2$), and survival was similar between rural East Greenland and the capital Nuuk ($p = 0.3$). Being carrier of the mutation for FIC1 did not associate with survival.

The two markers of inflammation found to be associated with age were hsCRP and YKL40 (spearman's rho = 0.167 and 0.173, $p < 0.001$ and $p < 0.001$). YKL40 was influenced by age ($p < 0.001$) in linear regression analysis and by BMI ($p = 0.002$) and HBV infection ($p = 0.022$). In contrast, hsCRP was influenced only by alcohol in the linear regression analysis ($p = 0.002$). Participants with HBV infection had higher YKL40 ($p < 0.001$) while hsCRP did not differ with HBV infection ($p = 0.5$) in the crude analysis.

Figure 2 illustrates the relation between survival and the markers of inflammation. Cox regression confirmed the influence on survival by hsCRP ($p < 0.001$) and by YKL40 ($p < 0.001$) after adjusting for age (hsCRP/YKL40; both, $p < 0.001$), BMI (hsCRP/YKL40; $p = 0.004/0.037$), and HBV infection (hsCRP/YKL40; $p = 0.002/0.016$) (Table 2). Additional testing for effect modification suggested no interaction between HBV infection and hsCRP ($p = 0.1$) or YKL40 ($p = 0.4$). Testing for an influence of familiar intra-hepatic cholestasis (FIC1) also showed no difference (hsCRP/YKL40, $p = 0.3/0.7$).

Figure 3 shows the rising percentage of deceased individuals at 10 years with increasing levels of hsCRP and YKL40 (both, $p < 0.001$).

3 | DISCUSSION

More than half of the population with chronic HBV infection had died at the 10-year follow-up compared with around one-third of the population without infection. The subjects with chronic HBV infection showed no signs of liver disease, and HBV infection had no influence on body-build.¹ There was no association between chronic HBV infection and liver biochemistry.^{1,13} In our population, more than 90% hosted the genotype B5, formerly B6,^{1,14} and our findings conformed to the notion of a lack of signs of liver disease among subjects chronically infected with this HBV sub-genotype.^{15,16} It was surprising to see the lack of liver-related disease and any other disease pattern suggesting a cause for the earlier deaths among

subjects with chronic HBV infection even when scrutinizing all available information in medical records and registries,³ and none with chronic HBV infection had HCC, but one without infection had HCC with metastasis to the lung according to the pathology report.³

The markedly reduced 10-year survival among an apparently healthy population albeit hosting chronic HBV infection refutes the previously suggested benign course of chronic HBV infection among Greenlanders and poses the question: why.

Progressive Greenlandic Familial Intrahepatic Cholestasis (Byler disease) is fatal among subjects homozygous for the mutation, and an influence on health should be considered for heterozygous subjects. However, we found no association with survival, neither in the crude nor in the adjusted analysis. Hence, harbouring FIC1 did not influence survival.

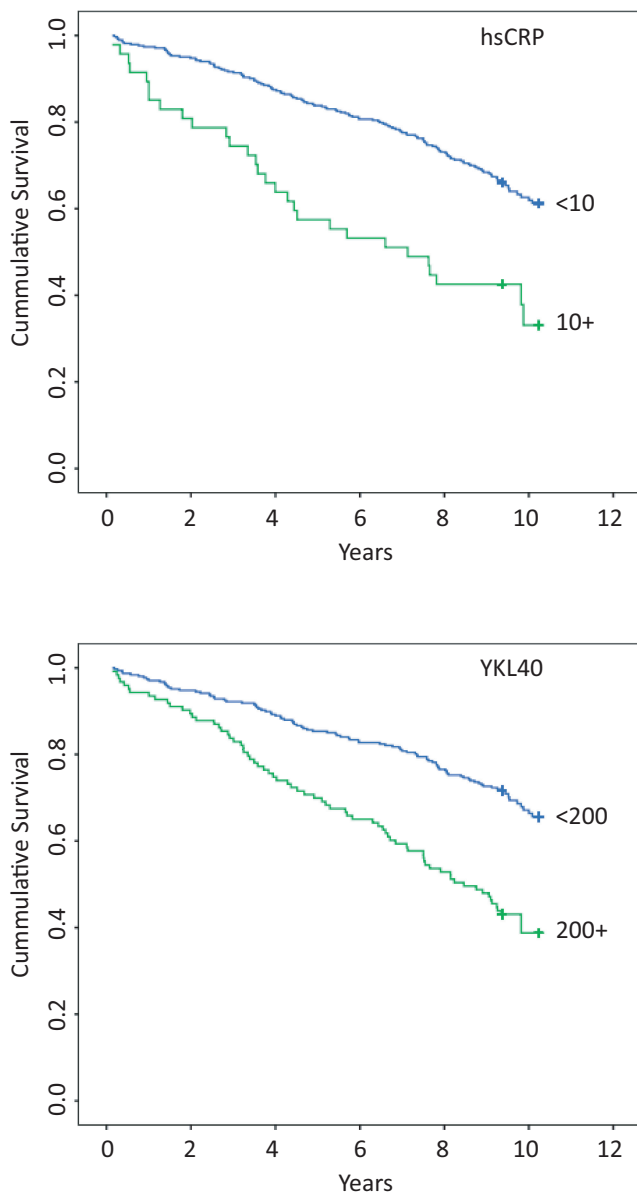


FIGURE 2 Kaplan-Meier plot of 10-year survival among Greenlanders separated by level of two markers of inflammation: hsCRP (upper panel) and YKL40 (lower panel)

The ageing process of the immune system includes changes that associate with age-related diseases such as cancer, type 2 diabetes, cardiovascular and rheumatic diseases. This immunosenescence also alters the inflammatory response to infections.¹⁷ Chronic viral infection has been linked to a rise in the age-associated proinflammatory environment.^{8,18} Our findings conform to the notion that chronic HBV infection augments the increase in low-grade inflammation that comes with the age-dependent dysregulation of innate immunity.⁸ The duration of exposure rather than the level of HBsAg

TABLE 2 Factors associated with survival among Greenlanders at 10-year follow-up in Cox regression analyses

	<i>p</i> -value [*]	<i>p</i> -value [*]
Age	<0.001	<0.001
BMI	0.004	0.037
HBV	0.002	0.016
hsCRP (<i>n</i>)	<0.001	
YKL40 (<i>n</i>)		<0.001

*The markers of inflammation were each included in separate Cox regression analyses.

