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SHORT COMMUNICATION

Age, ethnicity and proximity to clinic determine retention in care of chronic hepatitis B patients

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1 | INTRODUCTION

There is emerging evidence about rates and determinants of linkage to care for HBV-diagnosed patients.[1] However, to date, little attention has been paid to the important issue of CHB (chronic hepatitis B) patient retention in the outpatient setting.[2] In western centres, most CHB patients are first-generation migrants from countries of high HBV prevalence. Adherence with long-term follow-up may differ between ethnic groups. Also, infection is frequently diagnosed at a young age which is known to be associated with higher risk of loss to follow-up of many conditions.

The aim of our study was to examine, in a large multi-ethnic cohort attending a single specialist CHB clinic, the rate and determinants of patient loss to outpatient follow-up.

2 | PATIENTS AND METHODS

The adult HBV population attending the Birmingham Queen Elizabeth Hospital (QEH) reflects the ethnic diversity of the local population. The 2011 United Kingdom (UK) National Census found that 57.9% of the people of Birmingham were white, 26.6% were Asian (mainly South Asian, and 13.5% are Pakistani), 1.2% Chinese, 9.0% Black, and 2% were of another ethnic group. In this manuscript, the description "Asian" refers to the South Asian population. At the time of first hospital attendance, patients are asked to identify their ethnicity. For the sake of our analysis, patient ethnicity is categorized as *Asian* (includes Bangladeshi, Pakistani, and Indian), *Black* (includes African or Caribbean), *Chinese* and *White*. Patients without disclosure and patients of mixed ethnicity were not included in analyses that examined association of ethnicity with linkage to care and with retention in care. CHB patients are managed in specialist outpatient clinics according to agreed protocols. For patients with HBeAg-positive infection and hepatitis, review with blood tests is undertaken every 6 months. For patients with HBeAg-negative serology, review is 6 monthly for those with chronic hepatitis and annually for those with chronic infection. If a patient fails to attend, then another appointment (typically within 3 months of the first failed appointment) is sent to the patient. Failure to attend on a second occasion leads to patient discharge. Thus, the absence for a period of 18 months or longer should reliably identify a patient who has missed at least 2 consecutive outpatient appointments and is no longer in follow-up.

Patients were classified as "lost to follow-up" under the following circumstances:

- no visit in the 18 months prior to the cut-off date of 13/7/2022.
- no visit in the 18 months prior to death date.

Clinic attendance data were censored (on date of most recent visit) in the following circumstances:

- most recent visit within the 18 months prior to 13/7/2022.
- most recent visit within 18 months prior to registered date of death.
- HBsAg negative result at most recent visit (patient was assumed to be discharged instead of lost to follow-up).

Relevant data were extracted from multiple electronic sources and included basic demographic information, laboratory data, prescribing data, and clinical disease and event healthcare coding. Statistical analyses were performed with the Excel add-in, StatPages, and p values smaller than 0.001 are simply stated as $p < 0.001$. The study was approved by the Hospital's Research and Development Department (code CARMS-18094).

Eligible patients were those with a positive HBsAg blood test performed by the QEH laboratory during the period 1/1/2001 to 13/7/2022. All data were collected and up to date on 13th July 2022.

3 | RESULTS

In total, 3666 patients had a positive HBsAg result. Patients positive for IgM anti-core, HIV, HCV or HDV, and those undergoing liver transplantation during the study period were excluded. After exclusions, 3222 patients were included in the analysis (see supplementary Figure S1).

In total, 775 patients had either a single HBsAg measurement or more than one measurement but without a measurement of serum HBV DNA. We have assumed that these patients never achieved linkage to specialist care in the Liver Clinic (characteristics shown in Supplementary Table S1).

Our main analysis examines the 2447 patients who achieved linkage to care, and the "clinic survival" curve is shown in Figure 1A. Of the 2447 patients, 1598 were retained in care and 849 were lost to follow-up. 73.2%, 64.1%, 55.6% and 50.3% remained in follow-up at 5, 10, 15 and 20 years.

