



RESEARCH ARTICLE

The influence of ethnicity on disease outcome in patients with chronic hepatitis B infection

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Since the cultural diversity in Western Europe is growing, this study assessed whether foreign-born chronic hepatitis B (CHB) patients have more cirrhosis than Dutch- or Belgian-born patients, with a main focus on the Turkish population. Baseline characteristics (eg, socioeconomic status [SES]), biological characteristics, and disease outcome (eg, cirrhosis) were collected for all patients. Between December 2009 and January 2015, 269 CHB patients participated from the outpatient departments of three hospitals in the Netherlands, Belgium, and Turkey. Out of the 269 CHB patients, 210 were foreign-born and 59 were Dutch- or Belgian-born. Compared with Dutch- or Belgian-born patients, foreign-born patients had a higher prevalence of low SES (58% vs 31%; $P = 0.001$) and cirrhosis (27% vs 10%; $P = 0.007$). Among the Turkish population, there were no significant differences regarding the prevalence of low SES (73% vs 61%; $P = 0.170$), alcohol abuse (1% vs 5%; $P = 0.120$), anti-hepatitis C virus positivity (4% vs 0%; $P = 0.344$), anti-hepatitis D virus positivity (1% vs 6%; $P = 0.297$), and cirrhosis (37% vs 27%; $P = 0.262$) between patients ($n = 102$) living in Turkey (local) and Turkish CHB ($n = 38$) patients living in the Netherlands or Belgium (immigrant). In multivariate analysis, low SES (odds ratio, 5.7; 95% confidence interval, 2.3-14.5; $P < 0.001$) was associated with cirrhosis. In this study, foreign-born CHB patients were associated with more advanced HBV-related liver disease with 27% having cirrhosis. However, ethnicity was not associated with cirrhosis when SES was included in the multivariate analysis. The similar prevalence of cirrhosis in local Turkish compared to immigrant Turkish CHB patients is novel and warrants further investigation.

KEYWORDS

cirrhosis, disease outcome, ethnicity, hepatitis B, socioeconomic status, Turkish

1 | INTRODUCTION

Hepatitis B virus (HBV) infection is one of the major infectious diseases with an estimated two billion people infected with HBV worldwide and more than 240 million chronically infected in the year 2016.^{1,2} An estimated 15% to 40% of those with prolonged HBV infection will develop cirrhosis, liver failure, hepatocellular carcinoma (HCC), or early death.^{2,3} According to the Global Burden of Disease study in 2013, HBV is responsible for up to 700 000 deaths annually, making it together with hepatitis C virus (HCV) infection the seventh leading cause of mortality globally.⁴

Progression of chronic hepatitis B (CHB) to cirrhosis and HCC is determined by host-related factors like sex, as well as by viral and other factors (eg, alcohol use).^{3,5,6} However, a factor that has had less attention in scientific research is the influence of ethnicity on disease outcome. Furthermore, for HCV, ethnicity is an essential predictor of disease outcome. For instance, more advanced hepatic fibrosis in Hispanics compared to non-Hispanic whites was related to older age and higher occurrence of hepatic steatosis.⁷ In addition, studies determining the natural history of HCV have observed less cirrhosis in African Americans when compared with other groups.⁸ However, in contrast to HCV, there is little known about the influence of ethnicity on the outcome of HBV infection.

The impact of migration in the European Union (EU) is striking as a high proportion of newly diagnosed CHB infections are considered to have been acquired outside the EU. Migration to the EU occurs mainly from countries with high prevalence of viral hepatitis B.⁹ Therefore this study was designed to assess whether foreign-born CHB patients have more advanced fibrotic liver disease than Dutch- or Belgian-born patients, with a main focus on the Turkish population that is disproportionately affected by HBV and is a key risk group for CHB in different EU countries.^{10,11}

