The Diversity and Management of Chronic Hepatitis B Virus Infections in the United Kingdom: A Wake-up Call

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Background. Through migration, diversity of chronic hepatitis B virus (HBV) infection has changed, affecting disease burden and control. We describe clinical and viral characteristics of chronic HBV in the United Kingdom.

Methods. A total of 698 individuals with chronic HBV infection were recruited from referral liver centers. Demographic, clinical, and laboratory data were collected.

Results. Sixty-one percent of patients were male, 80% were not born in the United Kingdom, and the largest ethnicity was East/Southeast Asian (36%). Twenty-two percent were hepatitis B e antigen (HBeAg) seropositive; 20.4% (59/289) had cirrhosis and 10 (1.7%) had hepatocellular carcinoma. Genotype D was most common (31%) followed by A, C, B, and E (20%, 20%, 19%, and 9%, respectively). Genotype was significantly associated with country of birth, length of time in the United Kingdom, HBeAg status, and precore and basal core promoter mutations. One-third were on treatment, with men independently more likely to be treated. Only 18% of those on treatment were on recommended first-line therapies, and 30% were on lamivudine monotherapy. Among treated individuals, 27% had antiviral drug resistance. Testing rates for human immunodeficiency virus, hepatitis C virus, and delta coinfections were low.

Conclusions. We demonstrated diversity of chronic HBV infections in UK patients, suggesting that optimal management requires awareness of the variable patterns of chronic HBV in countries of origin. We also found less-than-optimal clinical management practices, possible gender-based treatment bias, and the need to improve testing for coinfections.

Keywords. hepatitis B virus; virology; genotypes; clinical outcomes; cross-sectional.

Persistent hepatitis B virus (HBV) is associated with chronic progressive liver disease including hepatocellular cancer (HCC). HBV exists as 10 major genotypes historically known to have specific geographic distribution and now thought likely to represent coevolution of virus within ethnically defined human populations [1]. Immigration and migration over the last 50 years have changed both host ethnic diversity
and virus genetic diversity in the United Kingdom. Immigration is currently estimated to increase the number of persistently HBV-infected persons by 6000 a year in the United Kingdom [2], with both host and viral characteristics reflecting the countries of origin.

HBV is not directly cytopathic and the host immune response is the likely principal cause of hepatocellular damage [3]. The relationship during persistence between host and virus is complex, dynamic, and influenced by genetic characteristics of both humans and viruses and by cofactors including other infections, hepatotoxic drugs including ethanol, and immunosuppression. Although variable, 4 phases are recognized [4]. The initial phase, characterized by hepatitis B e antigen (HBeAg), high levels of hepatitis B surface antigen (HBsAg), and HBV DNA in the plasma, is termed the “immune tolerant” phase, a misnomer in the face of a strong serological response to the viral internal component, during which serum aminotransferases are mildly elevated. This is terminated by a serological response to HBeAg (anti-HBe) and loss from the plasma. HBV DNA levels fall and a transient but significant lobular hepatitis often develops in what is referred to as the “clearance phase” [5]. This ushers in a period of effective host suppression termed the “inactive phase,” a further misnomer as virus replication persists, albeit at a lower level, with normalized serum aminotransferases. Selection of virus variants constitutively unable to translate HBeAg (e-null variants) arise through the loss of initiation codons or acquisition of premature stop codons in the precore region [6]. These e-null variants arise in many but not all persistently infected persons whose plasma contains anti-HBe. These viruses escape from host modulation in a series of flares, associated with varying degrees of acute hepatitis, leading to progressive fibrosis and establishment once more of high levels of viral replication [7]. This latter “reactive phase” is the end game of the persistent HBV infection for most anti-HBe seropositive patients with chronic hepatitis. It is characterized by high levels of e-null virus replication, facilitated by mutations in the basal core promoter (BCP). HBeAg inhibits T-cell responses to core peptides and acts as a specific tolerogen abrogating the cytotoxic T-cell response [8]. Increasing replication of e-null viruses in the absence of HBeAg-induced tolerance may be one mechanism of the enhanced pathogenicity of these variants.

