Differential Association of Hepatocellular Carcinoma Related to Hepatitis B Between Urban and Rural Areas in Africa Using Satellite Spatial Scaling Data

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ABSTRACT

PURPOSE Sub-Saharan Africa carries one of the highest burdens of hepatocellular carcinoma (HCC) in the world, with hepatitis B virus (HBV) as the most common cause. Studies in several regions of the world suggest important cancer differences in rural versus urban settings, but limited studies have been performed in Africa.

METHODS We performed a scoping review and pooled analysis of studies on HCC in Africa. Using land use data from the European Space Agency, we calculated the distance in kilometers from each study site to the nearest rural area. Regression models were fit to estimate the association between distance to the nearest rural area and HBV, sex, and weighted mean age.

RESULTS Data from 57 studies including 10,907 patients across 36 towns/cities were included in our analysis. Proximity to rural areas was associated with a higher frequency of HBV-associated HCC in assessment of distance both at midpoint and at quartiles after controlling for country: risk ratio (RR) 1.71 (95% CI, 1.52 to 1.93) and RR 1.51 (95% CI, 1.25 to 1.84), respectively. No association was found between sex and proximity to a rural area: RR 1.02 (95% CI, 0.96 to 1.08). The weighted mean age across the four distance quartiles was 50.09, 53.43, 47.98, and 53.35 years with no statistically significant difference found across the quartiles (P = .81).

CONCLUSION Individuals living in rural Africa have a higher rate of HBV-related HCC compared with other liver diseases. Increased HBV awareness efforts in these areas should be considered.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a disease of global importance with its highest burden found in sub-Saharan Africa and East Asia.[1] In Africa, HCC is a major cause of cancer and a leading cause of cancer-related deaths.[2,3] Over the past 40 years, chronic viral hepatitis B virus (HBV), a vaccine-preventable disease, has consistently been reported as the most important cause of HCC in Africa, owing to the high prevalence of chronic hepatitis B infection in the region and environmental factors unique to the continent.[4-6]

In sub-Saharan Africa where most cases of HBV-associated HCC occur, an earlier onset of HCC has been reported. This is thought to be related to earlier acquisition of HBV and environmental factors such as aflatoxin exposure.[4,7-9] Globally, there is evidence of disparities across geographic regions of resource-rich countries in the incidence and the epidemiology of cancers, including HCC.[10,11] Indeed, area of residence (rural *v* urban) has recently been found to account for important differences in the incidence of HCC in North America and Europe.[12-14] Higher incidence of HCC has consistently been found to be associated with lower-income groups, limited access to health care, poverty, higher prevalence of high-risk behaviors that contribute to suboptimal liver care, and rural populations.[15-17]

To our knowledge, very limited studies have addressed the impact of urban and rural settings related to HCC in the African continent. This information is of importance as prevention of infection-related cancers (such as HBV-related HCC) requires investment in public awareness, most of which is focused on urban areas in Africa, leaving rural settings at higher disadvantage.[18] The majority of studies reporting the epidemiology of HCC in Africa have predominantly come from large research institutions and teaching hospitals which are located in urban areas across the length and breadth of Africa.[4,5] This is of concern when

CONTEXT

Key Objective

This study examined the burden of hepatitis B virus (HBV)–related hepatocellular carcinoma (HCC) across Africa, with a focus on urban and rural disparities. Rural areas may be disproportionally affected by HBV-related HCC because of limited health care resources, lower disease awareness, and heightened exposure to environmental risk factors.

Knowledge Generated

By integrating satellite data with pooled findings from African studies (1997-2022), this analysis revealed that proximity to a rural area is associated with an increased risk of HBV-related HCC.