2 | PATIENTS AND METHODS

CHB patients, defined as patients with more than 6 months hepatitis B surface antigen positivity, who were still under follow-up between December 2009 and January 2015 at the hepatology outpatient department of three large educational hospitals, one in the Netherlands, one in Belgium, and one in the Northern Region of Turkey, were invited to participate in this study. Upon informed consent, missing data regarding socioeconomic status (SES), country of birth, mother's country of birth, risk factors for HBV infection (intravenous drug use [IDU], blood transfusion before 1974,^{12,13} dialysis, healthcare worker, sex worker, men who sex with men [MSM], infected family member), alcohol abuse, and smoking were collected by a questionnaire. Alcohol abuse was defined as having more than two units per day for women and more than three units per day for men.^{14,15} Smoking was recorded as yes or no. In the current study, SES was based on income and education¹⁶ as follows: Low/Middle/High (L/M/H):

L: net income beneath poverty line based on EU-SILC 2012¹⁰ / TÜRK-İŞ May 2014¹⁷ without a degree of higher education.

M: net income beneath poverty line with a degree of higher education or a net income above poverty line without a degree of higher education.

H: net income above poverty line with a degree of higher education.

Relevant biological characteristics of HBV were also extracted from computerized laboratory records. The stage of fibrosis was classified according to METAVIR classification and assessed by liver biopsy and/or transient elastography.^{18,19} The development of cirrhosis was defined as a clinical syndrome consisting of either (1) histological confirmation of cirrhosis or (2) ultrasonographic findings of cirrhosis (included liver surface, edge, echotexture, echogenicity, diameter of main portal vein and splenic vein, outline of hepatic veins, and liver and spleen size) and/or clinical signs of advanced liver disease such as esophageal or gastric varices, ascites, spontaneous bacterial peritonitis (SBP), and encephalopathy. Hepatic decompensation was defined as the appearance of at least one episode of clinical jaundice, variceal bleeding, ascites, SBP, or hepatic encephalopathy. Medical record verification of all HCC diagnoses was based on the following criteria: a histopathological examination or a positive lesion detected by at least two different imaging techniques (eg, computerized tomography, magnetic resonance imaging, transarterial chemoembolization, and dynamic contrast-enhanced ultrasonography with carbon dioxide).

The main focus of this study was to assess the disease outcome of CHB in the foreign-born patients compared to the Dutch- or Belgian-born patients. In a subanalysis, a comparison was made between Turkish immigrants, that is, patients living in the Netherlands or Belgium, and Turkish locals, that is, patients living in Turkey.

The ethnic groups have been compared regarding baseline characteristics (eg, mean age, sex, and SES), biological characteristics (eg, baseline hepatitis B e antigen [HBeAg] status, baseline alanine aminotransferase level), and disease outcome (eg, hepatic fibrosis, and cirrhosis). Baseline was defined as time of CHB diagnosis.

The Medical Research Ethics Committee Maastricht (13-4-067), Ethical Committee of Ziekenhuis Oost-Limburg (14/095U), and Clinical Research Ethical Committee of Ondokuz Mayıs University (B.30.2.ODM.0.20.08/1316) approved the study and the patients gave written informed consent.

2.1 | Statistical analysis

Anonymous data collection and analyses were performed using SPSS (Release 21; IBM, Armonk, NY). Categorical data were analysed with the χ^2 test or Fisher's exact test. In case, the observed value was zero a Laplace correction was applied, that is, adding one in all cells yielding a more honest test procedure.²⁰ Differences in two continuous variables were assessed by the independent *t* test. The Kolmogorov-Smirnov test and Levene's test were used to test whether a distribution was normal and for homogeneity of variance, respectively. When violating the assumptions for parametric tests, the Mann-Whitney test was used instead for comparing two continuous variables. Stepwise multiple logistic regression analysis was performed to determine independent predictors of cirrhosis. Results are presented as either with frequencies (%) or mean

