Causes, associated exposures, and outcomes of cirrhosis and hepatocellular carcinoma in Malawi: an observational cohort and case–control study

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Summary

Background African countries have the highest age-standardised mortality from liver disease. We studied patients with cirrhosis and hepatocellular carcinoma in Malawi to ascertain the causes, associated exposures, and outcomes after discharge, and identify opportunities for intervention strategies.

Methods In this case–control cohort study, we recruited patients aged 16 years or older who met the study definitions for cirrhosis or hepatocellular carcinoma from the Queen Elizabeth Central Hospital in Blantyre, Malawi. In the cirrhosis group, we excluded patients with a liver stiffness greater than 12 kPa if a cause of potential false elevation of liver stiffness was identified and a liver ultrasound did not show signs of cirrhosis; people with extrapulmonary tuberculosis or other non-hepatic causes of ascites; and pregnant people. In the hepatocellular carcinoma group, we excluded those with an extrahepatic malignancy or ultrasound features consistent with liver metastases, pregnant people, and indeterminate lesions as determined by consultant radiologists on serial ultrasounds. Research nurses identified potential participants on medical and surgical wards, the medical outpatient clinic, and endoscopy unit, using systematic case notes review and clinician referral during weekdays. Patients were followed up for 6 months. A community sample was recruited from the catchment area of the hospital to estimate the general population prevalence of diseases and exposures potentially associated with liver disease. For hepatitis B and C, we conducted a serological survey in individuals aged 16 years or older who were randomly selected from a census, and we randomly selected a proportion of individuals who were HBsAg positive or HBsAg negative to estimate the general population prevalence of HIV, alcohol, smoking, diabetes, hepatitis D and E, and autoimmune hepatitis serological markers. We estimated population attributable fractions (PAFs) for cirrhosis and hepatocellular carcinoma using community controls and the serological survey. PAFs were estimated from logistic regression models adjusted for age and sex, using the Bruzzi method with percentile bootstrap confidence intervals.

Findings Between Nov 1, 2017, and April 30, 2019, we prospectively screened 708 patients and enrolled 138 diagnosed with cirrhosis and 78 diagnosed with hepatocellular carcinoma. Patients had a median age of 40 years (IQR 35–51), 134 (62%) were male, and 82 (38%) were female. In those with hepatocellular carcinoma, median tumour size was 13·2cm (10·2–17·3) and median survival was 40 days (95% CI 30–51). The community sample comprised 3258 individuals with hepatitis B and 1661 with hepatitis C identified from the serological survey, and 120 individuals negative for HBsAg and 94 people who were HBsAg positive from the serological survey to estimate the general population prevalence of HIV, alcohol, smoking, diabetes, hepatitis D and E, and autoimmune hepatitis serological markers. At 6 months, 83 (60%) of 130 patients with cirrhosis and six (8%) of 78 patients with hepatocellular carcinoma were still alive. Hepatitis B was the main attributable cause of cirrhosis (PAF 25·3% [17·5–33·3]) and hepatocellular carcinoma (73·1% [62·6–82·9]). HIV was the second leading attributable exposure associated with cirrhosis (22·2% [12·2–32·2]) and hepatocellular carcinoma (18·0% [4·8–30·9]); the association persisted after adjusting for hepatitis B virus co-infection. For hepatocellular carcinoma (but not cirrhosis), smoking (23·6% [8·9 to 37·2]) and alcohol (14·5 [–0·2 to 28·4]) were secondary attributable exposures. Autoimmune hepatitis (five [4%] patients), primary biliary cholangitis (four [3%] patients), and hepatitis C (two [1%] patients) were uncommon causes of cirrhosis, and no patients in either group had hepatitis D or E viraemia.

Interpretation Hepatitis B is the leading cause of cirrhosis and hepatocellular carcinoma in Malawi. HIV was diagnosed at a much higher rate among patients with cirrhosis and hepatocellular carcinoma than community controls; it is uncertain whether the relationship is causal or influenced by confounding. Alcohol and smoking are modifiable exposures associated with hepatocellular carcinoma. Hepatocellular carcinoma and cirrhosis are diagnosed at an advanced stage, with a poor prognosis. Community screen-and-treat programmes for hepatitis B could substantially reduce liver-related mortality in this region.

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Introduction

In the WHO African region, liver disease is associated with the highest age-standardised mortality of all WHO regions.[1] Deaths are largely attributable to complications of cirrhosis and hepatocellular carcinoma and are increasing due to a high prevalence of hepatitis B and an ageing population.[1,2] In 2016, the World Health Assembly adopted targets to eliminate viral hepatitis B and C as a public health threat, aiming to reduce the incidence by 90% and mortality by 65% by 2030.[3] These targets are far off track in the WHO African region, where just 4% of people living with hepatitis B have been diagnosed and 0·2% are on treatment.[2] The relative importance of viral hepatitis and other causes of cirrhosis and hepatocellular carcinoma, as well as outcomes after discharge from hospital, have not previously been well characterised in this region—these data are needed to underpin effective public health strategies.

Due to the limited availability of specialist hepatology care, imaging, and laboratory diagnostics, and the

Research in context

Evidence before this study

Age-standardised mortality from liver disease is highest in the WHO African region and is rising, due to an ageing population, a high prevalence of hepatitis B virus (HBV), and limited implementation of HBV screening and treatment. We undertook a search of PubMed on Jan 17, 2025, for observational articles published since Jan 1, 2000, with search terms and synonyms of "cirrhosis" or "hepatocellular carcinoma" and the names of countries in the WHO African region, applying no language restrictions. It has been estimated that only 4% of people living with hepatitis B in the WHO African region have been diagnosed, and 0·2% have started antiviral treatment. Existing studies on the causes of cirrhosis and hepatocellular carcinoma in southern African countries have focused on alcohol, and hepatitis B and C, and there are limited data on outcomes of cirrhosis or hepatocellular carcinoma after discharge from hospital. A previous multicentre study of hepatocellular carcinoma cases from the WHO African region identified a relatively young age at diagnosis (median 46 years) and poor survival of median 3 months, but countries in southern Africa did not contribute data. A cohort study from The Gambia found that patients were frequently diagnosed with late-stage hepatocellular carcinoma, observed poor outcomes from cirrhosis, and identified a survival benefit of tenofovir treatment for people living with hepatitis B who had cirrhosis.

