

Indication for treatment and severity of disease in treatment-naïve chronic Hepatitis B infected patients referred for initial evaluation

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List of abbreviations in the order of appearance:

kPa	-	kilo Pascal
IQR	-	Interquartile range
WHO	-	World Health Organization
HBV	-	Hepatitis B virus
LMIC	-	low- or middle-income countries
HCC	-	Hepatocellular carcinoma
NA	-	Nucleos(t)ide analogue
EASL	-	European Association for the Study of the Liver
TE	-	Transient elastography
HBeAg	-	Hepatitis B virus envelope antigen
DNA	-	Deoxyribonucleic acid
PCR	-	Polymerase chain reaction
HBsAg	-	Hepatitis B virus surface antigen
AST	-	Aspartate transaminase
ALT	-	Alanine transaminase
GGT	-	Gamma-glutamyltransferase
AP	-	Alkaline phosphatase
HbA1c	-	Glycated hemoglobin A1c
INR	-	International normalized ratio (prothrombin time)
HIV	-	Human immunodeficiency virus
HCV	-	Hepatitis C virus
HDV	-	Hepatitis Delta virus
ANOVA	-	Analysis of variance
SD	-	Standard deviation
ULN	-	upper limit of normal

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Background & Aims

The prevalence of chronic hepatitis B virus (HBV) infection in Europe is variable and poorly defined. Data on the proportion of treatment-naïve patients eligible for antiviral therapy is lacking. The aims of our study were to provide an estimate of the need for antiviral treatment and to assess the prevalence of advanced liver disease in, treatment-naïve, chronic HBV-infected patients referred for specialized care.

Methods

We performed a retrospective, cross-sectional analysis of all treatment-naïve, chronically HBV-monoinfected patients referred to our ambulatory Infectious Diseases practice in Berlin, Germany. Baseline clinical assessments included recording of sociodemographic data, hepatitis B specific laboratory analysis and ultrasound-based measurements of liver stiffness.

Results

Between 2010 and 2017, 465 patients with chronic HBV infection were referred to our site. Of these, 301 (64.7%) were treatment naïve, HBV-monoinfected and are included in our analysis. Forty percent of subjects were female. The mean age was 39.3 ± 13.1 years. Sixty-one percent of subjects were born outside Europe, predominantly in the Asia Pacific region (30.2%, n=91). Median liver stiffness, obtained by transient elastography, was 5.2 kPa (IQR: 4.2 - 6.6 kPa). At initial evaluation, liver stiffness results indicating significant fibrosis were found in 96 out of 271 subjects (35.0%) including 20/271 (7.4%) patients with suspected advanced fibrosis/cirrhosis. Twenty-six percent of subjects met criteria to initiate antiviral treatment, while 69.4% did not require antiviral treatment but qualified for further surveillance. In only 4% of subjects, liver biopsy was recommended to determine if treatment is indicated.

Conclusions

In our cohort of more than three hundred patients, burden of advanced and treatment-eligible chronic HBV infection was significant, and about 7% had liver cirrhosis at presentation. Only in 4% of all subjects, a treatment indication could not be determined by our non-invasive approach. About a quarter met criteria for immediate antiviral treatment according to current guidelines. Most subjects acquired hepatitis B virus infection in highly endemic regions prior to emigrating. To our knowledge, our sample represents the largest HBV-infected therapy-naïve cohort reported in Europe over the past decade.

Lay summary

Initial evaluation of patients with chronic hepatitis B virus is essential to identify individuals in need of immediate antiviral treatment. We analyzed results from all hepatitis B infected patients who presented to our clinical center and who had not been previously treated. We found that 26.2% of the patients met the criteria to start antiviral treatment immediately and 7.4% already suffered from advanced liver disease (advanced fibrosis/cirrhosis).

Introduction

According to the World Health Organization (WHO), 257 million individuals worldwide are chronically infected with the hepatitis B virus (HBV). Chronic HBV infection may lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Current estimates suggest that 700,000 people die from complications related to chronic HBV annually. Without a scale-up of effective interventions, chronic HBV will lead to 11.8 million deaths by 2030.^{1–3}

The greatest burden of HBV-related morbidity and mortality is concentrated in low- and middle-income countries (LMIC) of the global South.^{4–7} Global strategies to address this disease burden comprise of a combination of preventative measures and improved access to antiviral treatment.⁸ Within Europe, prevalence of hepatitis B is highly variable between regions and social groups. Prevalence of chronic HBV in Western Europe is low, particularly in the native-born population.^{9–11} Over the past decade, global sociopolitical conditions have made Germany a target destination for immigrants born in regions with high HBV prevalence.¹²