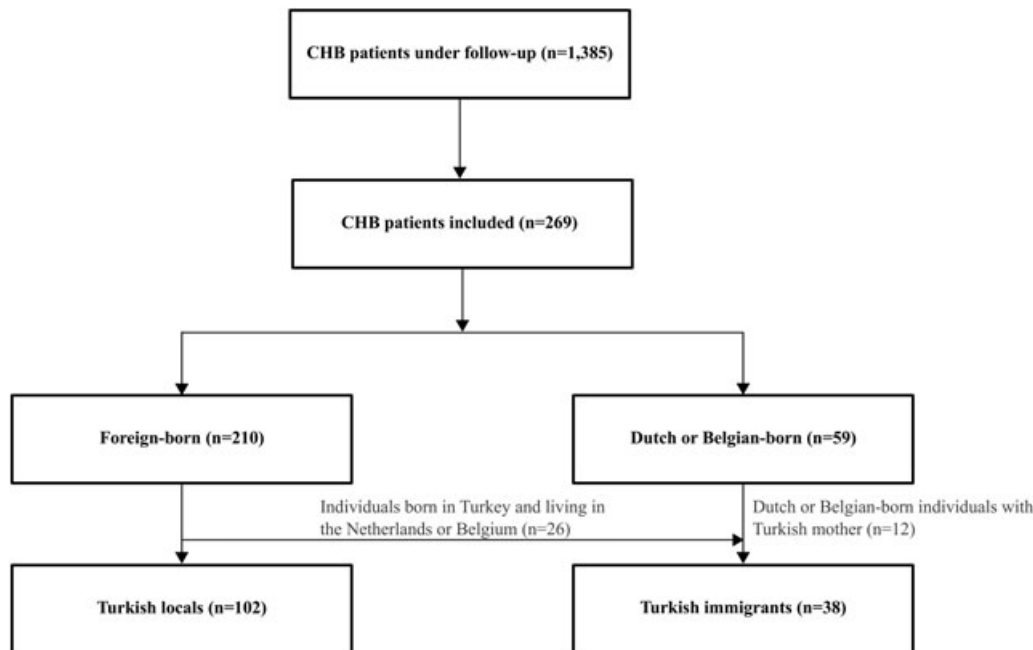


FIGURE 1 Flowchart of the study. Among 1358 CHB patients, 269 were included in our study. For the purpose of this study, we made a comparison between foreign-born and Dutch- or Belgian-born patients. In subanalysis, a further distinction was made between Turkish immigrants ($n = 38$), that is, patients living in the Netherlands or Belgium, and Turkish locals ($n = 102$), that is, patients living in Turkey. Turkish immigrants consisted of individuals born in Turkey and living in the Netherlands or Belgium ($n = 26$) and of Dutch- or Belgian-born individuals with a Turkish mother ($n = 12$). CHB, chronic hepatitis B

(standard error of mean). The level of statistical significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Baseline characteristics of the study population

Out of 1358 CHB patients, 269 participated in the study and provided additional information. Of the 269 CHB patients, 210 (78%) were foreign-born and 59 (22%) were Dutch- or Belgian-born. The foreign-born patients came from 35 different countries including 128 from Turkey (61%), 18 from China (9%), 5 from Morocco (2%), 5 from Italy (2%), 5 from Afghanistan (2%), and 5 from Indonesia (2%). With a focus on the Turkish population, a distinction was made between patients living in Turkey (local, $n = 102$) and Turkish CHB patients living in the Netherlands or Belgium (immigrant, $n = 38$). Figure 1 illustrates the flowchart of the study.

The baseline characteristics of the foreign-born group and Dutch- or Belgian-born group are presented in Table 1. The percentage of CHB patients with a low SES (58% vs 31%; $P < 0.001$) and an infected family member (47% vs 29%; $P = 0.011$) was higher in foreign-born patients compared with the Dutch- or Belgian-born group. However, in comparison to CHB patients born in the Netherlands or Belgium, there was a lower percentage of foreign-born patients with IDU (3% vs 10%; $P = 0.027$), MSM (1% vs 15%; $P < 0.001$), and alcohol abuse (3% vs 12%; $P = 0.017$).

Among the Turkish population, the percentage of CHB patients with a low SES (73% vs 61%; $P = 0.170$) and alcohol abuse (1% vs 5%; $P = 0.120$) was not different between local Turkish CHB patients and immigrant Turkish CHB patients. With regard to risk factors, there was no difference in the number of infected family members (46% vs 53%; $P = 0.490$).