Relevance

These findings underscore the increased burden of HBV-related HCC in rural areas in Africa. Efforts to increase HBV awareness, screening, and treatment in rural areas should be expanded, including strategies tailored to the needs of rural communities. Additional research is needed to further examine these disparities, including patient-level data that capture patient residence and individual risk factors for HCC.

considering the growing disparity in distribution and allocation of resources between urban and rural areas on the continent, with most efforts being focused on urban areas and larger cities.[19] Moreover, uneven distribution of risk factors such as aflatoxin exposure, dietary iron overload, and alcohol can contribute to the development progression of HBV-associated HCC in a disproportionate fashion in rural versus urban areas.[4] Indeed, multiple studies have found a higher risk of early-age HCC in HBV-infected individuals when compared with HCC associated with other liver diseases, making it critical to better understand the geographic distribution of HBV-related HCC and its early occurrence/early mortality impact in Africa.[8] A better understanding of how the epidemiology of HBV-related HCC varies across urban and rural settings in Africa is important for clinicians, public health professionals, and policy-makers working in this field, which can help better stratify resources.

We performed a scoping review of studies on HCC in Africa, and using land use/land cover data available from the European Space Agency (ESA), we calculated the distance in kilometers from each study site to the nearest rural area. We then performed a pooled analysis using data from those studies to assess the association of age, sex, and HBV status with HCC between rural and urban Africa.

METHODS

Search Strategy and Selection Criteria

The search of published studies was performed by two researchers in consultation with a public health librarian who created the search strategy in Ovid MEDLINE, using controlled vocabulary and free text that focused on three concepts: HCC, HBV, and African nations. EMBASE was searched using an identical search strategy. African Journals Online (AJOL) was searched using one phrase: HCC. Publication dates were filtered from 1997 to time of search (March 4, 2022). Ovid MEDLINE, EMBASE, and AJOL were chosen on the basis of their comprehensive content of health/medical and international literature.

Observational cohort, case-control, and cross-sectional studies were eligible for analysis. Studies were included if they met all the following criteria: (1) included age distribution, sex distribution, and an estimate of the prevalence of HBV among HCC cases; (2) indicated the study location(s); and (3) described an adult patient population. Non-English language articles were only included where an English language version of the abstract was available and the abstract met inclusion criteria.

Data were manually extracted into a standardized spreadsheet by a team of two researchers overseen by the study supervisor. Minimum data extracted for all studies included study title, authors, year of publication, publication name, study location(s) (country and city/town), sample size, age distribution, sex distribution, and prevalence of HBV. In addition to the final 37 studies identified in the literature review, unpublished data from a large, multisite study (n = 20) were provided to our analysis for total data from 57 studies.[5] The Data Supplement describes the search strategy, and the Data Supplement lists the studies identified in the review.

Classification of Rural and Urban Land

Study locations were categorized according to the land use/land cover as a proxy for urban development. Land use/land cover data were obtained from the publicly available ESA sentinel imagery. The ESA provides access to the Copernicus Program which supports a broad range of services and applications such as agricultural monitoring, land cover classification, or water quality. The data are provided as raster files (grid-based data files) that are available at 10-meter resolution annually from 2017 to 2020 over the entire African continent. The data systematically categorize land use into predefined categories. One of the categories is urban/build environments. We recategorized these environments into binary urban or nonurban areas using ArcGIS software (ESRI, Redlands, CA). The reclassified data were converted to polygons. The geographic locations of study locations were spatially layered within the urban/nonurban polygons. This process indicated which of the study locations were located inside an urban area. As nearly all the study locations were in urban areas by this methodology, we then calculated the distance from the study sites to the nearest nonurban area. The range of distances were divided into four equal quartiles with shortest quartile corresponding to the most nonurban area (shortest distance from study site to rural land) and the longest quartile corresponding to the most urban areas (longest distance from study site to rural land). For greater clarity, we refer to nonurban areas as rural in our analysis.

Studies were categorized by quartile and whether the study was above or below the midpoint of distances in the study. This dual approach was chosen to provide a comprehensive understanding of the data. The midpoint comparison serves as a direct method to examine the basic dichotomy across shorter and longer distances. The quartile-based analysis allowed us to assess variations across a range of distances, revealing more subtle trends and potential nonlinear relationships that could be missed in a simpler binary comparison.

