RESEARCH ARTICLE

Impact of the COVID-19 pandemic on routine surveillance for adults with chronic hepatitis B virus (HBV) infection in the UK

[version 1; peer review: 1 approved]

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Abstract

Background: To determine the impact of the COVID-19 pandemic on the population with chronic Hepatitis B virus (HBV) infection under

hospital follow-up in the UK, we quantified the coverage and frequency of measurements of biomarkers used for routine surveillance (alanine transferase [ALT] and HBV viral load).

Methods: We used anonymized electronic health record data from the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC) pipeline representing five UK National Health Service (NHS) Trusts.

Results: We report significant reductions in surveillance of both biomarkers during the pandemic compared to pre-COVID-19 years, both in terms of the proportion of patients who had ≥ 1 measurement annually, and the mean number of measurements per patient.

Conclusions: These results demonstrate the real-time utility of HIC data in monitoring health-care provision, and support interventions to provide catch-up services to minimise the impact of the pandemic. Further investigation is required to determine whether these disruptions will be associated with increased rates of adverse chronic HBV outcomes.

Keywords

hepatitis B virus, HBV, epidemiology, virology, viral hepatitis, COVID-19

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Any reports and responses or comments on the article can be found at the end of the article.

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Abbreviations

ALT	Alanine transferase
CHB	Chronic HBV
COVID-19	Coronavirus Disease 2019
GHSS	Global Health Sector Strategy
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIC	Health Informatics Collaborative
NHS	National Health Service
NIHR	National Institute for Health Research
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VL	Viral load
WHO	World Health Organization

Introduction

Mortality and morbidity associated with the Coronavirus Disease 2019 (COVID-19) pandemic can be directly attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but also result from indirect impacts on other conditions.

In order to progress towards elimination targets for Hepatitis B virus (HBV) infection¹ there is an urgent need for improvement of surveillance and treatment coverage. This will necessitate enhanced screening, followed by surveillance of individuals with chronic HBV (CHB) to determine treatment eligibility. Clinical follow-up includes routine monitoring of liver enzymes (e.g., alanine transferase (ALT)), hepatitis B virus (HBV) DNA viral load (VL), elastography, ultrasound, and occasionally liver biopsy^{2–4}. In those receiving antiviral treatment, laboratory parameters are monitored to ensure virologic suppression is achieved and maintained, and to identify complications.

Surveillance using VL and liver enzymes is recommended, typically at intervals of 3–12 months, and more frequently among males at older age, those with biochemically active hepatitis, risk factors for hepatocellular carcinoma (HCC), complications of liver disease, recent diagnosis, or changing treatment plans^{5,6}. COVID-19-attributable disruptions to HBV elimination efforts have been broadly described^{7,8}, but we set out to quantify the specific impact on routine HBV surveillance in secondary care services in England using individual-level patient data.

Methods

We undertook longitudinal and cross-sectional analyses using routinely-collected individual-level secondary care data collected across five NHS Trusts in England by the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC), as previously described^{9,10}. HBV treatment data were available from three NHS Trusts. We investigated how ALT and VL surveillance varied between pre-COVID-19 (years 2016–2019) to COVID-19 (year 2020 and part of 2021), comparing surveillance metrics in patients on and off antiviral therapy.

We calculated cumulative probabilities of undergoing ≥ 1 ALT and HBV DNA VL measurement each year using the Kaplan-Meier method, comparing probabilities across years using the log-rank test. We quantified the mean number of ALT and HBV DNA measurements per 100 patients, during pre-COVID-19 and COVID-19 years, with 95% CIs calculated using the normal distribution (whereby standard error (SE) is estimated by $\frac{s}{\sqrt{n}}$ with n denoting sample size and s denoting standard deviation). Official UK government COVID-19 incidence data are presented¹¹.

Ethics approval

The research database for the NIHR HIC viral hepatitis theme was approved by South Central - Oxford C Research Ethics Committee (REF Number: 21/SC/0060). All methods in this study were carried out in accordance with relevant guidelines and regulations. The requirement for written informed consent was waived by South Central - Oxford C Research Ethics Committee, because data has been anonymised before its use and the study is retrospective.

Results

Coverage of ALT and VL testing (proportion tested at least once a year)

We analysed data representing 3498 individuals in 2016; this increased to 4374 for 2020 (Figure 1). In 2016, 78.6% (95% CI 77.1–79.9%) of individuals with CHB had ALT measured on ≥ 1 occasion throughout the year; this significantly decreased to 57.0% (95% CI 55.5–58.4%) in 2020 (Figure 2A). Median time to 50% of the cohort achieving ≥ 1 ALT measurement was <140 days for 2016–19 and 301 days for 2020. Similarly, throughout 2016, 70.0% (95% CI 68.3–71.3%) of patients had VL measured at least once, whilst this significantly decreased to 50.0% (95% CI 48.9–51.8%) in 2020 (Figure 2B). Median time to 50% of patients having achieved ≥ 1 VL measurement was 158–167 days for 2016–19 and 357 days for 2020. COVID-19 incidence data are displayed in Figure 3.