3.2 | Biological characteristics of the study population

When the patients were categorized according to the country of birth, a lower anti-human immunodeficiency virus positivity (3% vs 13%; $P = 0.014$) was seen in foreign-born group compared to Dutch- or Belgian-born group (Table 2). Among the Turkish population, there were no significant differences regarding anti-HCV positivity (4% vs 0%; $P = 0.344$), anti-HIV positivity (0% vs 0%), anti-HDV positivity (1% vs 6%; $P = 0.297$), and HBeAg positivity (13% vs 26%; $P = 0.052$) between local Turkish CHB patients and immigrant CHB patients.

3.3 | HBV disease outcome

The HBV disease outcome in the ethnic groups is shown in Table 3. The foreign-born group had a significantly higher mean METAVIR fibrosis stage (1.9 ± 0.1) than the Dutch- or Belgian-born group (1.2 ± 0.2), $P = 0.003$. The prevalence of cirrhosis was 27% (foreign-born) and 10% (Dutch- or Belgian-born), $P = 0.007$. There was a trend of a higher prevalence of hepatic decompensation ($P = 0.175$) and HCC ($P = 0.027$) in the foreign-born group.

TABLE 1 Baseline characteristics of 269 CHB patients according to foreign-born and Dutch- or Belgian-born

Characteristics	Foreign-born, n = 210	Dutch- or Belgian-born, n = 59	P
Age, y	47 ± 0.9	46 ± 2.0	0.707
Males	117 (56)	43 (73)	0.018
SES			
Low	118 (58)	15 (31)	0.001
Middle	61 (30)	22 (46)	0.039
High	22 (11)	10 (17)	<0.001
Risk factors			
IDU	6 (3)	6 (10)	0.027
MSM	1 (1)	9 (15)	<0.001
Infected family member	99 (47)	17 (29)	0.011
Other	101 (48)	1 (2)	<0.001
None	3 (1)	26 (44)	<0.001
Alcohol abuse	7 (3)	7 (12)	0.017
Smoking	46 (22)	15 (25)	0.568

Abbreviations: CHB, chronic hepatitis B; IDU, intravenous drug use; MSM, men who have sex with men; SEM, standard error of mean; SES, socioeconomic status.

Values shown as mean ± SEM or as n (%).

Among the Turkish population, a comparison was made between local Turkish CHB patients and immigrant Turkish CHB patients. In comparison to immigrant Turkish CHB patients, there was a comparable mean METAVIR fibrosis stage (2.3 ± 0.2 vs 2.0 ± 0.2 ; $P = 0.334$), prevalence of cirrhosis (37% vs 27%; $P = 0.262$), hepatic decompensation (16% vs 11%; $P = 0.469$), and HCC (12% vs 3%; $P = 0.115$).

A forward stepwise multiple logistic regression analysis of cirrhosis was then performed including all variables that had a $P < 0.20$ on univariate analysis (Table 4). The following variables

were identified to be independent predictors of cirrhosis: low SES (odds ratio [OR], 5.7; 95% confidence interval [CI], 2.3-14.5; $P < 0.001$) and baseline bilirubin levels (OR, 1.1; 95% CI, 1.0-1.1; $P = 0.001$).

4 | DISCUSSION

The impact of migration to Western Europe is striking as migrants have become the majority of CHB patients in low endemic countries, such as the Netherlands and Belgium.²¹ The Turkish migrant population, one of the largest migrant groups in Western Europe, is also disproportionately affected by HBV and is a key risk group for CHB infections in different Western European countries.

As ethnicity is an essential predictor of disease outcome in some diseases, this study assessed whether foreign-born CHB patients have more advanced fibrotic liver disease than Dutch- or Belgian-born patients. The CHB populations in three hospitals, one in the Netherlands, one in Belgium, and one in Turkey, were chosen because it afforded us a chance to study the differences between local Turkish CHB patients and immigrant Turkish CHB patients in a subanalysis.

The most significant finding was that SES appeared to be more important than ethnicity in influencing disease outcome in CHB patients. Compared with Dutch- or Belgian-born patients, the foreign-born CHB patients were associated with more advanced HBV-related liver disease with 27% having cirrhosis. There was also a trend of higher prevalence of hepatic decompensation and HCC in the foreign-born group. However, ethnicity was not associated with cirrhosis when SES was included in the multivariate analysis.