Using the land use categorization methods described above, distances of the study site to the nearest rural area ranged from 0.29 to 12.67 km (km) with a midpoint of 6.3 km. The distance quartiles were <3.2 km, 3.2-6.3 km, 6.3-9.5 km, and >9.5 km. The Data Supplement includes a summary of all the articles included in the analysis. Note that the unpublished data shared with the study team are not included in the Data Supplement.

Data Analysis

Using the percentage of males reported in each study and the prevalence of HBV reported in each study, two analytic data sets were manually created to facilitate estimating regression models—one for sex and the other for HBV. In the sex data set, the fields included study ID, a unique (dummy) patient ID, and sex (male or female). As illustration, if a study had 100 patients and the study reported that 60% of patients were male, 60 of the records for this study were categorized as male in the analytic data set. Similarly, in the HBV data set, the fields included study ID, a unique (dummy) patient ID, and HBV (yes or no). The analytic data sets were linked to study-level attributes specifically country, region, and distance to rural area. Regression models were fit to (1) estimate the association between distance to the nearest rural area and patient sex among patients with HCC and (2) estimate the association between distance to the nearest rural area and HBV among patients with HCC. Poisson regression models were used to estimate risk ratios. Poisson regression was used rather than logistic regression given that HBV is not rare in this analysis and the odds ratio generated by logistic regression would overestimate the risk ratio.[20] Studies with multiple locations were excluded from analyses because a single distance to a rural area could not be assigned to patients in the analytic data set. The weighted mean age was calculated on the basis of the reported mean age in each study taking into account sample size. In cases where median age was reported (n = 6) rather than mean age, the median value was used instead. t-tests were performed to determine if differences in mean age were statistically significant across distance categories.

A total of 10,210 patients were included in the *sex analytic data set.* We analyzed the association between sex and distance to rural areas using two models. First, we used a binary distance category where studies were classified as either being above or below the distance midpoint. Second, we used distance quartiles. A crude model was estimated followed by a model that adjusted for country. The analyses were also run separately for studies from Nigeria. This was the only country with sufficient studies and variation in distances to run the analyses at a country level.

A total of 9,911 patients were included in the *HBV analytic data set* (HBV status was unavailable for 299 patients). As with the sex analysis, two series of regression models were fit to estimate the association between distance from a rural area and HBV. First, we used a binary distance category where studies were classified as either being above or below the distance midpoint. Second, we used distance quartiles. A crude model was estimated followed by a model that adjusted for country. The analyses were also run separately for studies from Nigeria. This was the only country with sufficient studies and variation in distances to run the analyses at a country level.

The total sample size available for the age analysis was 9,507. Five studies did not report a mean or median age, but rather reported the proportion of patients in age range categories, and were excluded from the age analysis. As with the previous analyses, weighted mean age was compared across binary distance categories and across distance quartiles.

RESULTS

Population Characteristics

Nine hundred seventy-eight citations were retrieved after an electronic database search following the methodology detailed above (Fig 1). Across all studies, there were a total of 10,907 patients across 19 unique countries and 36 unique towns/cities (Figs 2 and 3). Five of the studies included multiple towns/cities (n = 697) and were excluded from the analysis because a single distance to a rural area could not be