Added value of this study

We performed a prospective observational study of patients presenting to a hospital in Malawi, using screening criteria to identify patients with cirrhosis and hepatocellular carcinoma. We did an extensive investigation for diseases and exposures potentially associated with cirrhosis and hepatocellular carcinoma, and we used a census to randomly sample patients living in the community to estimate general population exposures and population attributable fractions of different diseases and exposures. We followed up patients for 6 months after hospital discharge to ascertain survival outcomes. We found that patients were diagnosed with hepatocellular carcinoma at a very late stage, with a median survival of 40 days, representing the worst outcomes reported for malignancy globally (relative to data from the CONCORD-3 global study). Among patients with cirrhosis, 60% of patients remained alive and in care at 6 months. We observed that hepatitis B was the leading cause of liver disease and the role of HIV as a contributor to cirrhosis and hepatocellular carcinoma, independently of viral hepatitis co-infection. Alcohol and smoking were modifiable attributable exposures associated with hepatocellular carcinoma, and previous tuberculosis infection was associated with cirrhosis. We found no evidence of viraemic hepatitis D or E infection in cases or controls in either group but found that hepatitis C was an uncommon cause of cirrhosis. Autoimmune hepatitis is a rare but treatable cause of cirrhosis, and currently there is insufficient access to diagnostic assays in low-income countries. We estimate that in this region, community screen and treat programmes for HBV, similar to the models used for HIV care, could substantially reduce the burden of liver disease.

Implications of all the available evidence

This study, together with existing evidence, highlights public health opportunities to address late diagnosis and high mortality associated with cirrhosis and hepatocellular carcinoma in the WHO African region. Our findings from southern Africa are in keeping with previous evidence from west Africa and central Africa. Hepatitis B is the leading cause of cirrhosis and has a particularly strong association with hepatocellular carcinoma. With the new and simplified 2024 WHO HBV guidelines, there is an increased scope for expanded models of decentralised community treatment, with the advent of cheap (<US$2) point-of-care HBsAg diagnostics and generic tenofovir antiviral treatment (<$2·4/month). Researchers should evaluate implementation models of community HBV care. Policy makers should prioritise investment in community screening and treatment for HBV, which represents the best opportunity to prevent liver-related death in this region.

limitations of verbal autopsy (a method used to ascertain cause of death using a structured interview with family or caregivers), the relative importance of cirrhosis and hepatocellular carcinoma and their causes in the region remain uncertain. Modelling studies based on sparse data inputs have estimated that in southern Africa, 40% of hepatocellular carcinoma cases are attributable to alcohol, 29% to hepatitis B, and 20% to hepatitis C.[4] Existing studies have focused on viral hepatitis and alcohol, whereas outcome data have focused on inpatient mortality.

We aimed to undertake a detailed characterisation of the causes and associated exposures, such as viral hepatitis B and C, HIV, alcohol, smoking, and rarer causes of liver disease, following a diagnosis of cirrhosis or hepatocellular carcinoma and patient outcomes after discharge at a tertiary hospital in Malawi. We used a case–control design (randomly sampling a community control population and undertaking a serosurvey) to estimate population attributable fractions (PAFs) of diseases and exposures and identify opportunities for interventions to tackle rising liver-related mortality.

Methods

Study design and participants

We recruited patients with cirrhosis or hepatocellular carcinoma aged 16 years or older from the Queen Elizabeth Central Hospital in Blantyre, Malawi. Research nurses identified potential participants on medical and surgical wards, the medical outpatient clinic, and endoscopy unit, using systematic case notes review and clinician referral during weekdays. Patients with symptoms and signs of possible chronic liver disease including jaundice, ascites, splenomegaly, spider telangiectasia, gynaecomastia, dilated veins of the lower abdominal wall, upper gastrointestinal bleeding, or suspected hepatocellular carcinoma due to an abdominal mass detected in the right upper quadrant or from ultrasound imaging were eligible for screening.

Patients were eligible for participation if they met the study definitions for cirrhosis or hepatocellular carcinoma. Cirrhosis was defined by clinical features of chronic liver disease together with a liver stiffness measurement of 12 kPa or higher after fasting for 3 h or more by transient elastography (Fibroscan 430-Mini, Echosens, France) with a reliability criteria (IQR/median) of less than 0·3.[5] We excluded patients with a liver stiffness greater than 12 kPa if a cause of potential false elevation of liver stiffness was identified and a liver ultrasound did not show signs of cirrhosis (appendix 1 pp 4–5). We also excluded individuals with extra-pulmonary tuberculosis or other non-hepatic causes of ascites, and pregnant people. For hepatocellular carcinoma, we used an ultrasound-based definition of an intrahepatic mass measuring 2 cm or more with sonographic appearances consistent with hepatocellular carcinoma (appendix 1 pp 6–7). We excluded those with extrahepatic malignancy or ultrasound features consistent with liver metastases, pregnant people, and indeterminate lesions as determined by consultant radiologists (EJ or KC) on serial ultrasounds; contrast-enhanced imaging was not available locally during the study. We classified hepatocellular carcinoma according to the 2022 Barcelona Clinic Liver Cancer criteria.[6] Transient elastography and ultrasound were performed for all patients.

We also recruited participants residing in a community population in the hospital catchment area (appendix 1 p 3) to estimate the general population prevalence of diseases (hepatitis B, C, and E, Wilson's disease, HIV, and alpha-1 antitrypsin deficiency), and exposures (alcohol and smoking exposure, metabolic dysfunction-associated steatotic liver disease [MASLD] risk factors) potentially associated with liver disease (appendix 1 pp 2–3). For autoimmune markers of autoimmune hepatitis or primary biliary cirrhosis, these were obtained not as diseases or exposures, but to estimate the community reference values of these markers in the general population to support a diagnosis of these conditions in patients with cirrhosis (appendix 1 p 12). For hepatitis B (n=3258) and C (n=1661), we conducted a serological survey in individuals aged 16 years or older who were randomly selected from a census, as previously reported.[7,8] To estimate the prevalence of other diseases and exposures in this population, we randomly selected a proportion of individuals from the serological survey who were HBsAg positive or HBsAg negative to estimate the general population prevalence of HIV, alcohol, smoking, diabetes, hepatitis E, and autoimmune hepatitis serological markers. Hepatitis B-positive cases were oversampled for the primary aim of estimating hepatitis B virus (HBV) treatment eligibility.[8] Participants testing positive for HBsAg were also tested for hepatitis D (anti-HDV).

For inclusion as control populations, individuals had to be older than 16 years, and selected from single-stage random probability sampling from the demographic census of the catchment area. For the serosurvey, if a randomly selected individual could not be located or did not consent, another household member from the same age stratification group was requested to participate or, secondarily, a replacement was selected by further randomisation from the census age stratum.

Ethical permission to conduct this study was obtained from the National Health Sciences Research Committee of Malawi (16/11/1698) and the University of Liverpool (1954). Participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (2013).