Although we are not aware of any other study that has examined the effect of ethnicity on disease outcome in CHB patients, there is evidence of greater HCV disease progression among Hispanics compared with non-Hispanic whites.⁷ In addition, several studies have observed less HCV-associated cirrhosis in African Americans than other ethnic groups.^{8,22}

TABLE 2 Laboratory characteristics of 269 CHB patients according to foreign-born and Dutch- or Belgian-born

Characteristics	Foreign-born, n = 210	Dutch- or Belgian-born, n = 59	P
Anti-HCV positivity	10 (5)	5 (10)	0.325
Anti-HIV positivity	6 (3)	7 (13)	0.014
Anti-HDV positivity	5 (3)	1 (2)	1.000
Baseline HBeAg positive status	32 (16)	18 (32)	0.008
Baseline HBV DNA level, log copies/mL ^a	3 ± 4.7	7 ± 6.0	0.091
Baseline ALAT level, U/L ^a	39 ± 48.0	125 ± 81.0	0.005
Baseline albumin level, g/L ^a	43 ± 7.7	42 ± 7.7	0.520
Baseline bilirubin level, μmol/L ^a	11 ± 9.7	16 ± 11.3	0.367
Baseline platelets level, 10 ⁹ /L	201 ± 5.6	212 ± 9.7	0.370

Abbreviations: ALAT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HDV, hepatitis delta virus; SEM, standard error of mean.

Values shown as mean ± SEM or as n (%).

^aMedian ± interquartile range is shown instead of mean ± SEM as Mann-Whitney test was used for these variables.

TABLE 3 Disease outcome of 269 CHB patients according to foreign-born and Dutch- or Belgian-born

Characteristics	Foreign-born, n = 210	Dutch- or Belgian-born, n = 59	P
Fibrosis stage (METAVIR)	1.9 ± 0.1	1.2 ± 0.2	0.003
Cirrhosis	57 (27)	6 (10)	0.007
Hepatic decompensation	23 (11)	3 (5)	0.175
HCC	16 (8)	0 (0)	0.027

Abbreviations: HCC, hepatocellular carcinoma; SEM, standard error of mean.

Values shown as mean ± SEM or as n (%).

However, the investigators assessing the influence of ethnicity on HCV-related liver disease did not attempt to adjust ethnic groups for socioeconomic status to mitigate the confounding effects on minority groups of lower SES.²³ Disparities in disease outcome can be attributed to host genetics and environmental factors.²⁴⁻²⁶ Additionally, patient-related factors including SES become important during long and difficult course of disease management. Lower socioeconomic status in the foreign-born group may explain the worse disease outcome in this group as early diagnosis requires an awareness about HBV infection and associated risk factors, while some knowledge about the natural history of HBV may contribute to follow-up adherence. Delays in disease detection may result in worsened health outcomes in infected people.²⁷

In line with our findings, the study by Haworth et al²⁸ reported excess mortality from cirrhosis and HCC among first generation migrants in England and Wales. Moreover, different studies showed a higher incidence of HCC in the Asian immigrant population.²⁴⁻²⁶ Hypothesized explanation for the difference in liver disease outcome in the migrant population included earlier viral infection. In our study, we found a higher prevalence of infected family member as risk factor in the foreign-born group. On the contrary, MSM and IDU as risk factors were more prevalent in the Dutch- or Belgian-born group. These findings may indicate an earlier viral hepatitis B infection by perinatal or childhood horizontal transmission in foreign-born patients compared to HBV transmission through IDU or high-risk sexual behavior in adult age in the Dutch or Belgian patients. The predominant routes of transmission vary according the endemic frequency of HBV infection. In areas with low HBV endemicity, such as the Netherlands and Belgium, IDU and unprotected sexual intercourse in adults are the main routes of transmission, whereas in areas with high HBV endemicity, perinatal transmission is the predominant route.²⁹⁻³¹ Childhood horizontal transmission is accepted as the most common route in intermediate HBV endemic areas, such as Turkey.³² It has furthermore been accepted that horizontal transmission in early childhood may correlate with poor socioeconomic and hygienic conditions.^{33,34}