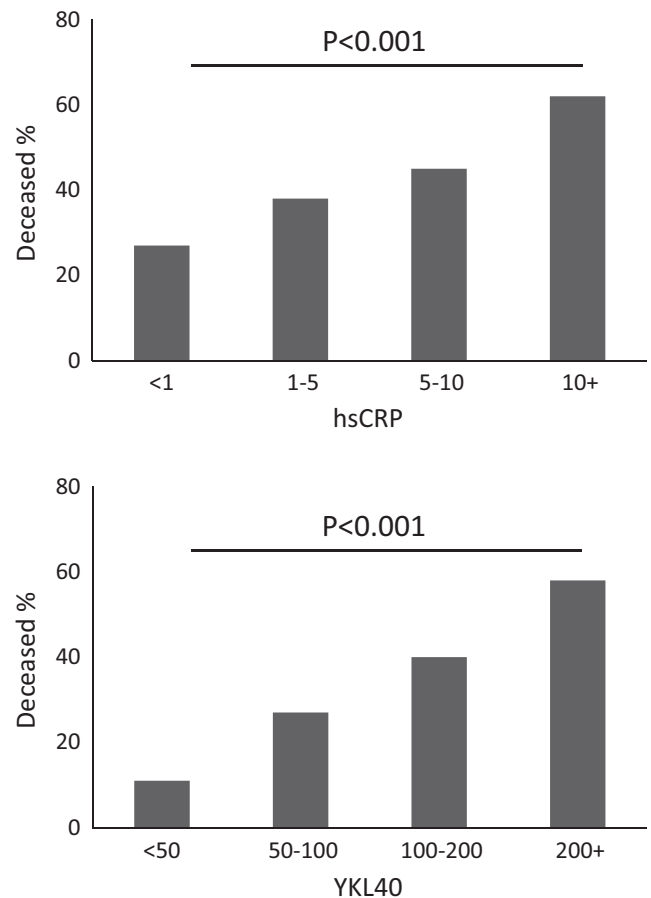


FIGURE 3 Bar plot showing the percentage of Greenlanders dead at 10-year follow-up by rising levels of two markers of inflammation: hsCRP (upper panel) and YKL40 (lower panel). *p*-values are for differences between groups (Kruskal-Wallis test)

is important for the immune response to HBV.¹⁹ Our study population had chronic HBV infection and hence low-grade inflammation for decades.

Adiposity provides an environment that supports low-grade inflammation.⁸ Interestingly, mortality among Greenlanders in our study showed a distinct decreasing trend with rising BMI. Thus, mortality was only half in participants with a BMI above 27 kg/m² compared with a BMI < 18.5 kg/m². Interestingly, 10-year mortality was 42% with BMI 18.5–27 kg/m² while just 26% with higher BMI. The raised mortality with BMI below 27 kg/m² could be influenced by the raised BMI cut-off for overweight in Greenlanders²⁰ in conjunction with the known nadir of mortality with a BMI of around 25 kg/m² in other populations,²¹ rising with age to 27 kg/m² in the above 70 years olds.^{22,23}

Nearly one in three Greenlanders were alcohol abstainers, and this group had a ten percent higher 10-year mortality compared to Greenlanders with any alcohol intake. This finding is in keeping with reports from other populations of a protective effect of some alcohol intake compared to none, heavy and binge drinking.²⁴ The number of heavy drinkers was too few to allow for valid analysis of the relation to mortality. Mortality was eight percent higher in smokers compared with non-smokers. However, more than three out of four Greenlanders were smokers, and the difference between the groups was not statistically significant.

The two markers of inflammation's relation to mortality showed similar trends. The groups with the lowest levels of hsCRP and YKL40 had 10-year mortality of around 25% and 10%, respectively, rising gradually to around 60% with hsCRP above 10 and YKL40 above 200. The marked increase in mortality with inflammation shown in other populations²⁵ was, thus, extended to account for Greenlanders as well.

YKL40 and hsCRP have different origins. YKL40 has been used as a marker of fibrosis of the liver, while hsCRP is a more global marker of inflammation.^{26,27} We included two markers of inflammation to describe the relation between inflammation and mortality. Future studies could include further markers in order to add details on the inflammatory process.

A limitation to our study was the size of the study population. This was due to the limited size of the total population in the two areas in Greenland. Conversely, a strength was the very high participation rate of 95%, and that the study was population-based. Moreover, we had a more than 99% follow-up with only 2 out of 434 lost to follow-up. It may be a further strength that the authors collected clinical and biochemical data at baseline. Also, the 10-year duration of follow-up on a population aged 50 through 69 years at baseline in a population with a median lifespan around 70 years supports the validity of our findings. Thus, an event (death) occurred in 38% of participants during follow-up.

In conclusion, chronic low-grade inflammation and being infected with HBV were independent markers of mortality in otherwise healthy subjects. Thus, the 7-year shorter lifespan among Greenlanders with chronic HBV infection seems related to the

long-lasting infection. Our findings call for caution in perceiving a chronic infection as benign.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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