There is increasing evidence that genotypes display different phenotypic expression of chronic disease [9]. This may be due to the molecular basis for evolution of viral e-null and BCP variants, which may be influenced by their genetic backbone [10]. Similarly it is possible that aspects of both innate and adaptive host responses may differ according to ethnicity. HBV DNA quantification used to measure viral replication and response to drug therapy also predicts disease progression [11]. Current drug therapies do not eradicate persistent HBV but aim to lower DNA levels, either by restoring immune control or by targeted antiviral therapy, reducing inflammation and progression to end-stage liver disease [12]. Treatment choices include interferon and a range of nucleoside/nucleotide analogues, with published guidelines recommending drug regimens that reduce the likelihood of acquiring future therapy-limiting drug resistance [13, 14].

Given the absence of UK-wide data, a nationwide cross-sectional study was conducted to characterize persistent HBV infection in patients attending referral liver centers and compare clinical practice to the guidelines for best practice available at the time.

**METHODS**

**Patients**

Patients aged ≥18 years with chronic HBV infection (presence of HBsAg in serum for at least 6 months) were enrolled to this cross-sectional study regardless of antiviral treatment history. Between 1 March 2007 and 1 March 2009, 698 patients were recruited from 13 hepatology centers across the United Kingdom.

The study design was endorsed by The Nuffield Trust and approved by both the North-West Multi-Centre Research Ethics Committee–Haydock Park and the Research and Development Departments of the participating centers. All patients provided written informed consent.

**Data Collection**

Study-specific questionnaires and case report forms recorded demographic and lifestyle data directly from patients at the time of recruitment (including alcohol consumption, based on average units per week). Clinical information was extracted from medical and laboratory records. If a serological result for hepatitis C virus (HCV), human immunodeficiency virus (HIV), or hepatitis delta virus (HDV) was not available, it was presumed unknown. Data were recorded at one time point only with no longitudinal follow-up. Study blood samples taken at the time of enrollment were sent to the Health Protection Agency (HPA), Colindale, for further virological analysis (See Supplementary Data for virological and statistical methods).

**RESULTS**

**Demography**

Almost two-thirds of patients were men (425 [60.9%]), who were older than women (mean age, 45 years vs 38 years, respectively, P < .0001). Participants were born in 61 countries with all major ethnic groups represented, the largest being East and Southeast Asian (253 [37%]), then white (174 [25%]), South Asian (140 [20%]), and black African (100
Table 1. Sociodemographic and Clinical Factors of Study Patients (N = 698), by Hepatitis B Virus Genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>HBV DNA Detected by Sequencing PCR</th>
<th>HBV Genotypes (in HBV DNA–Positive Patients, n = 523)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HBV DNA Negative (%)</td>
<td>HBV DNA Positive (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>A</td>
</tr>
<tr>
<td>No. of Patients (%)</td>
<td>698</td>
<td>175 (25)</td>
<td>525 (75)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>425</td>
<td>120 (28.2)</td>
<td>305 (71.8)</td>
</tr>
<tr>
<td>Female</td>
<td>273</td>
<td>55 (20.2)</td>
<td>218 (79.9)</td>
</tr>
<tr>
<td>Ageb, y, median [IQR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicityc (n = 692)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East &amp; Southeast Asian</td>
<td>253</td>
<td>51 (20.2)</td>
<td>202 (79.8)</td>
</tr>
<tr>
<td>White</td>
<td>174</td>
<td>51 (29.3)</td>
<td>123 (70.7)</td>
</tr>
<tr>
<td>South Asian</td>
<td>140</td>
<td>37 (26.4)</td>
<td>103 (73.6)</td>
</tr>
<tr>
<td>Black African</td>
<td>100</td>
<td>28 (28.0)</td>
<td>72 (72.0)</td>
</tr>
<tr>
<td>Middle Eastern &amp; Arab African</td>
<td>16</td>
<td>6 (37.5)</td>
<td>10 (62.5)</td>
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<tr>
<td>Other</td>
<td>9</td>
<td>2 (22.2)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>Born outside the UK (n = 682)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>544</td>
<td>133 (24.5)</td>
<td>411 (75.6)</td>
</tr>
<tr>
<td>No</td>
<td>138</td>
<td>37 (26.8)</td>
<td>101 (73.2)</td>
</tr>
<tr>
<td>Alcohol abstinent (n = 590)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>411</td>
<td>113 (27.5)</td>
<td>298 (72.5)</td>
</tr>
<tr>
<td>No</td>
<td>179</td>
<td>36 (20.1)</td>
<td>143 (79.9)</td>
</tr>
<tr>
<td>Anti-HDV positive (n = 544)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>9 (60.0)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>No</td>
<td>529</td>
<td>161 (30.4)</td>
<td>368 (69.6)</td>
</tr>
<tr>
<td>HBeAg+/anti-HBe– (n = 622)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>136</td>
<td>10 (7.4)</td>
<td>126 (92.7)</td>
</tr>
<tr>
<td>No</td>
<td>486</td>
<td>129 (26.5)</td>
<td>357 (73.5)</td>
</tr>
<tr>
<td>Had a liver biopsy (n = 672)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>289</td>
<td>88 (29.4)</td>
<td>204 (70.6)</td>
</tr>
<tr>
<td>No</td>
<td>383</td>
<td>81 (21.2)</td>
<td>302 (78.9)</td>
</tr>
</tbody>
</table>
Eighty percent (544) were non-UK born and 31% (179) regularly consumed alcohol.