See Online for appendix 1

Procedures

Study investigations are detailed in the appendix 1 (pp 8–10). Alcohol consumption was assessed using WHO AUDIT[9] and we asked about current or past

smoking history using a self-report questionnaire (appendix 1 pp 8–10). HIV testing was conducted using sequential rapid diagnostic tests, with HIV positivity requiring a positive result on both the first and confirmatory tests (appendix 1 p 9). We tested for HBsAg (Monolisa, Bio-Rad, France), and samples with a signal-to-cutoff ratio greater than 0·9 were retested in duplicate. HBeAg, anti-HBe, anti-HBc, hepatitis C virus (HCV or hepatitis C virus antibodies; Bio-Rad), anti-hepatitis D virus (ETI-AB-DELTAK-2, Diasorin, Italy), and hepatitis E IgG and IgM (Wantai BioPharm, China) were tested by ELISA. HCV antigen-positive and HCV antibody-positive samples underwent RNA quantification (GeneXpert, Cepheid, South Africa). HBV DNA was quantified with an in-house PCR in all participants; occult HBV infection was defined as individuals who were HBsAg negative but with detectable HBV DNA.[8] We detected hepatitis D and hepatitis E RNA with in-house PCR on a Cobas 6800 (Roche, Germany).[10] We measured alpha-fetoprotein (Siemens Atellica Solutions, Germany) among patients with hepatocellular carcinoma and reported patient characteristics stratified by those above or below 200 ng/mL (appendix 1 p 29). We used point-of-care urinary circulating cathodic antigen (Rapid Medical Diagnostics, South Africa) and an in-house PCR assay on plasma with *Schistosoma mansoni*-specific primers (Institute for Tropical Medicine, Hamburg, Germany) to diagnose schistosomiasis.[11] Indirect immunofluorescence was used to detect ANA, GP210, SP100, smooth muscle antibody, antimitochondrial antibody, liver-kidney-microsomal type 1 antibodies, and F-actin. For patients with cirrhosis, we calculated the Child–Pugh score to assess the severity of cirrhosis. We also tested for Wilson disease, alpha-1 antitrypsin deficiency, and MASLD risk factors (diabetes) using standard methods (appendix 1 pp 8–9). International Autoimmune Hepatitis group criteria with a score of 6 or more was considered compatible with autoimmune hepatitis. An autoimmune hepatitis expert (CWN) and study physicians (AJS, BK) reviewed complete clinical and laboratory data to make a diagnosis of autoimmune hepatitis (appendix 1 pp 11–13).[12] Primary biliary cholangitis was defined according to international criteria.[13] We followed up hospital participants by telephone and home visits monthly for 6 months to ascertain mortality.

Statistical analysis

We estimated that for an exposure with a prevalence of 5% among control populations, with a power of 0·8 and one-sided alpha of 0·025, to ascertain a PAF of 15% or more, an estimated 96 cases and controls were required.[14] We fitted logistic regression models to estimate odds ratios for diseases (hepatitis B and C, HIV, and previous tuberculosis) and exposures (smoking, alcohol, and MASLD risk factors [as indicated by diabetes]), comparing cases (cirrhosis and hepatocellular carcinoma) and community controls. For hepatitis B and C, serosurvey data were used as control populations. For all other diseases and exposures, we used the general population samples of people recruited from the serosurvey who were either HBsAg negative or HBsAg positive. As HBsAg-positive patients were oversampled in this control group, we applied model weights to adjust to the community HBsAg prevalence observed in the serosurvey. All logistic regression models were adjusted for participant age and sex. Multivariable logistic regression models were then fitted, including variables known to be associated with cirrhosis and hepatocellular carcinoma pathogenesis (identified from the extant literature) based on causal inferences are illustrated by directed acyclic graphs (appendix 1 pp 14–15). Variables with low prevalence (<5%) among cases were excluded to avoid unstable estimates and inflated standard errors. Alcohol consumption was excluded in the model for cirrhosis as we suspected information (under-reporting) bias in the cases. We considered spline terms and interactions between HBV and HIV, and HIV and previous tuberculosis, and evaluated model fit using Aikake and Bayesian information criteria and compared models with the likelihood ratio test.

We then estimated PAFs using estimates from the fitted logistic regression models, as implemented in the *graphPAF* package in R (version 2.0.0; appendix 1 pp 16–18).[15] After fitting each model, we used the Bruzzi method to estimate PAF, applying percentile bootstrap calculated CIs with 5000 replications.[15] For the multivariable cirrhosis model, we estimated the joint PAF for HIV and tuberculosis since they were causally associated variables on our directed acyclic graphs (appendix 1 pp 14–15).

Predictors of 6-month mortality were modelled using Cox proportional hazards regression (appendix 1 pp 19–20). To categorise the Child–Pugh classification for patients with cirrhosis, we imputed missing international normalised ratio values (25%; appendix 1 p 21). We fitted two multivariable models to investigate the prognostic utility of the Child–Pugh score and of the liver stiffness measurement and ascites (appendix 1 pp 19–25). We produced a marginal prediction plot for logistic regression models and for survival using the marginal effects package in R (appendix 1 pp 26–28). Analyses were conducted in Stata (version 18.5) and R (version 4.2.1).

Role of the funding source

The funders had no role in the study design, analysis, writing or decision to submit.

Results

Between Nov 1, 2017, and April 30, 2019, we prospectively screened 708 patients with features of chronic liver disease for cirrhosis or hepatocellular carcinoma. Of the 373 potentially eligible patients, 272 consented to participate, and after evaluation 216 patients were included in the study (138 with cirrhosis and 78 with

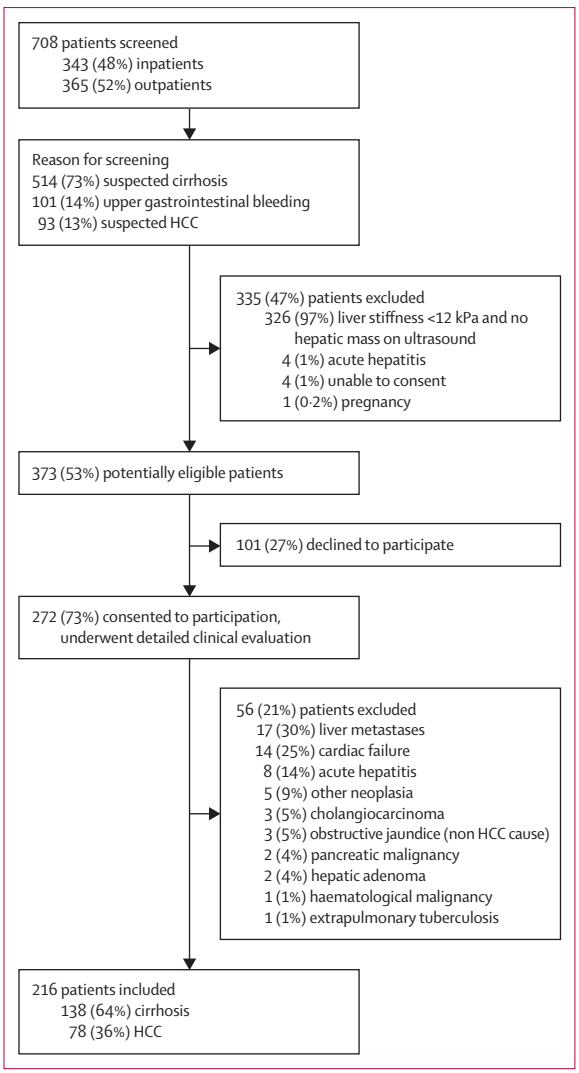

Figure 1: **Participant selection**
HCC=hepatocellular carcinoma.