The aim of HBV treatment is to prevent liver-related complications and the occurrence of HCC. Nucleos(t)ide analogue (NA) therapy accounts for >95% of prescribed treatment.¹³ NA therapy is associated with near complete long-term virologic suppression with low rates of treatment-emergent antiviral resistance.¹⁴ Most guidelines recommend lifelong treatment to achieve viral suppression. Although alternative strategies, including treatment interruption, are now being considered¹⁵, initiation of therapy still requires lifelong pharmacological adherence for the majority of the patients. In the current treatment guidelines of the European Association for the Study of the Liver (EASL), treatment decisions are based on three key features of the disease: HBV viral replication, hepatic

inflammation, and the presence of liver fibrosis. Additional factors in the treatment algorithm include HBeAg status combined with age, as well as patient comorbidities. While liver biopsy remains the histological gold standard for determining stage of fibrosis, non-invasive testing with transient elastography (TE) and serum biomarkers have replaced invasive tissue sampling in many clinical settings.¹⁶

We performed a retrospective, cross-sectional analysis of all treatment-naïve, chronically HBV infected patients referred to our specialized Infectious Diseases center in Berlin, Germany. The aims of our study were to 1) provide a descriptive analysis of the referral population; 2) quantify the burden of advanced liver disease in the referral population; 3) determine rates of eligibility for immediate HBV treatment using current EASL guidelines (s. figure 1).

Patients and methods

Patients evaluated at our clinic were either referred by their primary care physicians or presented directly to our center. For the analysis, we included patients seen for an initial evaluation between May 2010 and April 2017. Initial data collection included basic demographic information (age, gender, height and weight, country of origin), as well as HBV specific laboratory data set (HBV-DNA-PCR, quantitative hepatitis B virus s antigen (qHBsAg), HBeAg status, liver-related (AST, ALT, GGT, AP) and metabolic parameters (cholesterol, triglyceride, HbA1c/serum glucose), platelets, INR, and co-infection status (HIV, HCV, HDV). Transient elastography as measured by FibroScan® and abdominal ultrasound were performed on-site.

Patients with chronic hepatitis B infection, defined by HBsAg positivity, were eligible for inclusion in the study if they were treatment-naïve and showed no clinical evidence of decompensated liver disease. Patients with HIV-, HCV- or HDV- coinfections were excluded. Eligible subjects needed to have both laboratory and radiographic evaluation performed within 6 months of each other. A valid FibroScan® estimation was defined as at least 10 valid shots, a success rate of at least 60% and an IQR/median-ratio of less than 30%, as defined in the EASL guidelines for non-invasive tests of liver diseases.¹⁷ The study was approved by the local ethics committee of the Charité Universitätsmedizin, Berlin.

Statistical analyses were performed using IBM SPSS Statistics version 24.0.0.0. We report means and standard deviation for all metric and normally distributed variables. If normal distribution could not be assumed, median and interquartile ranges (IQR) from 25th to 75th percentile are presented. T-test and Pearson correlation were performed to compare normally distributed variables while Mann-Whitney-U tests and Spearman correlation were used for those without normal distribution. Categorical variables were compared by chi-squared-test and comparisons between categorical and metric variables were performed by ANOVA. For post-hoc testing, Tukey's HSD was performed. A 2-sided P value of less than 0.05 was considered statistically significant.

Results

Between May 2010 and April 2017, 465 patients were referred to our center for specialist evaluation of chronic hepatitis B infection. A total of 79 patients were co-infected with either HCV, HIV or HDV and were excluded from further analysis. 72 patients were excluded because HBV treatment had already been initiated by their primary care

physician. In another 11 patients, our quality criteria were not met due to the time gap between laboratory and radiographic diagnostic procedures. The final sample included 301 treatment-naïve, monoinfected patients referred for assessment of chronic HBV (s. figure 2).

Gender, age and origin

Of the 301 subjects, 123 (40.9%) were female. The mean age was 39.3 ± 13.1 years (range 15-71 years) with no significant difference between male (38.4 ± 13.0 years) and female (40.6 ± 13.2 years, $p=0.15$) subjects. About a quarter of subjects were of European origin ($n=72$, 23.9%), 183 (60.8%) subjects reported a history of immigration, while no information on region of origin could be found for the remaining 46 (15.3%). Within the immigrant group, most subjects had emigrated from the Asia Pacific region ($n=91$, 30.2%) followed by equal proportions from the Middle East ($n=46$, 15.3%) and Africa ($n=46$, 15.3%,) (s. figure 3). Subjects born in Europe had a higher mean age (43.6 ± 13.4 years); subjects emigrating from Africa were significantly younger (30.9 ± 11.4 years) when compared to those originating from all other regions.