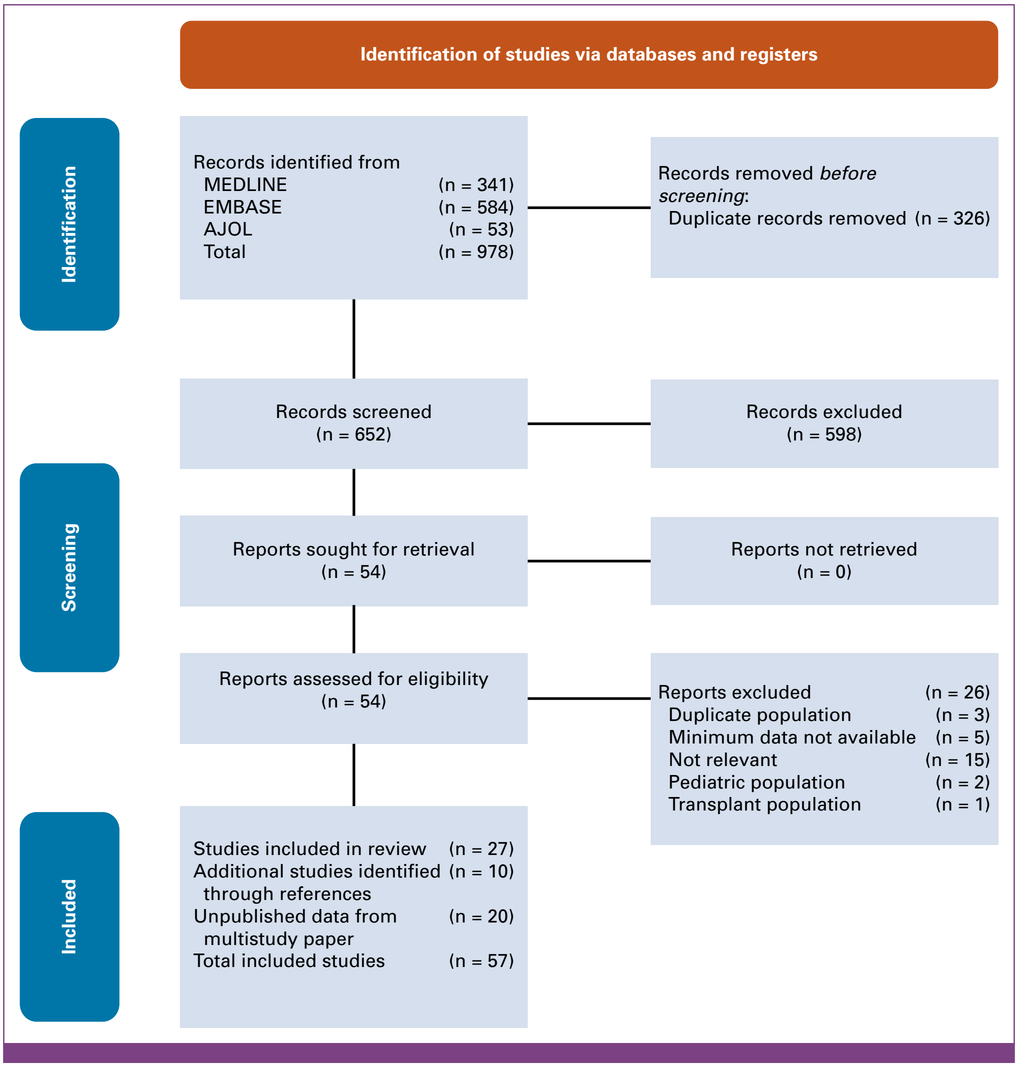

FIG 1. Flowchart of the electronic database search and study selection process. A comprehensive search of Ovid MEDLINE, EMBASE, and AJOL was conducted, focusing on HCC, HBV, and African nations. A total of 978 articles were identified initially. Duplicate records (n = 326) were removed, and titles/abstracts (n = 598) were screened for relevance. After excluding 26 full-text articles, 27 studies remained. A reference review added 10 more studies, and unpublished data from a large, multisite study were provided to us (n = 20), for a total of 57 studies. AJOL, African Journals Online; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

assigned to patients in the analytic data set. Mean ages across all studies ranged from 32.00 years to 65.40 years with a crude mean age of 49.04 years and a weighted mean age of 52.47 years across all studies. Seventy-four percent of patients were male, and 32% had HBV with a substantial regional variation. Among the studies conducted in northern Africa included in our analysis, 14.4% of patients with HCC were positive for HBV compared with 59.8% of patients with HCC in studies conducted in western Africa.