Univariate analysis shows that patients who are Asian and those who are older at baseline are more likely to be retained in outpatient follow-up (Table 1).

Kaplan–Meier analyses shown in Figure 1B,C demonstrate the association of age at baseline and ethnicity with risk of loss to follow-up (log rank $p < 0.001$ for both). The likelihood of loss is high in patients under the age of 35. The interaction of ethnicity and baseline age is explored in Figure 1D,E. The overwhelming difference between Asian and non-Asian ethnicities is observed for the younger ($p < 0.001$) but not for the older ($p = 0.45$) patients.

For the Cox multivariate analysis, 1407 patients had complete data (i.e., including self-disclosed ethnicity). The analysis confirms the strong and independent associations of patient ethnicity (superior for Asian patients) and older age at baseline with reduced risk for loss to follow-up. Non-Asian patients have a 68% higher risk for loss to follow-up, and risk decreases by about 1.5% for each year increase of age at baseline.

We wondered if internal migration (i.e., within the UK) with movement away from Birmingham might explain our observations. The patient NHS records include the patient's current registered address (i.e., on date of data capture 13/7/2022), and we calculated the distance of patient's residence from the QEH Liver Clinic. There was a strong association between current distance of residence from QEH with loss of clinic follow-up. Supplementary Table S2A summarizes the distance of a population from QEH for 8 groups of patients, segregated by ethnicity, age and outcome of follow-up. Statistical comparison (Supplementary Table S2B), shows that internal migration is much more likely in the young and in non-Asian patients, and emphasizes the association of distance from clinic with loss to follow-up in all patients, but particularly in young non-Asian patients.

Multiple logistic regression analysis was used to examine the relative impacts of baseline age, self-declared ethnicity (Asian vs non-Asian) and current distance from clinic with sustained retention in outpatient care. The best fit model included all 3 parameters ($p = 0.006$ for ethnicity, $p < 0.001$ for age and $p < 0.001$ for distance from clinic).

At most recent visit to clinic, those lost to follow-up had an average age of 38 (median 36, range 17–83), 10.3% were HBeAg-positive, 25.6% had serum HBV DNA greater than 2000 IU/ml, 31.2% had an elevated FibroScan value, and 16.5% were taking antiviral treatment (Supplementary Table S3).

4 | DISCUSSION

WHO elimination objectives for HBV include a massive increase in case ascertainment and an upscaling of antiviral therapy for those in care. Case ascertainment needs to be matched by patient retention in care to maintain long-term supervision of this chronic disease. Electronic datasets with longitudinal information are ideal for analysis of time-dependent outcomes, including antigen clearance and retention in care of CHB patients. Our cohort of CHB patients is typical of those seen in the UK's large cities, so the findings of our study can certainly be applied across the UK, possibly beyond.

Our analysis shows a disappointing rate of retention in care, with loss of one quarter at 5 years, one-third at 10 years and one-half at 20 years of follow-up. We show that patient age at baseline, Asian ethnicity and distance of residence from clinic are all strongly associated with retention in care versus loss to follow-up. Published figures for retention in care of CHB patients agree that rates of loss to follow-up of CHB patients are high.[3–6] The observation that younger patients have lower rates of retention in care is not surprising and has been shown to be a major determinant of outpatient attendance in the UK National Health Service.[7]

The effects of age and ethnicity on retention in care may be explained by rates and patterns of population internal migration in the UK.[8] The UK National Census showed remarkable differences between people in the under 30 versus over 30 age group, and between Asian versus other ethnicities. Census data clearly show that the 3 Asian ethnicities (Indian, Pakistani and Bangladeshi) have the lowest rates of internal migration.

We examined the demographic and clinical characteristics at time of loss to follow-up for 817 patients. The characteristics of this population and the "lookback" experience of Beekman and colleagues[5] support a strategy of patient identification and retrieval. Our analysis does not tell us if the patient is lost to all CHB follow-up or simply lost to QEH CHB follow-up. Further studies will be required to establish this important difference.