	Cirrhosis (n=138)	Hepatocellular carcinoma (n=78)	Community control population (n=120)*
Sex			
Male	80 (58%)	54 (69%)	50 (42%)
Female	58 (42%)	24 (31%)	70 (58%)
Age, years	40 (33–51)	40 (35–50)	35 (27–45)
Body mass index, kg/m²	21·2 (19·5–22·9)	21·1 (19·2–22·8)	24·1 (21·3–29·7)
Underweight (<18·5)	14 (10%)	19 (24%)	5 (4%)
Normal (18·5–24·9)	112 (81%)	55 (71%)	65 (54%)
Overweight (25–29·9)	12 (9%)	4 (5%)	22 (18%)
Obese (≥30)	0	0	27 (23%)
Comorbidities			
Diabetes mellitus	3 (2%)	2 (3%)	1 (1%)
Hypertension†	17 (12%)	10 (13%)	31 (26%)
History of tuberculosis	21 (15%)	3 (4%)	3 (3%)
Symptoms			
Abdominal swelling	80 (58%)	44 (56%)	..
Abdominal pain	38 (28%)	54 (69%)	..
Peripheral oedema	43 (31%)	21 (27%)	..
Gastrointestinal bleeding	35 (25%)	4 (5%)	..
Shortness of breath	13 (9%)	14 (18%)	..
Weight loss	16 (12%)	15 (19%)	..
Fever	2 (1%)	3 (4%)	..
Duration of symptoms, days	30 (10–100)	37·5 (14–90)	..
Signs of chronic liver disease			
Cachexia or sarcopenia	105 (76%)	66 (85%)	4 (3%)
Ascites	89 (64%)	47 (60%)	0
Peripheral oedema	63 (46%)	36 (46%)	0
Icterus	38 (28%)	30 (38%)	0
Dilated abdominal veins	23 (17%)	23 (29%)	1 (1%)
Digital clubbing	4 (3%)	2 (3%)	1 (1%)
Gynaecomastia among male patients	1 (1%)	2 (3%)	0
Haemoglobin, g/dL	10·3 (7·6–12·5)	11·5 (9·7–12·9)	14·3 (13·3–15·4)
Platelets, ×10⁹/L	78 (49–154)	229 (157–376)	246 (207–309)
Alanine aminotransferase, U/L	31 (21–50)	54 (31–90)	..
Total bilirubin, µmol/L	14·9 (6·8–29·1)	34·7 (13·4–101·1)	..
Albumin, g/L	25·2 (18·5–30·9)	24·9 (20·1–29·8)	..
INR	1·2 (1·1–1·4)	1·2 (1·1–1·4)	..
Liver stiffness measurement, kPa	25·2 (16·7–54·1)	>75 (46·6–>75)	4·5 (3·6–5·4)

Data are n (%) or median (IQR). INR=international normalised ratio. *Data from HBsAg negative controls are shown here, which contribute 95% of the weight for the control population in logistic regression models. †Hypertension defined as resting blood pressure greater than 140/90 mm Hg or receiving antihypertensive treatment.

Table 1: **Participant characteristics**

hepatocellular carcinoma; figure 1). Reasons for exclusion of patients after consent included suspected liver metastases (n=17), non-hepatocellular carcinoma neoplasia (n=13), cardiac failure (n=14), acute hepatitis (n=8), and extrapulmonary tuberculosis (n=1). The community sample tested 3258 individuals with hepatitis B and 1661 with hepatitis C (appendix 1 p 2). We randomly selected 120 individuals negative for HBsAg and 94 people who were HBsAg positive from the serological survey to estimate the general population prevalence of HIV, alcohol, smoking, diabetes, hepatitis D and E, and autoimmune hepatitis serological markers.

Patients had a median age of 40 years (IQR 35–51), 134 (62%) of 216 participants were male, and 82 (38%) were female. Median symptom duration was 30 days (10–100) in patients with cirrhosis and 37·5 days (14–90) for hepatocellular carcinoma. Participant characteristics, including presenting symptoms and liver disease signs, can be found in table 1.

Of the 138 patients with cirrhosis, 33 (24%) were Child–Pugh class A, 85 (62%) were class B, and 20 (14%) were class C. Renal impairment (defined as an estimated glomerular filtration rate <60 mL/min per 1·73 m²) was observed in 28 (20%) patients and 21 (15%) had an estimated glomerular filtration rate of

	Cirrhosis (n=138)	Hepatocellular carcinoma (n=78)	Community controls*
Hepatitis B			
Hepatitis B infection or exposure	93/138 (67%)	71/78 (91%)	39·1%†
HBsAg positive	40/138 (29%)	58/78 (74%)	150/3258 (5%)
HBsAg positive participants			
HBeAg positive	18/40 (45%)	22/58 (37·9%)	10/94 (11%)
HBV DNA concentration, log_{10} IU/mL)	4·3 (2·6–6·3)	4·3 (2·7–6·1)	1·9 (<1·5–2·9)
HBV DNA >2000 IU/mL	25/40 (63%)	38/58 (66%)	19/94 (20%)
HBV DNA >20 000 IU/mL	19/40 (48%)	30/58 (52%)	11/94 (12%)
Hepatitis D antibody positive‡	0/40	2/57 (4%)	2/94 (2%)
HBsAg negative participants			
Anti-HBc positive	53/98 (54%)	13/20 (65%)	219/634 (35%)
Occult HBV§	2/98 (2%)	2/20 (10%)	0/120
Hepatitis C			
HCV Ag/Ab positive	9/138 (7%)	5/78 (6%)	13/1661 (1%)
HCV RNA positive	2/138 (1%)	4/78 (5%)	3/1661 (<1%)
Alcohol (WHO AUDIT score)			
Non-hazardous (0–7)	102/138 (74%)	36/78 (46%)	94/120 (78%)
Hazardous (8–15)	12/138 (9%)	12/78 (15%)	9/120 (8%)
Harmful (16–19)	3/138 (2%)	3/78 (4%)	1/120 (1%)
Alcohol dependence (≥20)	3/138 (2%)	6/78 (8%)	3/120 (3%)
Hazardous consumption or worse (≥8)	18/138 (13%)	21/78 (27%)	13/120 (11%)
HIV status			
HIV positive	41/136 (30%)	21/77 (27%)	11/119 (9%)
Among HIV positive participants			
CD4 count, cells/mm^3	198 (112–353)	378 (162–578)	340 (35–578)
On ART	16/41 (39%)	7/21 (33%)	6/11 (55%)
Schistosomiasis			
Urinary CCA positive	42/138 (30%)	27/78 (35%)	3/120 (3%)
Schistosoma mansoni PCR positive	50/138 (36%)	9/78 (12%)	7/120 (6%)
Ultrasound features of hepatic schistosomiasis	16/128 (13%)	0/78	NA
Autoimmune disease			
Autoimmune hepatitis	5/138 (4%)	NA	NA
Primary biliary cholangitis	4/138 (3%)	NA	NA
Other causes			
Caeruloplasmin <0·1 g/L	1/138 (2%)	NA	0/120
Alpha-1 antitrypsin <100 mg/dL	0/138	NA	2/120 (2%)
Hepatitis E IgG positive	17/138 (12%)	15/78 (19%)	21/120 (18%)
Hepatitis E RNA positive	0/138	0/78	0/120
Diabetes (risk factor for MASLD)	3/138 (2%)	2/78 (3%%)	1/120 (1%)
Ultrasound signs of fatty liver disease	4/128 (3%)	0/78	NA
Current or former smoker	19/138 (14%)	26/78 (33%)	11/120 (9%)
Current smoker	2/138 (1%)	0/78	7/120 (6%)
Former smoker	17/138 (12%)	26/78 (33%)	4/120 (3%)
Pack-years (among smokers)	5·5 (1·1–9·9)	3·4 (0·9–7·4)	0·5 (0·2–2·3)