Sex, HCC, and Proximity to Rural Settings

We found no association between sex and distance to the nearest rural area across any of the analyses after controlling for country (Table 1). Similarly, when comparing studies located in the quartile furthest from an urban area (>9.5 km) with studies in the other three distance quartiles (6.3-9.5 km, 3.2-6.3 km, and <3.2 km), there were no associations between sex and distance across any of the comparisons: risk ratio (RR) 0.96 (95% CI, 0.76 to 1.19), RR 1.01 (95% CI, 0.95 to 1.07), and RR 1.05 (95% CI, 0.90 to 1.22), respectively.

HBV-Associated HCC and Proximity to Rural Settings

We found a statistically significant association between HBV-associated HCC and distance to the nearest rural area in both analyses (Table 2). Patients in studies located closer to rural areas (<6.3 km) had 1.71 times higher risk of HBV-HCC (95% CI, 1.52 to 1.93) compared with patients in studies

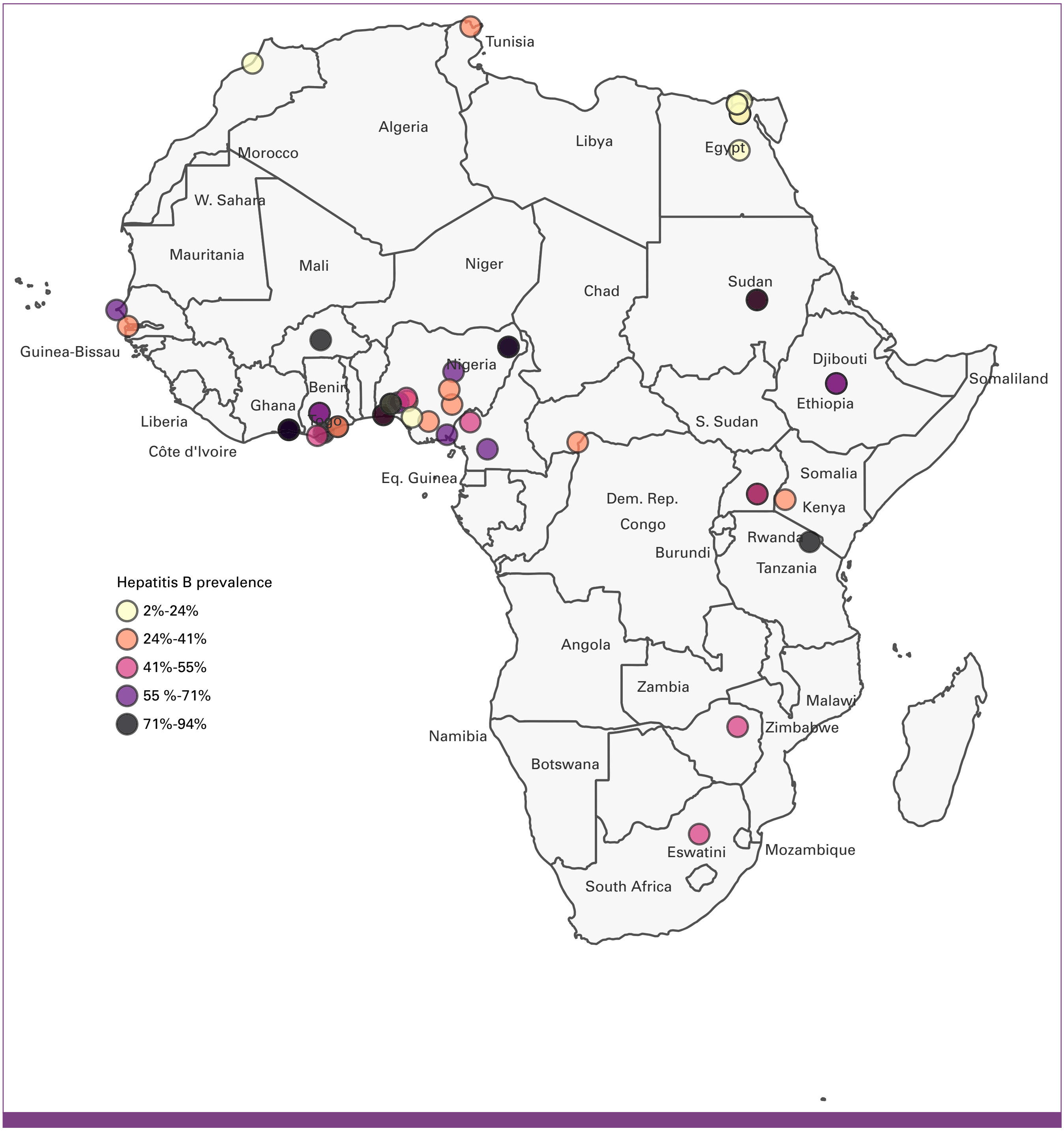

FIG 2. Prevalence of hepatitis B in studies included in the analysis. The map displays the prevalence of hepatitis B reported in the studies included in the analysis, ranging from 2% to 94%. Symbols are color-coded to represent prevalence levels, with lighter colors indicating lower prevalence and darker colors indicating higher prevalence. The lowest prevalence was observed in North Africa, whereas the highest prevalence was concentrated in West Africa.

located farther from rural areas (>6.3 km) after controlling for country. Similarly, when assessing quartiles, locations nearest to a rural area (<3.2 km) had 1.51 times higher risk of HBV-HCC (95% CI, 1.25 to 1.84) compared with patients in locations furthest from a rural area (>9.5 km) after controlling for country. When looking only at studies in Nigeria (the only country with sufficient studies and variation in distances to run the analyses at a country level), patients in studies located closer to rural areas (<6.3 km) had 1.25 times higher risk of HBV-related HCC (95% CI, 1.03 to 1.51) compared with patients in studies located farther from rural areas (>6.3 km).