**Clinical Characteristics**

Overall, 21.8% (136) of patients were HBeAg seropositive (24.4% of men vs 18% of women, \( P = .056 \)). Men were more likely than women to have undergone liver biopsy (226/425 [53.1%] vs 63/273 [23%], \( P < .0001 \)). Of those biopsied, 20.4% (59/289) had cirrhosis (23.9% of men vs 7.9% of women, \( P = .006 \)). Cirrhosis was more commonly seen with genotypes A and D (18% [8/44] and 18% [10/56] compared with genotypes B, C, and E [8% [3/37]; 14% [7/49], and 13% [2/15]; Table 1). Ten (1.7%) individuals had been diagnosed with HCC (9 were men, 6 of white ethnicity); where known, 4 had genotype A, 3 genotype C, and 1 genotype D.

**Antiviral Treatment**

One-third of patients (236 [34.4%]) were taking antiviral treatment (80% were men; Table 2) with 31% on lamivudine monotherapy (72/236). Only 18% of treated patients were on recommended first-line therapies of pegylated interferon (11/236 [5%]), entecavir monotherapy (15/236 [6%]), or tenofovir (16/236 [7%]). HBV DNA levels when last measured were >10^4 IU/mL in 277 of 451 untreated persons (of whom 176 were HBeAg seronegative), >10^5 IU/mL in 200 and >10^6 IU/mL in 63. Serum alanine aminotransferase (ALT) levels were elevated (greater than the upper limit of normal [ULN]) in 153 of 451 patients not on treatment and >2× ULN in 52. Overall, 72 of 451 (16%) patients not on treatment had HBV DNA levels >2000 IU/mL and serum ALT greater than the ULN, indicating a need for consideration of treatment based on histological assessment [14]. Of those with cirrhosis on biopsy, 80% (47/59) were currently on antiviral treatment. The reasons for not being on antiviral treatment were not available and it was not possible to determine whether it was physician or patient choice.

Factors independently associated with treatment included being male, or per year older; having had a liver biopsy; and being seropositive for anti-HDV or HBeAg (Table 2).