HBV parameters and phase of infection

43 (14.3%) subjects were HBeAg-positive and 223 (74.1%) HBeAg negative. For 35 (11.6%) subjects, HBeAg status was not available. HBeAg-positive subjects had a significantly higher viral load (median HBV-DNA-PCR: $52 \cdot 10^4$ IU/mL, IQR: $185 \cdot 10^3$ - $273 \cdot 10^4$ IU/mL) than HBeAg-negative subjects (1200 IU/mL, 200 – 7300 IU/mL, $p<0.001$). Overall, 145 (48.2%) subjects had an HBV viral load of over 2,000 IU/mL.

The median ALT level was 32 U/L (IQR: 22 – 47 U/L). ALT levels were significantly higher in male (median: 38 U/L, IQR: 28 – 56 U/L) compared with in female subjects (23 U/L, IQR 18 - 35 U/L, $p<0.001$). 103 (34.2%) subjects had ALT levels above 40 U/L, the proposed upper limit of normal (ULN) by EASL criteria. A significant difference in ALT levels was observed between HBeAg positive (ALT: 46 U/L; IQR: 32 – 81 U/L) and HBeAg negative subjects (ALT: 31 U/L; IQR 22 – 46 U/L; $p=0.001$). A positive correlation between ALT levels and HBV viral load was also observed ($\rho=0.396$; $p<0.001$).

In terms of current disease classification,^{14,18} 14 (4.7%) subjects were classified as HBeAg-positive chronic HBV infection (formerly termed ‘immune-tolerant’); 23 (7.6%) were classified as HBeAg-positive chronic hepatitis B, (formerly ‘immune-active phase’), 145 (48.2%) as HBeAg-negative chronic HBV infection, (formerly ‘inactive carriers’) and 76 (25.2%) as HBeAg-negative chronic hepatitis B, (formerly ‘immune reactivation phase’). 43 (14.3%) HBsAg-positive patients could not be classified because their HBeAg status was either unknown or due to probable transition to HBeAg-negative status (s. figure 4).

Liver stiffness

All subjects underwent transient elastography (FibroScan®). Out of 301 FibroScan® examinations performed, 30 (10%) did not meet the criteria of quality determined by the EASL guidelines, leaving 271 subjects available for analysis. The median liver stiffness was 5.2 kPa (IQR: 4.2 – 6.6 kPa).

In accordance with EASL guidelines,¹⁷ we grouped the results of the liver stiffness measurements as shown in figure 5. Since TE results are affected by elevated liver enzymes,¹⁹ figure 5 also stratifies liver stiffness results by ALT values above and below 40

U/L. Based on our transient elastography results, no fibrosis was found in 64.6% (n=175) using a cut off of <6 kPa. Advanced fibrosis/cirrhosis was detected in 5.9% (n=16) based on liver stiffness measurements of >12.0 kPa. An additional 4 patients had liver stiffness results above 9kPa combined with normal ALT levels, resulting in an overall number of 20 subjects (7.4%) with suspected advanced fibrosis/cirrhosis. The remaining subjects had liver stiffness scores between 6.0 - 9.0 kPa (n=70, 23.3%) and between 9.0 - 12.0 kPa (n=10, 3.3%) (s. figure 5).

We found a significant correlation between liver stiffness and ALT levels ($\rho=0.39$, $p<0.001$) as well as HBV virus-DNA load ($\rho=0.16$, $p=0.008$). We also found a correlation between patient gender and liver stiffness, with male subjects have a higher median result (5.6 kPa, IQR: 4.6 - 6.9) compared with females: 4.8 kPa, 4.0 - 6.1 kPa, $p=0.002$).

Therapy indication

Using 2017 EASL criteria, we grouped our study sample into three treatment categories (s. figure 1): 1) subjects meeting criteria for initiation of antiviral treatment (n=79, 26.2%) 2) subjects who do not meet criteria for treatment initiation but remain under routine clinical surveillance (n=209, 69.4%) and 3) subjects with inconclusive findings on non-invasive assessment who may benefit from liver biopsy for further evaluation of liver fibrosis and necroinflammation (n=13, 4.3%).