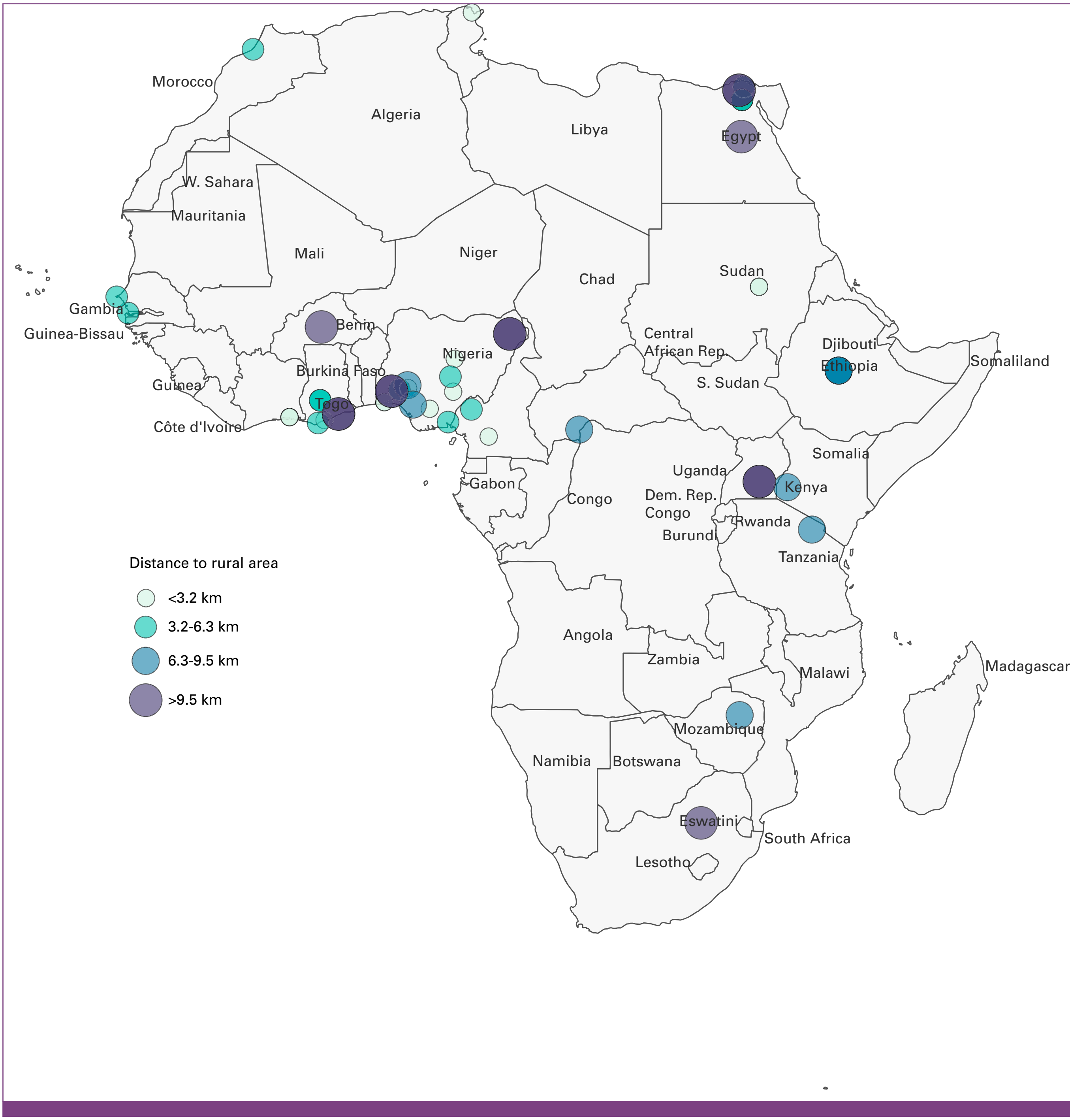

FIG 3. Distance of study to nearest rural area. The map displays the distance of each study site to the nearest rural area, categorized into quartiles. Distances ranged from 0.29 to 12.67 km with a midpoint of 6.3 km. Quartiles are represented as follows: <3.2 km, 3.2-6.3 km, 6.3-9.5 km, and >9.5 km. The size of the circles corresponds to the quartile, with larger circles indicating greater distances to the nearest rural area.

Assessment Between Age, HCC, and Proximity to Rural Settings

The weighted mean age for studies further and closest from midpoint was similar, 52.22 years and 52.57 years for studies above and below the midpoint of 6.3 km, respectively (P = .81). For each of the distance quartiles (3.2 km, 3.2-6.3 km, 6.3-9.5 km, and >9.5 km), the weighted mean age across the four quartiles was 50.09, 53.43, 47.98, and 53.35 years, respectively. When comparing the mean age for the >9.5-km quartile with the other three quartiles, no differences were statistically significant across any comparisons, suggesting no substantial association between age and proximity to rural areas. There was, however, a trend

TABLE 1. Regression of Sex and Distance to Nearest Rural Area

	Unadjusted—All Studies (n = 10,210)			Adjusted—All Studies (n = 10,210)			Nigeria Only (n = 953)		
Reference: >6.3 km	Rate Ratio	95% CI	*P*	Rate Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*
<6.3 km	1.01	0.96 to 1.06	.62	1.02	0.96 to 1.08	.54	1.04	0.89 to 1.21	.65

	Unadjusted—All Studies (n = 10,210)			Adjusted—All Studies (n = 10,210)			Nigeria Only (n = 953)		
Reference: >9.5 km	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*
6.3-9.5 km	0.89	0.80 to 0.99	.03	0.96	0.76 to 1.19	.68	0.94	0.74 to 1.20	.64
3.2-6.3 km	1.00	0.95 to 1.06	.92	1.01	0.95 to 1.07	.67	1.00	0.80 to 1.24	.98
<3.2 km	0.95	0.89 to 1.02	.18	1.05	0.90 to 1.22	.55	1.03	0.85 to 1.25	.77

toward younger age HCC in studies closer to rural areas compared with those furthest from rural areas, 50.09 versus 53.35 years, respectively, but it was not statistically significant ($P = .40$).