In a subanalysis among the Turkish population, there was no difference in mean fibrosis stage, cirrhosis, hepatic decompensation, and HCC between local Turkish CHB patients and immigrant Turkish CHB patients. Factors affecting prognosis of CHB infection and

TABLE 4 Stepwise forward analysis for cirrhosis as outcome variable

Factors significantly associated with cirrhosis on univariate analysis	P			
Foreign-born group	0.007			
Low SES	<0.001			
Middle SES	0.001			
High SES	0.009			
Anti-HCV positivity	0.058			
Baseline HBV DNA level	0.027			
Baseline ALAT level	0.040			
Baseline albumin level	0.023			
Baseline bilirubin level	<0.001			
Stepwise forward analysis	B	SE	P	95% CI
Step 1				
Constant	-1.809	0.319	0.000	
Baseline bilirubin level	0.046	0.015	0.002	1.0-1.1
Step 2 [†]				
Constant	-3.027	0.524	0.000	
Baseline bilirubin level	0.053	0.017	0.001	1.0-1.1
Low SES	1.743	0.475	0.000	2.3-14.5

Abbreviations: ALAT, alanine aminotransferase; B, coefficient for the constant in the model; HCV, hepatitis C virus; SES, socioeconomic status; SE, standard error around the coefficient for the constant.

[†]Variables excluded in the forward stepwise analysis are: foreign-born group, middle SES, high SES, anti-HCV positivity, baseline HBV DNA level, baseline ALAT level and baseline albumin level.

cirrhosis, including alcohol abuse and coinfection (HCV, HIV, and HDV), were equally important among local Turkish CHB patients and among immigrant Turkish CHB patients and thus may explain the same prevalence of cirrhosis in both groups. According to the reported high number of infected family member of 46% and 53% in the local Turkish and in the immigrant Turkish CHB patients in our study, childhood horizontal transmission could be evenly important in both groups.

There are some limitations to the present study. First, this study has some selection bias toward the CHB population; those cured and deceased have not been included in this study, and there is also a possibility that there are CHB patients that have not yet visited the hepatology outpatient department. Second, the data must be interpreted carefully due to the small sample size of the study. Third, even though the patients' income and highest education was recorded upon informed consent, the study by Karlson et al²³ explained the variability in conclusions of previous studies on the role of SES due to the fact that the income is an unstable measure of SES. However, in that study, 83% of the patients reported no change in income over the 42-month interval. Thus, we believe that changes in income status probably were not an important factor in our study. Fourth, participants may not have been 100% truthful with their answers to the questionnaires due to social desirability bias. Fifth, we cannot exclude the possibility that factors not included in this study might have a role in the examined

worse disease outcome in foreign-born groups (eg, flares of hepatitis, HBV genotype, HBV variant, steatosis, diabetes, and obesity). HBV genotype varies according to ethnic backgrounds and there is growing evidence that the response to antiviral treatment and progression to cirrhosis and HCC differ according to HBV genotypes.³⁵ However, since the determination of HBV genotype is not part of the standard procedure, information on genotype was not available to analyze their effect on disease outcome. Moreover, Fattovich et al³ showed that age, male sex, high levels of HBV replication, coinfection, and heavy alcohol consumption were the most important factors associated with increased risk of progression to cirrhosis. Each of these important factors were further incorporated in the current analysis.

In conclusion, these data suggest that SES and not ethnicity is likely to be associated with advanced fibrotic liver disease in patients with CHB. The finding of a similar prevalence of cirrhosis among local Turkish CHB patients and immigrant Turkish CHB patients is novel and warrants further investigation. Since the cultural diversity in Western Europe is growing, it is important to further assess the impact of ethnicity on a pandemic disease such as hepatitis B, whether this difference is biological, cultural or environmental, so that patient care can be improved. It would be recommended to conduct a large prospective cohort study in which the genotypes of all CHB patients are assessed and their biological parameters (including HDV) in combination with additional measurements like FibroScan and sonography are registered over a longer period of time. Next to quantitative research, we also highly advocate for qualitative research. Firstly to adequately assess ethnic background, SES, mode of transmission, and risk factors. Secondly to get an idea of the disease perception and perception of the received care and treatment of CHB patients to improve treatment and thus increase survival rates and quality of life.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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