Coverage of ALT and VL testing stratified by treatment status

A subset of 82% of patients had treatment data recorded (which remained consistent during the period observed). In treated patients, the proportion with ≥ 1 ALT measurement decreased significantly from 95.2% (95% CI 85.6–98.4%) in 2016 to 74.0% (95% CI 69.7–77.6%) in 2020 (Figure 2C), and in untreated patients from 65.4% (95% CI 63.5–67.3%) to 53.0% (95% CI 51.1–54.8%) in 2020 (Figure 2E). The proportion of treated patients with VL measured decreased from 81.0% (95% CI 68.3–88.6%) in 2016 to 69.2% (95% CI 64.8–73.1%) in 2020 (Figure 2D), and from 56.7% (95% CI 54.7–58.7%) to 45.6% (95% CI 43.7–47.4%) in untreated patients (Figure 2F).

Frequency of ALT and VL testing

Pre-COVID, the mean number of ALT measurements varied from 14 (95% CI 14–14) to 26 (95% CI 26–26) per 100 patients per month, with annual dips in August and December (Figure 4A). From March 2020 to June 2021, this range reduced to between 7 (95% CI 7–7) and 14 (95% CI 14–14), with a loss of the seasonal patterns previously observed, and reaching a

Figure 1. Number of HBV patients included in study period sample. Denotes number of patients overall, and those with treatment information available. Our analysis included 3,498 individuals in 2016; this increased to 4,374 for 2020. The proportion of patients with treatment data available remained consistent throughout our study period at 2852/3498 (81.6%) in 2016 and 3,564/4,374 (81.5%) in 2020.

nadir of 7 per 100 patients (95% CI 6–7) in April 2020 during the first lockdown. The same trend was observed for VL (Figure 4B), with mean numbers of measurements ranging from 7 (95% CI 7–7) to 12 (95% CI 12–12) per 100 patients pre-COVID, and from 2 (95% CI 2–2) to 7 (95% CI 7–7) during the COVID-19 period, with a nadir of 2 measurements per 100 patients (95% CI 2–2) in April 2020.

Frequency of testing by HBV treatment status

VL and ALT measurements were more frequent in treated (Figure 4 C, D) compared to untreated (Figure 4 E, F) patients throughout the study period. In treated patients pre-COVID, mean number of ALT measurements fluctuated between and within years but remained >25 measurements per 100 patients per month (Figure 4C); hence, treated patients had ALT measured on average once every 4 months (in keeping with the routine interval for clinic visits in patients on treatment).

Mean numbers of monthly tests fluctuated between 19 (95% CI 18–21) and 35 (95% CI 34–37) per 100 patients

during the COVID-19 period but were generally significantly lower compared to pre-COVID-19 years. This pattern was also observed for VL, with mean numbers of measurements ranging from 11 (95% CI 11–12) to 23 (95% CI 23–24) during pre-COVID-19 years and 6 (95% CI 6–7) to 13 (95% CI 12–13) during the COVID-19 period (Figure 4D).

In untreated patients pre-COVID, mean number of ALT measurements per 100 patients per month ranged from 10 (95% CI 10–11) to 23 (95% CI 22–23), with a significant drop in the COVID-19 period to between 5 (95% CI 5–5) and 15 (95% CI 14–15) (Figure 4E). This pattern was also observed for VL, with pre-COVID-19 and COVID-19 measurements ranging from 6 (95% CI 6–7) to 11 (95% CI 11–11) and from 2 (95% CI 2–2) to 7 (95% CI 7–7) measurements per 100 patients, respectively (Figure 4F).

Discussion/conclusions

These data demonstrate the negative impact of the COVID-19 pandemic on routine clinical surveillance for patients with

Figure 2. Kaplan-Meier plots demonstrating the cumulative proportion of adults with chronic Hepatitis B virus (HBV) infection undergoing routine laboratory surveillance. Plots show patients who have had ≥ 1 alanine transferase (ALT) (panels A, C, E) and ≥ 1 HBV DNA viral load (VL) (panels B, D, F) measurement each year for pre-COVID-19 (2016–19) and COVID-19 (2020 and part of 2021) years. For both ALT and VL, plots are stratified by treated (panels C and D, respectively) and untreated (panels E and F, respectively) patients. Dashed lines depict median time for 50% of the cohort to have the laboratory assessment undertaken. Cumulative probabilities for each year were calculated using the Kaplan-Meier method, comparing probabilities across years using the log-rank test, with 2016 serving as the reference/baseline year.