Figure 4 displays these results, with additional data on phase of infection in each group. 60.5% (n=26) of the HBeAg-positive patients met criteria for initiation of treatment while 4.7% (n=2) needed further diagnostic evaluation. Only 22.0% (n=49, $p<0.001$) of subjects with negative HBeAg status met criteria for treatment. 100% (n=23) of the subjects in the

HBeAg-positive chronic hepatitis B phase (immune active) met treatment criteria. Within the group of HBeAg-negative chronic HBV infection (inactive carrier) most subjects (n=134, 92,4%) did not meet criteria for initiation of treatment, seven (4.8%) required further diagnostic steps due to inconclusive results, and four subjects (2.7%) required treatment based on transient elastography results. The most inhomogeneous results could be observed in the group of HBeAg-negative chronic hepatitis B patients (reactivated). 45 (59.2%) subjects of this group met criteria for initiation of treatment, one (1.3%) subject was inconclusive and 30 (39.4%) required routine clinical surveillance.

Regarding the demographic characteristics of our patients, we observed a significantly larger proportion of male subjects requiring treatment (n=58, 34.5%) compared to female (n=21, 17.5%, $p=0.001$). No correlation was found between the patient's age or region of origin and indication for treatment.

Factors associated with therapy indication

Treatment-eligible patients had significantly higher AST and GGT levels (both $p<0.001$) and significantly lower platelet levels ($p=0.005$) than subjects who did not meet criteria for treatment initiation. A correlation between need for treatment and elevations in serum-bilirubin ($p=0.022$) and quantitative HBsAg levels ($p=0.003$) was also found.

Among the subjects meeting treatment criteria, 74 (93.7%) had HBV DNA levels above 2000 IU/mL. In other words, only five subjects with DNA-PCR level under 2000 IU/mL met criteria for immediate treatment initiation. Based on these data we calculated a sensitivity of 93.7% for HBV DNA<2000 as an indicator of HBV treatment initiation. 56 subjects (26.8%) had a DNA-PCR >2.000 IU/mL but did not meet the EASL criteria to start

treatment directly resulting in specificity of DNA-PCR >2.000 IU/mL of 73.2%. Elevated ALT-levels >ULN (>40 U/L) had a sensitivity of 87.3% and a specificity of 83.7%.

For 35.0% (n=50) of patients with a DNA-PCR >2.000 IU/mL, transient elastography results suggested no or minimal fibrosis (<6 kPa) and normal ALT levels.

Discussion

In this large, global population including, single center cohort from Berlin, Germany, we found a significant burden of untreated chronic HBV infection and advanced liver disease at presentation. In our study sample, 7.4% of subjects had evidence of liver cirrhosis or severe fibrosis by transient elastography. An additional 28% had transient elastography scores >6kPa.

The rate of advanced disease found in our population is lower than that reported in other studies. In a previous retrospective analysis of hospital records conducted in Germany, Stahmeyer et al. found that 9.3% of untreated patients presented with cirrhosis/advanced fibrosis as diagnosed by ultrasound and/or TE examinations.²⁰ In a cross-sectional nationwide study observing the period between 2004 - 2007, Fischer et al. found 8.7% of patients diagnosed with cirrhosis but included treated patients in the analysis²¹ In other European cross sectional studies, rates of cirrhosis detected by liver biopsies varied between 12-24%.^{22,23} Nevertheless, our study is unique in that all subjects were treatment naïve and presented for first evaluation of disease activity and liver fibrosis. Our combined findings demonstrate a high burden of preventable morbidity in this population and underscores the need for specialized diagnostics and care.

Our data confirms the high correlation between history of migration from endemic regions and infection with chronic HBV infection. In our study population, 24% of subjects were European, whereas 30% were from the Asia Pacific region, the world's highest prevalence region. Despite the diversity of our study sample, region of origin did not affect treatment indication or liver stiffness results. Consistent with prior reports¹³, we found that elevations in ALT and male gender were independent risk factors for the presence of fibrosis. Surprisingly, we found no significant correlation between the patient's age at first presentation and transient elastography results. The higher proportion of male patients with HBV-infections also matches the higher HBV-prevalence in men that is reported in Germany.^{13,20,21,24,25}

EASL guidelines establish criteria for treatment initiation which include non-invasive markers such as HBV-DNA and ALT levels and transient elastography. While liver biopsy remains the gold standard for the assessment of liver fibrosis and necro-inflammatory activity, it has largely been replaced by these non-invasive markers, particularly in the ambulatory setting.²⁶⁻²⁸ In our study, immediate treatment was indicated in 26% of subjects. These subjects were mainly in the HBeAg positive- (8%) or HBeAg negative-chronic Hepatitis B (15%) phases of the disease, historically known as immune active or reactivated phase of infection, respectively. The majority of subjects, 69%, did not meet criteria for immediate treatment. Most patients who did not require treatment were classified as HBeAg negative chronic infection (inactive-carriers) (48%).