**Testing for Viral Coinfections**

Only 31% of patients (219/698) had documented anti-HIV results generated during management in their hepatology clinic, and 9 were HIV infected. Of those currently on antiviral medications, only 28% (66/235) had a documented HIV result. Nearly half (301/698) were known to have been tested in clinic for anti-HCV, and 7 were seropositive. One-third had been tested for HDV at the clinical sites (247/698 [35%]). Because of the wish to use the more stringent test cutoff described in the Methods, HDV testing was undertaken on all available study samples at the HPA; 15 of 544 (2.8%) serum samples contained anti-HDV. Only 5 of these seropositive
patients had been identified previously through testing at the clinical sites.

**HBV DNA Levels and Genotype**

Quantification of HBV DNA was undertaken in samples from 558 patients; 526 (94%) had detectable HBV DNA. The surface/polymerase regions of 383 samples and the x/precore/core regions of 352 samples were successfully amplified.

Eight HBV genotypes were identified (Table 1). Genotype D was the most common, comprising 31%; genotypes A, B, and C were found in similar proportions (approximately 20%); genotype E was less common (9%); and genotypes F, G, and I were very rare (<1%). HBV genotype was significantly associated with ethnicity and country of birth.
Association of HBV Genotype, Viral Load, and e Status
There was a strong association between e status (detectable plasma HBeAg, anti-HBe, or neither) and genotype ($P = .001$; Table 1). Patients with genotype A and C viruses were more likely to be HBeAg seropositive (30% and 41%, respectively), whereas only 23%, 17%, and 20% of patients harboring genotypes B, D, and E, respectively were HBeAg seropositive. In 247 treatment-naive patients who were known not to be HCV, HDV, or HIV coinfected, there was a significant difference ($P < .0001$) in the median viral load levels between HBeAg-seropositive ($7.9 \log_{10} \text{IU/mL}$) and anti-HBe seropositive groups ($3.3 \log_{10} \text{IU/mL}$). There was no significant association between viral load and genotype in either the HBeAg ($P = .30$) seropositive or the anti-HBe–positive group ($P = .10$).

Precore and Basal Core Promoter Variants
Mutations in the precore (PC) region associated with prevention of HBeAg expression were found in 221 of 352 (63%) samples. Several pathways were observed. Premature stop codons within the PC region were found in 177 (80%) samples, almost exclusively at codon 28 (W28*; 175/177). Loss of the methionine at codon 1 was seen in 28 (13%) samples, 9 (4%) samples had both the M1 and W28 mutations, and 7 (3%) samples had nucleotide insertions or deletions causing a frame shift within the PC region.

The A1762T/G1764A BCP variant, associated with enhanced viral replication, was found in 109 (31%) samples. Sixty (17%) harbored both PC and BCP variants. A minority (82 [23%]) were wild type at both the BCP and PC regions, most commonly in genotype A (31%). BCP-only variants were commonly seen in genotypes A (27%) and C (34%). Genotype E viruses were most likely to carry dual mutations at the BCP and PC regions (30%).

Predictors for Viral Load
In the 197 monoinfected, treatment-naive patients who were anti-HBe seropositive, those infected by viruses bearing only BCP variants had median viral loads 0.9 log$_{10}$ IU/mL higher than in those with wild-type virus ($P = .002$; Figure 1). There was no significant difference in viral load levels between patients with wild-type viruses and those bearing only PC variants.

Mutations Associated With Antiviral Resistance
Polymerase drug resistance mutations were identified in 30 of the 112 treatment-experienced patients (27%). Twenty-nine patients had or were currently on lamivudine monotherapy. The majority of the observed mutation profiles were associated with resistance to this drug and included rtL180M M204V/I, present in 17 (15%) patients; rtL80I/V M204I, present in 6 (5%) patients; rtM204I/V, present in 3 (3%) patients; and rtT184A M204V, present in 1 (1%) patient. The L180M M204V/I mutation profile also confers resistance to telbivudine and emtricitabine and forms part of the resistance pathway for entecavir. Three (3%) patients harbored the rtA181T/V mutation known to confer cross-resistance to lamivudine and adefovir. One of the 263 treatment-naive patients harbored an antiviral-resistant variant (V173L, L180L/M).