Figure 3. UK coronavirus disease 2019 (COVID-19) incidence, displayed as number of incident daily COVID-19 cases¹². Data from March 2020 to July 2021 are displayed.

CHB infection in the UK. Reduction in rates of surveillance closely track SARS-CoV-2 incidence (Figure 3) and thus periods of population lock-down.

During lockdown periods, much clinical care was switched to telemedicine^{13,14}, intended to maintain contact between patients and healthcare providers, but at the detriment of laboratory monitoring. Although patients may have an option to attend phlebotomy appointments, services have been stretched, and clinicians and/or patients may have elected to defer routine blood tests. Telephone appointments are impractical for certain patients, and contact may have been lost altogether – for example, for those who do not communicate confidently in English. Furthermore, CHB patients who left the UK early in the course of the pandemic may have been unable to return due to travel restrictions, thereby foregoing routine surveillance.

The impact of the pandemic was seen across treated and untreated individuals. However, the impact on ALT measurement was greater in those on treatment during lockdowns.

We were unable to investigate how imaging-based surveillance strategies were impacted due to lack of complete elastography

and ultrasound data in our current dataset. Furthermore, as complications of CHB evolve over the long-term (months to years), it is not yet possible to quantify how service disruptions may impact incidence of HCC and other adverse endpoints. Surveillance disruption may be associated with an increased risk of CHB progression and delays in starting antiviral therapy. Further prospective data are required to determine the impact on long-term outcomes.

Our data represent only five large, urban centres, in the South East of England; trends may differ across settings and additional data will be required to determine the extent to which our observations apply in other regions. HIC data collection is being expanded¹⁰, providing enhanced opportunities to incorporate a wider view of the UK over time. Effort and resources are required to refine telemedicine services and optimise access to laboratory surveillance¹⁵, re-establish face-to-face services and catch-up on monitoring and interventions. Future analyses are warranted to investigate how imaging surveillance and telemedicine service uptake have been impacted when these data become available in the NIHR HIC database. Longitudinal follow-up is warranted to ascertain how COVID-attributable disruptions will impact the incidence of HCC and other

Figure 4. Mean numbers of ALT and HBV DNA VL measurements per 100 patients per month during pre-COVID-19 (COVID-19, 2016–19) and COVID-19 (2020 and part of 2021) periods. Data are shown overall and stratified by treatment status for both viral load (VL, panels **A, C, E**) and alanine transferase (ALT, panels **B, D, F**). Dates of UK national COVID-19 lockdowns are denoted in overall plots. 95% CIs were calculated using the normal distribution (whereby standard error (SE) is estimated by $\frac{s}{\sqrt{n}}$ with n denoting sample size and s denoting standard deviation).

relevant endpoints, and to ensure activity is re-aligned to support progress to elimination goals.

Data availability

Individual-level electronic health record were used to conduct this investigation. Data are anonymised and collected using National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC) data resources. In order to ensure patient confidentiality and data privacy, raw underlying data cannot be made publicly available, and data are made available to researchers via a controlled access repository. The NIHR HIC Viral Hepatitis data repository is hosted by Oxford University Hospitals NHS Foundation Trust under a governance framework which includes a data sharing agreement and terms on confidentiality, contractual responsibilities, intellectual property, and publication. A scientific steering committee, comprised

of at least one representative from each participating NIHR HIC site, meets regularly to review data collection, feedback progress on active projects, consider updates to the database, and review all data requests. Any potential collaborations are welcomed, and data are available to researchers on request following review by the steering committee. Further details are available at <https://hic.nihr.ac.uk>. Queries regarding data access should be directed to orh-tr.nihrhic@nhs.net.

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Thank you for the manuscript. This paper focused on how the pandemic impacted routine care for CHBV patients on treatment and those not on treatment. A number of articles have been published which looked at similar issues for other patients like HIV clients and other sin routine care prior to the pandemic. I am happy about the approach used here where the dataset set used is verifiable and the number of data points is large enough. The analysis has been done rigorously enough and clearly brings out the fact that laboratory services were very much negatively impacted compared with other aspects which telemedicine provided a solution.

I am very happy and did not see any significant point to make to improve this manuscript. It is well written. The authors could propose or give some suggestions as to how this impact particularly on laboratory services could be mitigated in future similar situations. That would be helpful. And again what do you consider as further research that could offer more insight into what has been reported here? I am also wondering why the team did not look at the laboratory results where available and see if there was any trend pre- and during the pandemic? That could have implications for the care received.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, infectious disease epidemiology, laboratory science

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.