(Table 2 continues on next page)

less than 15 mL/min per 1·73 m². Ultrasound features included a coarse or heterogenous liver echotexture in 114 (89%), nodular or irregular surface in 115 (90%), and ascites in 82 (64%) patients. Splenomegaly was present in 95 (74%) and median spleen size was 17 cm (IQR 13–19).

Of the 78 patients with hepatocellular carcinoma, the median size of the largest lesion was 13·2 cm (IQR 10·2–17·3) and 31 (40%) had multiple hepatic lesions. Compression or invasion of the portal vein was observed in 72 (92%) patients and 56 (72%) had ascites. Cirrhosis was observed in 69 (93%) of 74 patients with hepatocellular carcinoma with sufficient visualised parenchyma. Median alfa-fetoprotein concentration was 5696 IU/mL (IQR 14–44 243) and was less than 200 ng/mL in 22 (30%) patients; stratifying by levels above or below 200 ng/mL, no clinically relevant differences in hepatic ultrasound findings, tumour size, morphology, or background cirrhosis was observed (appendix 1 p 29). Impaired liver function (Child–Pugh class B or C, or hepatic decompensation) was present in 71 (91%) patients with hepatocellular carcinoma. Barcelona Clinic Liver Cancer staging was class C in seven (9%) patients and D in 71 (91%) patients.

40 (29%) of the 138 patients with cirrhosis and 58 (74%) of the 78 patients with hepatocellular carcinoma were HBsAg positive (table 2). An additional 53 (38%) patients with cirrhosis and 13 (17%) with hepatocellular carcinoma were anti-HBc positive (indicating previous HBV exposure) and two of (1%) 138 patients with cirrhosis and two (3%) of 78 patients with hepatocellular carcinoma had occult hepatitis B, respectively. PAF estimates for hepatitis B infection were 25·3% (95% CI 17·5–33·3) for cirrhosis and 73·1% (95% CI 62·6–82·9) for hepatocellular carcinoma (table 3) by univariate analysis. Only 11 (5%) of 216 included patients and five (4%) of 120 community controls had heard of hepatitis B.

Hepatitis C was uncommon, with HCV RNA detected in two (1%) patients with cirrhosis and four (5%) with hepatocellular carcinoma, with similar PAFs on univariable analysis (table 3). Community HCV RNA prevalence was 0·2% (95% CI 0·1–0·5) among the 1661 serosurvey participants who were assessed for hepatitis C. No co-infection of HCV and HBV was observed. Hazardous or greater alcohol consumption (WHO AUDIT score ≥8) was reported at a similar frequency among patients with cirrhosis (18 [13%] of 138) and community controls (13 [11%] of 120), but was higher among patients with hepatocellular carcinoma (21 [27%] of 78), who had a corresponding PAF of 14·5% (95% CI –0·2 to 28·4) on univariable analysis. Smoking was an attributable cause for 23·6% (8·9 to 37·2) of hepatocellular carcinoma cases, whereas no association between smoking and cirrhosis was observed (PAF 1·4% [–10·5 to 10·9]; table 3). The prevalence of diabetes in patients with cirrhosis or hepatocellular carcinoma was similar to community controls. Fatty liver was observed in four (3%) patients with cirrhosis on ultrasound (table 2).

HIV prevalence was higher among patients with cirrhosis (41 [30%] of 136) and hepatocellular carcinoma

(21 [27%] of 77) than community controls (11 [9%] of 119; table 2). For HIV, we estimated PAFs of 22·2% (95% CI 12·2–32·2) for cirrhosis and 18·0% (4·8–30·9) for hepatocellular carcinoma on univariable analysis (table 3). Most of the effect was attributable to people who had not started antiretroviral therapy (ART; PAF 14·6% [95% CI 7·0–22·3] for cirrhosis and 14·6% [5·4–24·2] for hepatocellular carcinoma). In a multivariable model, HIV was associated with cirrhosis after adjustment for hepatitis B and previous tuberculosis (adjusted PAF 12·5% [4·9–19·3]). The joint PAF estimate for cirrhosis for HIV and tuberculosis was 15·7% (8·6–23·4; table 3). No co-infection was observed between HIV and HCV. We observed an interaction between HIV and HBV; HIV was associated with cirrhosis in individuals who were HBsAg negative, but did not moderate the risk of cirrhosis among individuals who were HBsAg positive (appendix 1 p 26). No clinically relevant differences in symptoms, signs, or laboratory variables of cirrhosis patients were seen based on HIV status, except for higher platelet counts and a higher rate of primary biliary cholangitis associated with HIV (appendix 1 pp 30–31). For hepatocellular carcinoma, hepatitis B (73·0% [95% CI 62·4 to 82·9]), smoking (22·0% [0·3 to 36·0]), HIV (among patients not receiving ART; 15·3% [4·5 to 25·1]), and alcohol (10·1% [–20·9 to 28·5]) were attributable factors in a multivariable model (table 3).

In patients with cirrhosis, autoimmune hepatitis was diagnosed in five (4%) and primary biliary cholangitis in four (3%; appendix 1 pp 11–13). Caeruloplasmin was less than 0·1 g/L in one patient but no neurological signs nor Kaiser–Fleisher rings were seen. All patients had normal alpha-1 antitrypsin levels. No excess serological exposure of hepatitis E (by IgG) relative to controls was observed and hepatitis E RNA was negative in all patients. Hepatitis D RNA was negative in all participants who were HBsAg positive. Schistosomiasis was a common exposure, with a third of cirrhosis patients having microbiological evidence of infection—42 (30%) were positive for urinary circulating cathodic antigen, 50 (36%) for *S mansoni*-specific PCR, and 16 (13%) had ultrasonographic features of hepatic schistosomiasis.