To provide a better understanding of the importance of each treatment indicator in influencing treatment eligibility, we evaluated each factors influence on clinical decision making. Eighty-six percent of those subjects meeting criteria for treatment initiation did so

on the basis of two factors: HBV DNA >2000 IU/ml and ALT >ULN. Elastography added 6 (8%) individuals to the group in need of treatment based on liver stiffness measurements of >9kPa. Looking at each factor separately, we found a sensitivity of 93.7% for DNA-PCR >2.000 IU/ml for meeting the treatment indication criteria and for ALT-levels >ULN (>40 U/L) a sensitivity of 87.3%. This result is expected, given the importance assigned to viral replication in pathogenesis of disease and its upstream inclusion in the EASL evaluation algorithm.²⁹

Transient elastography identified a substantial proportion of subjects with intermediate results (17%) who did meet criteria for initiation of antiviral treatment. Out of this group we identified 13 patients who had an HBV-DNA-PCR >2.000 IU/ml but normal ALT levels in whom liver biopsy would be recommended. On the other hand, 48 patients (15.9%) had high HBV-DNA-PCR levels >2.000 IU/mL with normal ALT levels and transient elastography results. In these cases, neither immediate initiation of pharmacological treatment nor invasive diagnosis by means of a liver biopsy were recommended. Thus, potential harmful interventions for the patients could have been avoided.

Our data confirms the high correlation between history of migration and HBV infection. Since the global burden of hepatitis B is unevenly distributed and the North-Western countries of Europe have low prevalence of hepatitis B^{5-7,30}, only 38.4% of our patients had a European or unknown background. Region of origin did not affect treatment indication or liver stiffness results in our cohort.

Our study has a number of methodological limitations. We used retrospective data obtained during routine clinical care at a single referral center. We based our analysis on a

one-time, initial serological and radiographic assessments; we did not obtain follow-up information regarding rates of treatment initiation and response. Finally, our study was performed in a resource-rich health care setting where access to viral PCR assays is universal and elastography is available at specialized centers. Our study also has some notable strengths. We report results from the largest sample of treatment-naïve chronically HBV-infected patients in Europe over the past decade. We performed liver elastometry in all study subjects and were able to match this information with serological assessment. Finally, our data is consistent with a number of previously epidemiological results reported in Germany, confirming the validity of our assessment.^{13,23}

In conclusion, we found significant rates of advanced and untreated chronic hepatitis B infection in the largest European cohort of treatment-naïve patients. Treatment decisions in our multi-ethnic setting were predominately based on serology including viral DNA PCR results and transaminase levels. Transient elastography was most notable for its role in confirming advanced fibrosis/cirrhosis and precluding unnecessary treatment or invasive studies in those with normal results.¹⁶ It is important to place our conclusions in the context of a European health care system where viral PCR is accessible and affordable on a large scale and elastography can be performed in specialized centers. In settings of low or middle income countries, alternative strategies for evaluation have been developed, including algorithms like the Treat-B-score.²⁸ Further study of our population should address disease progression over time, particularly in untreated patients. Finally, prevention strategies and early referral are essential to reduce the rates of advanced disease at presentation.

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Figures and Tables

Table 1: Baseline characteristics (n=301)

Figure 1: Treatment eligibility due to EASL 2017¹⁴ and EASL-ALEH¹⁷ Clinical Practice Guidelines

Figure 2: Study Flowchart

Figure 3: Region of origin (n=301)

Blue: unknown origin
Green: Pacific Asian
Purple: Europe
Yellow: Middle East
Brown: Africa

Figure 4: Phase of HBV-infection and treatment indication for HBV-mono-infected patients (n=301).

Blue: no indication to start treatment, surveillance.
Green: indication to start treatment due to EASL 2017¹⁴ and EASL-ALEH¹⁷ Clinical Practice Guidelines
Brown: inconclusive findings, biopsies are recommended to verify stage of fibrosis/necroinflammation.

Figure 5: Transient elastography results (n=271)

Blue: ALT<ULN (40U/L)
Green: ALT>ULN (40U/L)