Hepatitis B Surface Antigen Variants
Mapping of amino acid changes from the wild-type consensus sequence was undertaken across the HBsAg region to identify potential mutation “hot spots” (Figure 2). Seventy-three (19%) individuals carried viruses harboring variations between codons 120 and 150, which encompass the major antigenic region. Mutations known to be associated with immune escape were identified at the following codons: 120-4 (1%); 126-15 (4%); 133-12 (3%); 134-11 (3%); 144-4 (1%); and 145-11 (3%).

DISCUSSION
This national cross-sectional study of persistent HBV infection presents a snapshot of current disease burden of patients attending secondary and tertiary care liver clinics in the United Kingdom. Data were collected using a standardized pro forma questionnaire and case report form to reduce measurement bias. There are limitations inherent to a cross-sectional study with difficulty establishing temporal relationships between infection and outcome as well as selection bias, as patients were...
recruited from secondary and tertiary care centers. Nevertheless, we believe that the patients in this study are likely to be representative of the clinic population from which they are drawn and that the study provides characterization of both patients and viruses, confirming once more that with an increasingly interconnected world, health trends in one country may have both local and global implications [15], especially with the historical links between the United Kingdom and Commonwealth countries. Four of five patients identified in this study were born outside the United Kingdom. Our data reflect this and highlight an ethnic and genotypic diversity in the infected population where ethnicity predicted the infecting genotype, reflecting dominant genotype, in the country of birth. Previous reports of HBV genotypes in the United Kingdom have been limited both by geographic scope and the number of subjects involved [16, 17]. By contrast, we identified infection with 8 of the 10 recognized HBV genotypes, including a substantial proportion (9% of all patients) of genotype E infection, which is rarely reported outside countries in Africa [18].

The majority of patients (78%) were in the reactive phase of hepatitis B persistence and seropositive for anti-HBe, and many were harboring e-null viruses, a significant proportion of which also carried mutations in the BCP. The importance of this lies both in the increased likelihood of developing HCC when one is infected by viruses carrying BCP mutations [4] and in the continued replication of viruses not producing HBeAg. This protein acts as a tolerogen modulating the cytotoxic T-cell response to the core antigen [8]. Virus replication in its absence is associated with the progression of liver fibrosis [19]. The value in knowing the genotype and other viral characteristics when considering and predicting outcome of antiviral treatment is now accepted [20, 21]. Genotype and mutation determination were provided from a central laboratory and formed an integral part in this study; such measures are not usually available for clinical management in the United Kingdom. Nevertheless, those planning, commissioning, and managing hepatology services must now take host and virus diversity into account despite the complexity of relationships between virus characteristics, genotypes, and host [9]. If, as has been postulated, HBV genotypes have arisen through an archaic interaction between the host “immunome” and the virus, held in place by self-normalization [22], it is interesting to speculate what may happen when HBV genotypes become transmitted outside their usual ethnic host. Setting that question aside, there are also public health ramifications to knowing or inferring genotypes. For example,
persons infected with genotype C are more likely to remain seropositive for HBeAg and will therefore be of higher infectivity, and persons infected with e-null viruses may pose a significant risk to their partners both through exhibiting high infectivity in the absence of plasma HBeAg and by passing on viruses of enhanced pathogenicity [23]. Both scenarios lend urgency to institution of public health interventions.

Overall, one-third of the study population was undergoing antiviral treatment with evidence of gender bias, as males were 2.5 times more likely than females to be on treatment independent of other factors. It remains unclear if clinicians were less likely to offer treatment to women or whether social or peer pressure may have influenced this decision, but gender inequalities in access to treatment have been demonstrated in other areas such as cardiovascular disease [24]. Therefore, although there are limitations to our data, with lack of accurate disease staging in those who did not undergo biopsy, the possibility of gender-based treatment bias in persistent HBV infection warrants further study. Perhaps more importantly some two-thirds of patients, the majority of whom carried plasma HBV DNA levels >10⁴ IU/mL when last measured, were not on therapy, with no clinical reason being given. The importance of treating patients with high viral loads to prevent disease progression including HCC is well documented [5, 25], and associated elevation of serum aminotransferases in this untreated group indicates the potential for disease progression. While this may be explained by a proportion of patients being new or recent referrals undergoing longitudinal monitoring to determine the need for treatment, the high prevalence of significant HBV viral load suggests potential for an emerging burden of disease among undertreated patients. The severity of disease in this cohort in the study was clearly evident, with 20% of those patients biopsied having evidence of cirrhosis and 10 patients having HCC.