At 6 months, 39 (28%) of patients with cirrhosis had died, 16 (12%) were lost to follow-up, and 83 (60%) were alive and under follow-up (figure 2). Among patients with hepatocellular carcinoma, mean survival was 40 days (95% CI 30–51; figure 2). At 6 months, 66 (85%) had died, six (8%) were lost to follow-up, and six (8%) remained alive. In multivariable Cox regression models, we found that increasing age, male sex (hazard ratio 2·12 [95% CI 1·05–4·26]; p=0·035), and the Child–Pugh classification (3·49 [0·82–14·95] class B *vs* A; 17·22 [3·97–74·8] class C *vs* A; p<0.0001) predicted all-cause mortality. In a second model without requiring laboratory tests, the presence of ascites (6·93 [2·07–23·23]; p=0·017) and increasing liver stiffness (1·01 [1·00–1·03];

	Cirrhosis (n=138)	Hepatocellular carcinoma (n=78)	Community controls*
(Continued from previous page)			
Multiple exposures¶			
HIV and HBV co-infection	10/138 (7%)	16/78 (21%)	2·4%
HBV and WHO audit score ≥8	5/138 (4%)	16/78 (21%)	0·6%
HCV and WHO audit score ≥8	1/138 (1%)	0/78	0·0%
No cause identified‖	28/138 (20%)	5/78 (6%)	NA
No cause identified, excluding schistosomiasis infection**	15/138 (11%)	4/78 (5%)	NA

Data are n (%) or median (IQR). ART=antiretroviral therapy. CCA=circulating cathodic antigen. HBeAg=hepatitis B e-antigen. HBV=hepatitis B virus. HCC=hepatocellular carcinoma. HCV=hepatitis C virus. HCV Ag/Ab=hepatitis C antigen/antibody. MASLD=metabolic dysfunction-associated steatotic liver disease. NA=not applicable. *Community control populations comprised: community serosurveys of HBsAg prevalence (n=3258), anti-HBc prevalence (n=634), anti-HCV and HCV RNA prevalence (n=1661) and for alcohol, HIV status and markers of other aetiologies (n=120) among HBsAg-negative individuals aged ≥16 years in Blantyre, Malawi. †Combined prevalence estimates from serosurveys of HBsAg (n=3258) and anti-HBc prevalence among HBsAg-negative (n=634) participants aged ≥16 years. ‡No participants were hepatitis D RNA positive. §Occult HBV is defined as HBsAg negative and detectable HBV DNA. ¶Community prevalence of multiple exposures is estimated from the product of HBV or HCV prevalence in the serosurvey and prevalence of HIV, or hazardous alcohol in HBV or HCV positive individuals diagnosed in the serosurvey who consented to further evaluation. ‖No cause identified refers to testing negative for HBsAg, anti-HBc, HBV DNA, HCV RNA, having normal alpha-1 antitrypsin, not meeting criteria for autoimmune hepatitis or primary biliary cholangitis, having a non-hazardous alcohol consumption, no MASLD risk factors, and absence of ultrasound signs of fatty liver or schistosomiasis. **Additionally excludes patients testing with urinary CCA or positive *Schistosoma mansoni* specific-PCR or with ultrasound signs of schistosomiasis.

Table 2: **Diseases and exposures associated with cirrhosis and HCC**

	Cirrhosis		Hepatocellular carcinoma	
	Univariable	Multivariable	Univariable	Multivariable
HBsAg positive	25·3 (17·5 to 33·3)	22·9 (11·6–31·8)	73·1 (62·6 to 82·9)	73·0 (62·4 to 82·9)
HCV RNA positive	0·9 (–0·1 to –3·3)	..	4·9 (0·6 to 10·3)	..
WHO AUDIT alcohol consumption score ≥8	–1·7 (–15·0 to 8·6)	..	14·5 (–0·2 to 28·4)	10·1 (–20·9 to 28·5)
Current or former smoker	1·4 (–10·5 to 10·9)	..	23·6 (8·9 to 37·2)	22·0 (0·3 to 36·0)
Diabetes†	1·2 (–1·6 to 4·3)	..	1·5 (–1·1 to 5·8)	..
HIV positive	22·2 (12·2 to 32·2)	12·5 (4·9–19·3)	18·0 (4·8 to 30·9)	..
HIV positive and not receiving ART‡	14·6 (7·0 to 22·3)	..	14·6 (5·4 to 24·2)	15·3 (4·5 to 25·1)
Previous tuberculosis therapy	12·4 (5·3 to 19·2)	4·9 (0·9–9·4)	0·2 (–8·3 to 6·3)	..
HIV and tuberculosis (joint population attributable fraction)	..	15·7 (8·6–23·4)	..	..

Data are % (95% CI). ART=antiretroviral therapy. HBsAg=hepatitis B surface antigen. HBV=hepatitis B virus. HCV=hepatitis C virus. *All models are adjusted for age (with a natural spline with 2 df for cirrhosis) and sex. Logistic regression model odds ratios used to estimate population attributable fractions are shown in the appendix (p 16). Multivariable model for cirrhosis includes hepatitis B infection (HBsAg positive), HIV positive status, and previous tuberculosis therapy with an interaction term between HIV and HBV. For HCC it includes hepatitis B infection, HIV (not receiving ART), alcohol (harmful or greater status on the WHO AUDIT tool), and smoking (current or former). †Diabetes was included as the main risk factor for metabolic-dysfunction associated steatotic liver disease. ‡Counterfactual exposure category for HIV; not on ART is being either HIV negative or HIV positive and not receiving ART.

Table 3: **Population attributable fractions (%) among patients with cirrhosis or HCC relative to community control populations***