In summary, our findings suggest that young non-Asian patients require additional support and interventions to promote retention in care.

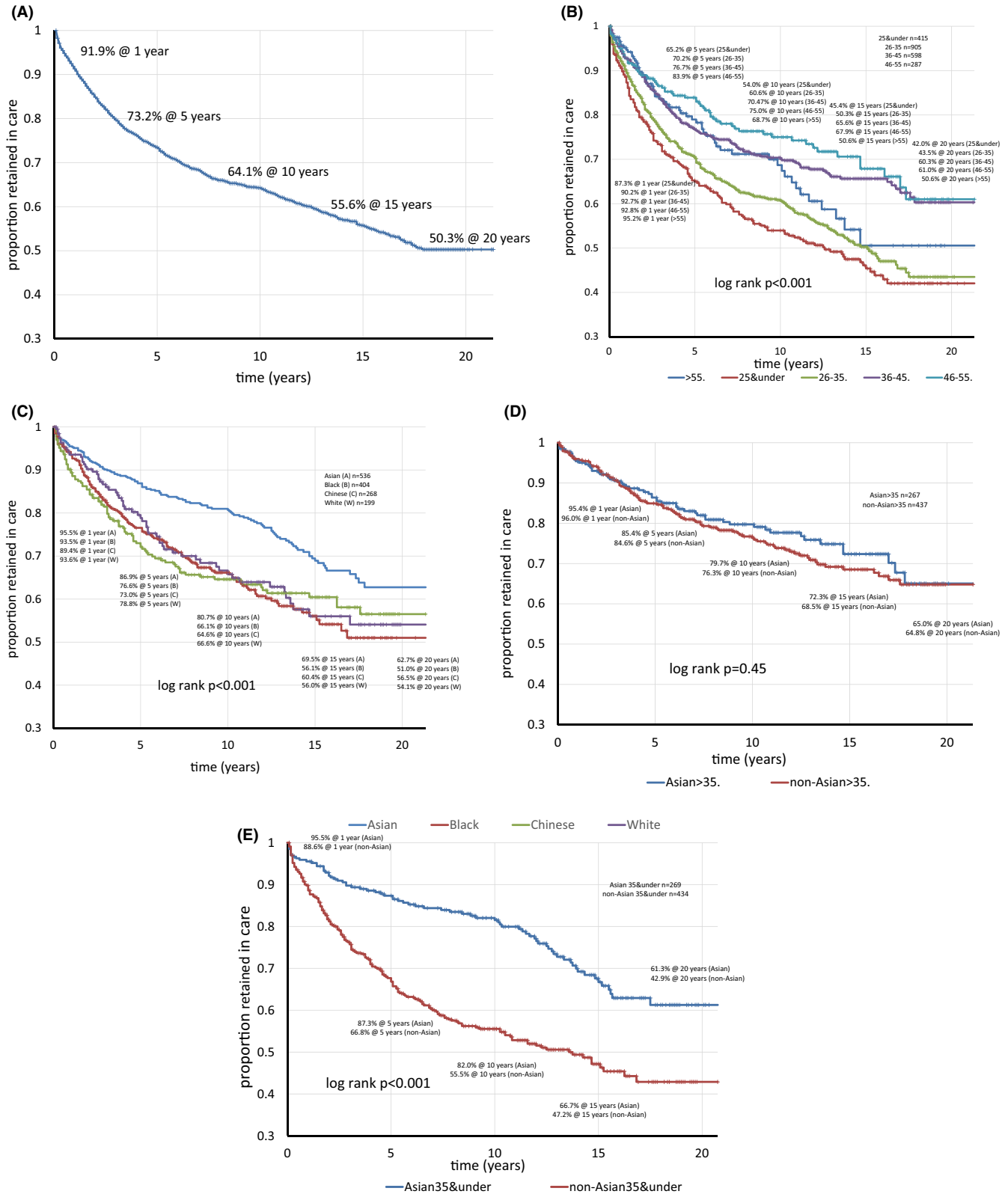

FIGURE 1 (A) Kaplan–Meier analysis of retention in care for the population of 2447 patients who were linked to specialist care. (B) Kaplan–Meier analysis of retention in care according to age at baseline. (C) Kaplan–Meier analysis of retention in care versus self-declared ethnicity. 1407/2447 patients declared single ethnicity. In total, 1040 patients did not declare or declared mixed ethnicity. There is a statistically significant difference between the retention in care of Asian patients versus those of other ethnicities. There is no significant difference between the outcome of White, Chinese and Black ethnicities. (D) Kaplan–Meier analysis comparing retention in care of Asian versus non-Asian patients, all older than 35. The difference is not statistically significant (log rank $p = 0.45$). (E) Kaplan–Meier analysis comparing retention in care of Asian versus non-Asian patients, all 35 years and younger. The difference is highly significant, more than 20% at 5 years and more than 25% at 10 years ($p < 0.001$)

TABLE 1 For the group that achieved linkage to care ($n = 2447$), this table compares the populations of patients that were maintained in follow-up versus those who were lost to follow-up

		Patients lost to follow-up	Patients retained in care	Univariate analysis	Cox multivariate analysis[c]	HR (95% CI)
Number of patients		849	1598		1407	
Follow-up mean, median, total (yrs)		4.06, 2.58, 3450	9.09, 8.58, 14 526			
Sex male: female (% male)		452:397 (53.2%)	862:736 (53.9%)	$p = 0.11$[a]	$p =$ ns	1.0317 (0.8500–1.2522)
Age at baseline (years) mean, median (range)		34.4, 32 (16–85)	38.5, 36 (16–87)	$p < 0.001$[b]	$p < 0.001$	0.9842 (0.9759–0.9926)