Guidelines in place at the time of the study recommended that all patients presenting with persistent HBV infection should be screened for significant coinfections including HDV, HIV, and HCV. HDV coinfection is associated with a more rapidly progressive clinical course [26]. HIV-induced immunosuppression potentiates the escape of HBV from immune control, and the use of nucleos(t)ide analogues against HBV can result in development of treatment-limiting antiretroviral drug resistance. HCV potentiates progression to severe liver disease but is treatable, with the opportunity for cure. In this study, one-third of patients were tested for HDV infection; less than one-third had been tested for HIV, and less than half for HCV. That only 28% of patients on antiviral therapy had a documented HIV test indicates the need to adopt routine opt-out HIV testing in patients with persistent HBV infection, in line with current guidance [27].

Treatment choices were driven by clinician choice, and it was disconcerting to see that one-third of patients remained on lamivudine monotherapy, which is associated with rapid development of resistance, severe hepatic flares, and decompensation as well as limitation of future treatment options. Drug-related mutations detected in 30 patients on treatment underline this concern. Although lamivudine monotherapy was not recommended at the time of this study [14], we recognize that clinical practice often lags behind recommended “best” practices. Nevertheless, we believe it is an important public health measure to promote evidence-based practice in this arena and that the use of potent, high-genetic-barrier agents such as tenofovir or entecavir will improve outcome for many patients [14]. A further concern of drug-induced resistance is the potential impact of polymerase codon changes leading to nonsynonymous change in the overlapping surface antigen gene [28]. This gene independently showed considerable acquisition of codon changes from the consensus genotype, perhaps the result of interaction with the host immune system, in many patients including codon mutations classically considered likely to alter the HBsAg phenotype. Drug-driven changes in HBsAg may also lead to increased pathogenicity through altered export from the hepatocyte [29, 30]; they may also cause reduced antigenicity with the potential to induce a vaccine escape–like phenotype [31, 32].

So, what can be said about the nature of persistent HBV infection in the United Kingdom in patients attending hepatology services? It is notable in diversity of both the virus and the host, reflecting the major impact population movement has had upon the disease burden. It is common in segments of the British population that are often difficult to reach and for which a community-based approach may be required. It is now a very different scenario in the United Kingdom from the 1960s and 1970s when "Australia antigen" testing became available and the burden of infection was characterized by the genotype A2 phenotype. That paradigm is no longer appropriate. Patients today are most likely be in the anti-HBe phase, have viruses carrying core/precore mutations acquired in countries of origin, and need treatment that will be long term, if not lifelong. Persistent HBV infection has changed its face in the United Kingdom. We fail to recognize this at our peril and would encourage those caring for patients with chronic HBV in both this and other countries to recognize this and adapt practice and service provision to take account of the changing landscape brought about by globalization.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
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**Author contributions.** R. S. T., A. J. R., S. L., and G. R. analyzed the data, drafted the manuscript, and wrote the final version of the paper. N. N., R. W., J. B., A. M. J., and W. R. conceived the study and contributed to the study design and writing of the paper. A. M. J. assisted in drafting the paper and is the principal investigator for the study and the overall guarantor. L. F. was a study coordinator, oversaw study implementation and was involved in data analysis and drafting. M. T. took part in discussions of the analytical approach and paper writing and contributed to interpretation of the data. All authors were involved in data collection and reviewed and approved the final manuscript.

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