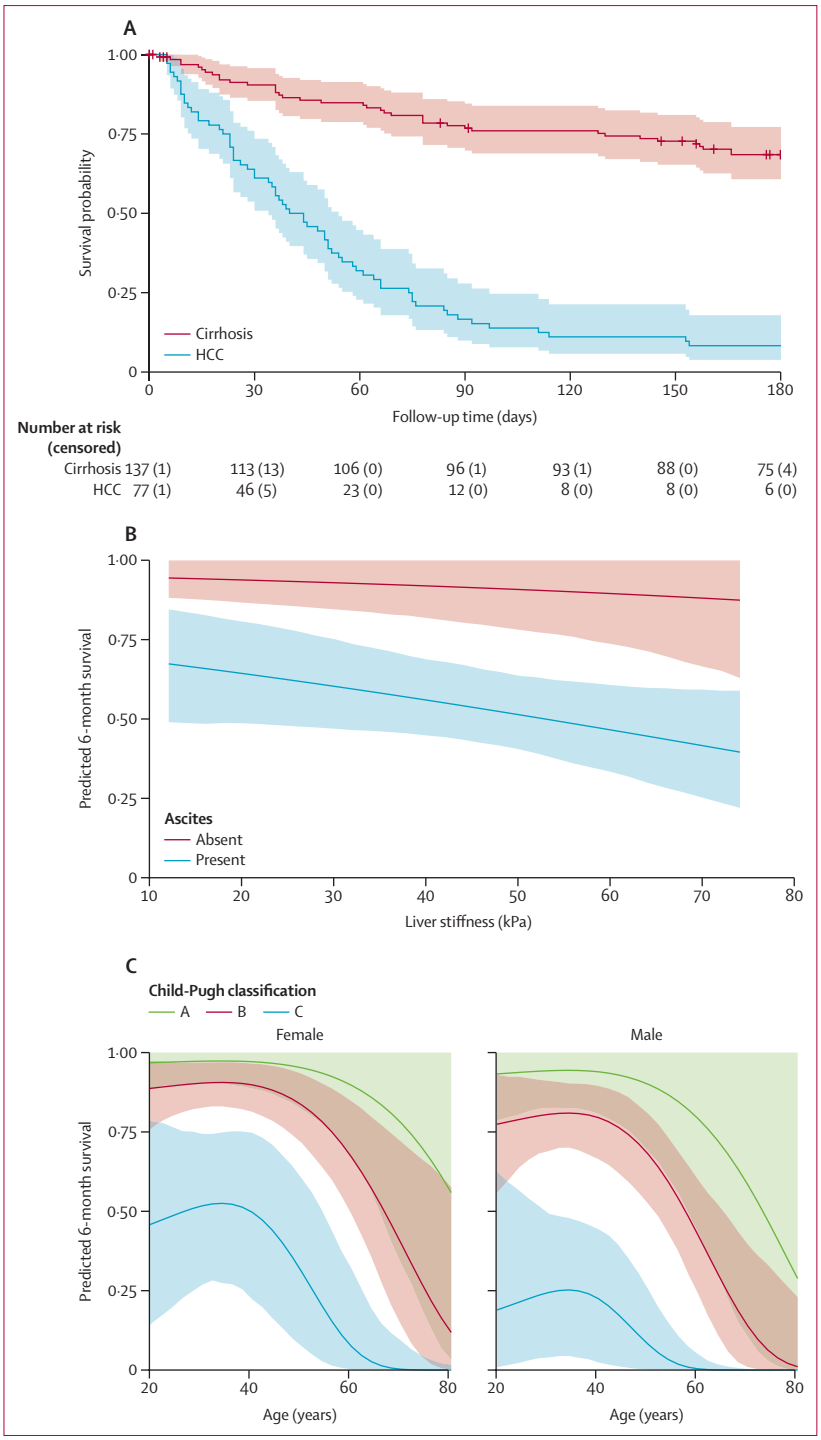

Figure 2: **Survival outcomes over 6 months of follow up**
(A) All patients with cirrhosis or hepatocellular carcinoma; Kaplan–Meier plot. (B) Patients with cirrhosis and its association with liver stiffness measurement and ascites; marginal prediction plot. (C) Patients with cirrhosis and its association with Child-Pugh classification, age, and sex; marginal prediction plot. Shaded areas indicate 95% CIs. Marginal prediction plots are from Cox proportional hazards models with age (restricted cubic spline term), sex, and linear term for liver stiffness and age (B); age (restricted cubic spline term), sex, and Child-Pugh classification (C; model estimates shown in appendix [pp 19–20]). HCC=hepatocellular carcinoma

p=0·053) were associated with increased 6-month mortality (figure 2, appendix 1 pp 19–20). In patients with cirrhosis, mortality was not associated with HIV status (1·00 [0·50–1·97]; p=0·99).

Discussion

Through a comprehensive assessment of hospital patients and a randomly selected control population, we gained novel insights into community-level exposures, population attributable fractions, and outcomes of cirrhosis and hepatocellular carcinoma in Malawi. We found that hepatitis B was the dominant cause of liver disease and was an attributable cause for almost three-quarters of hepatocellular carcinoma cases and a quarter of cases of cirrhosis. Occult HBV was observed rarely in this setting (<3%) in contrast to 2022 data from The Gambia where it was seen in 18% of patients with advanced liver disease.[16] This finding might be related to HBV genotypes, with genotype A1 prevalent in Malawi versus the predominant genotype E in West Africa.[17] Despite the importance of HBV, only 5% of all participants had previously heard of it, highlighting the need for improved awareness. In keeping with previous evidence from southern Africa, hepatitis D viraemia was not observed.[18] Hepatitis C was an infrequent cause of both cirrhosis and hepatocellular carcinoma with less than 5% of people having viraemic infection. Alcohol excess was an important contributor to hepatocellular carcinoma and was attributable to 14% of cases. No excess of alcohol consumption was reported for patients with cirrhosis relative to community controls, which could represent under-reporting due to self-stigmatisation.[19]

HIV was associated with both cirrhosis and hepatocellular carcinoma and was attributable in about a fifth of cases. The association persisted among patients who were negative for hepatitis B and C, and we excluded a possible role of hepatitis E. Not receiving ART, and previous tuberculosis, were mediators of this association, suggesting a role of immunosuppression. It is possible that the observed association with HIV represents unmeasured confounding. Our findings are consistent with a case–control study from west Africa, where HIV was associated with hepatocellular carcinoma (odds ratio 2·2 [95% CI 1·0–5·8]), adjusting for age, sex, number of sexual partners, and country.[20] In a study in Zambia, liver stiffness declined significantly after a year of ART at a similar rate in people living with HIV and HBV co-infection and people with HIV monoinfection, suggesting that HIV was contributing to liver inflammation.[21] Among patients with HIV and HBV in Ghana, the magnitude of HIV viraemia was positively associated with liver stiffness.[22] In our cohort, HIV was not associated with mortality, and this result might be due to ART and clinical monitoring in the HIV programme, contrasting with the limited provision for HBV monoinfection more widely. This so-called treatment advantage for HIV co-infection has also been

described in South Africa and could explain why, in our cohort, HIV infection was associated with an increased risk of cirrhosis among the HBV-negative population, but not among people living with HBV, who benefitted from access to treatment.[23]

Several mechanisms have been proposed for the role of HIV in the development of liver disease, and the relationship we observed merits further study. HIV can enhance fibrogenesis through interactions with hepatic stellate cells, Kupffer cells, and adipocytes, resulting in a profibrotic and steatotic cellular environment.[24] ART has been associated with hepatotoxicity, particularly with non-nucleoside reverse transcriptase inhibitors including stavudine, used in first-line regimens until 2011 in Malawi.[24] An association between HIV and MASLD has been observed and a lean MASLD phenotype has been described in people living with HIV.[25] Finally, HIV infection mediates an increased risk of tuberculosis infection—this could be linked to cirrhosis by tuberculosis directly involving the liver, hepatotoxicity from tuberculosis treatment, or confounding related to diminished immune function.