Ethnicity (% of self-declared patients in cohort)	Asian	131	405	$p = 0.001$[a]	$p < 0.001$	1.8822 (1.3674–2.0694)
	Black	141	263			
	Chinese	95	173			
	White	63	136			
	unknown or mixed	418	619			
HBeAg-pos: HBeAg-neg ($n = 2433$) (%HBeAg-pos)		137:710 (16.1%)	271:1315 (17.0%)	$p = 0.29$[a]		
HBV DNA (log IU/ml) ($n = 2447$) mean, median (range)		3.24, 2.80 (1–9)	3.40, 2.93 (1–9)	$p = 0.22$[b]		
ALT (IU/ml) ($n = 2410$) mean, median (range)		43.6, 26 (5–2015)	53.5, 27 (5–4034)	$p = 0.54$[b]		
FibroScan (kPa) ($n = 1525$) mean, median (range)		6.0, 5.3 (2.1–50.2)	6.0, 5.1 (2.1–75)	$p = 0.54$[b]		
Treatment with antivirals (%)		149 (17.6%)	603 (37.7%)	$p < 0.001$[a]		
Died (%)		32 (3.8%)	137 (8.6%)	$p < 0.001$[a]		
Distance of residence from Liver Clinic (km) (on 13/7/22) mean, median (range)		45.5, 9.48 (0–494)	17.2, 6.47 (0–441)	$p < 0.001$[b]		

[a]Chi-squared test.

[b]Mann–Whitney U test.

[c]Cox multivariate analysis includes 1407 patients with complete data.

AUTHOR CONTRIBUTIONS

D.M. designed the study, analysed the data and wrote the paper. He is guarantor of the manuscript. In relation to this manuscript, he has no conflicts of interest to declare. A.E. designed the study and reviewed the document for intellectual content. In relation to this manuscript, he has no conflicts of interest to declare. E.H. reviewed the document for intellectual content. In relation to this manuscript, she has no conflicts of interest to declare. S.A. designed the study, acquired the data from electronic sources and reviewed the document for intellectual content. In relation to this manuscript, she has no conflicts of interest to declare.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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