We observed a late presentation of patients with hepatocellular carcinoma and a poor prognosis. Mean survival was only 5 weeks from diagnosis (representing the worst reported outcome for malignant disease) and is consistent with outcomes from The Gambia,[26] showing a clear need for public health intervention. At the time of diagnosis, over 90% of patients had a terminal stage (Barcelona Clinic Liver Cancer stage D) due to impairment of underlying liver function and portal vein involvement.

The high prevalence of hepatitis B infection we observed among patients with hepatocellular carcinoma (74% HBsAg positive and 91% having current or past infection) also represents an opportunity.[27] Interventions to interrupt hepatitis B transmission from mother to child and screening and treatment for adults could together effectively tackle the second most common cause of cancer death in men and fourth most common in women in the WHO African region.[28] Liver disease attributable to hepatitis B is projected to rise in Africa until 2040, and our study confirms the need to invest in community screening and treatment services for hepatitis B.[29] We observed poor outcomes for patients with cirrhosis, and this emphasises an urgent need to improve services, including capacity-building in hepatology, interventional radiology, and endoscopy.[30]

With urbanisation and dietary trends, the role of MASLD in causing cirrhosis in low-income and middle-income countries could be increasingly important.[31] Ultrasonographic features of fatty liver were uncommon in this cohort, although this is an insensitive measure; none had obesity, and 2% had diabetes—a rate similar to controls. We only considered current obesity in this study and past obesity might be followed by sarcopenia arising from cirrhosis, which could have masked the presence of MASLD risk factors. We did not prospectively screen for diabetes leading to underestimation. Similarly, we did not use controlled attenuation parameter or liver biopsy, factors that might have underestimated the importance of MASLD in the development of cirrhosis and hepatocellular carcinoma.

We observed a high prevalence of *S mansoni* with microbiological evidence of infection in a third of patients, and this could be an important contributor of elevated liver stiffness. Ultrasound features of hepatic schistosomiasis were present in 13% of patients with cirrhosis. Consistent with these findings, in patients from Madagascar, ultrasound had low sensitivity (16%) when compared with a liver biopsy evaluation for eliciting schistosomiasis-induced fibrosis among patients with serological evidence of exposure.[32] Hepatic schistosomiasis might mimic cirrhosis with varices and ascites, leading to misclassification, particularly where diagnostics are limited.

We identified autoimmune hepatitis and primary biliary cholangitis as uncommon but important causes of cirrhosis in this population and with a prevalence comparable to HCV. Limited availability of autoantibody testing locally presents a challenge and an argument for strengthening laboratory capability, considering the treatable nature and severe clinical course associated with autoimmune hepatitis.

This study has several limitations. First, our definitions for cirrhosis and hepatocellular carcinoma were pragmatic but due to the absence of contrast-enhanced imaging, hepatocellular carcinoma definitions could be susceptible to misclassification. We aimed to minimise this with serial imaging with experienced radiologists for indeterminate lesions. Most patients presented with extensive disease and 70% had alfa-fetoprotein levels greater than 200 ng/mL, in keeping with studies that used multiphase contrast-enhanced imaging.[33] Our requirement for clinical evidence of liver disease has increased specificity, but might have excluded patients with compensated cirrhosis. Second, we did not perform liver biopsies, which could have improved ascertainment of alternative causes of liver disease, autoimmune disease, and MASLD, and helped delineate the role of schistosomiasis. Third, our estimation of the contribution of alcohol to cirrhosis was compatible with under-reporting, and the WHO AUDIT tool does not consider the role of past heavy alcohol exposure; alcohol consumption patterns might have changed in response to the development of symptomatic liver disease. Finally, our community control populations were based in an urban population; therefore, estimates of community exposures might not fully represent the hospital catchment and we were unable to estimate PAFs for schistosomiasis using the control population (due to likely different levels of exposure to freshwater sources).

Our study has several strengths. These include the use of community control populations within the hospital

catchment area using random selection from a census to facilitate an accurate assessment of population attributable fractions for liver disease. Second, we maximised ascertainment of patients with liver disease using active case finding methods. We increased the specificity of cirrhosis and hepatocellular carcinoma case definitions, through exclusion of patients with potential reasons for falsely elevated liver stiffness. Finally, we made extensive efforts to ascertain outcomes, including home visits.

In the current study, hepatitis B was the most important cause of liver disease and is the attributable cause of a quarter of cirrhosis and over three quarters of liver cancer cases. HIV was the second most important exposure associated with cirrhosis and hepatocellular carcinoma, attributable for a fifth of overall cases. The association between HIV and liver disease was observed independently of co-infection with viral hepatitis. Patients currently present with hepatocellular carcinoma at an advanced stage when only palliative care can be offered and outcomes from cirrhosis are poor. Strengthening hepatology services and community screen-and-treat programmes for hepatitis B, following the models for HIV care, could substantially reduce the burden of liver disease in this region.

Contributors

AJS, BK, ITS, AMG, and MAG conceived the study and developed the analysis plan. AJS, BK, NMS, BM, KC, EJ, JM, and PF recruited patients and conducted study investigations. ET, CWN, ML, and ECT conducted analyses and contributed to data curation. AJS and BK performed data analysis and visualisation. PCM, EW, and MD did the laboratory analyses. All authors contributed to writing, reviewing, and editing the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

See Online for appendix

Declaration of interests

AMG reports personal fees from Abbott, Gilead Sciences, GSK, MSD, Roche, and ViiV Healthcare; and research funding (to the institution) from Gilead, Roche, and ViiV Healthcare both outside of the submitted work. EJ reports grants from Bayer PLC for ultrasound training in Ghana, outside of the submitted work. ML received speaker honoraria and related travel expenses from Roche Diagnostics and QIAGEN; and research funding from Roche, both outside of the submitted work. PCM has previously received funding from GSK to support a doctoral fellow in her team, outside the scope of this work; and receives funding from the University College London National Institute for Health and Care Research (NIHR) Biomedical Research Centre. ECT received funding from Novavax and AstraZeneca, Oxford University, and the University of Southampton outside the submitted work; and is supported by the Medical Research Council (UK; grant MC_UU_00034/6). MAG was supported by the NIHR and UK Department of Health and Social Care as a Research Professor (NIHR300039). EW, MD, and PCM are supported by core funding from the Francis Crick Institute (ref. CC2223). All other authors declare no competing interests.

Data sharing

De-identified participant data underlying the results reported in this Article, together with the study protocol and informed consent forms, will be made available on reasonable request from the corresponding author. Requests will require a data use agreement and data sharing is subject to restrictions applied by Malawi Data Protection Law and the National Health Science Research Committee of Malawi.

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