DISCUSSION

Our study, to our knowledge, a first of its kind using pooled analysis and satellite data to address cancer differences in Africa, found that proximity to rural areas was associated with an increased risk of HBV-associated HCC after controlling for country. This association was found both when comparing studies above and below the midpoint of distances to rural settings and across distance quartiles. Locations <6.3 km from a rural area (midpoint) had 1.71 times higher risk of HBV-HCC compared with patients in locations 6.3 km or greater from a rural area after controlling for country. Similarly, locations nearest to a rural area (<3.2 km) had 1.51 times higher risk of HBV-HCC compared with patients in locations furthest from a rural area (>9.5 km) after controlling for country. No association was found between sex or age and proximity to a rural area.

Our study found notable differences in the prevalence of HBV among patients with HCC across regions in Africa, which is unsurprising given the greater burden of HBV in sub-Saharan Africa and the higher prevalence of hepatitis C in northern Africa. Among studies conducted in northern Africa included in our analysis, 14.4% of patients with HCC were positive for HBV compared with 59.8% of patients with HCC in studies conducted in western Africa.

While most of the studies in our analysis did not report the percentage of patients residing in rural areas, some studies reported data on HCC patterns across levels of urbanization. Two studies of patients with HCC in Tanta, Egypt, found that between 85% and 90% of HCC cases in their study resided in rural regions.[21,22] Similarly, in sub-Saharan Africa, a study in Ido-Ekiti, Nigeria, found that most of the patients with HCC resided in rural/semiurban communities.[23] Moreover, a study performed in South Africa found that the relative risk of HCC was elevated when comparing farmers with nonfarmers, those with pesticide exposure with those without pesticide exposure, and those with schistosoma infection with those without.[24] All these factors speak of a higher environmental and infectious disease burden in populations that live closer to rural areas in the continent.

The primary limitation of our study is the lack of patient-level residence information and other characteristics at the individual patient level such as vaccination history, comorbidities, socioeconomic factors, and other known risk factors for HCC such as aflatoxin or dietary iron overload. Our analysis used study location and proximity to a rural area as a proxy for the patient-level residence. Patients, particularly those in rural areas, may travel to seek care at facilities that are not necessarily close to where they live. Using study location as a proxy for patient-level residence can introduce

TABLE 2. Regression of Hepatitis B Virus and Distance to Nearest Rural Area

	Unadjusted—All Studies (n = 9,911)			Adjusted—All Studies (n = 9,911)			Nigeria Only (n = 902)		
Reference: >6.3 km	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*
<6.3 km	1.48	1.37 to 1.61	<.001	1.71	1.52 to 1.93	<.001	1.25	1.03 to 1.51	.027

	Unadjusted—All Studies (n = 9,911)			Adjusted—All Studies (n = 9,911)			Nigeria Only (n = 902)		
Reference: >9.5 km	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*
6.3-9.5 km	2.02	1.73 to 2.36	<.001	1.00	0.72 to 1.41	.95	0.80	0.56 to 1.13	.20
3.2-6.3 km	1.33	1.20 to 1.47	<.001	1.77	1.56 to 2.02	<.001	1.31	1.02 to 1.68	.034
<3.2 km	3.12	2.80 to 3.48	<.001	1.51	1.25 to 1.84	<.001	1.06	0.83 to 1.36	.62

misclassification bias, potentially diluting or inflating the observed associations between distance to the nearest rural area and HBV, sex, and age. Future studies with more precise data on patient residence are needed to further validate these findings.

Our study also relied on existing data, which introduces several limitations. First, there was limited variation in distance categories within regions and within countries. This limited our ability to study associations within more granular geographic areas such as the country level, which was only possible for studies conducted in Nigeria. Second, our study pooled analysis across multiple studies conducted by different study teams across different institutions. Despite these limitations, our study leveraged existing studies and took the next step of attempting to quantify the association between proximity to a rural area and risk of HBV-related HCC previously reported in these studies.

While urbanization in Africa has increased over the past several decades, only 50% of the population across the African continent lives in an urban area with a substantial variation across regions.[25] For example, nearly 80% of the population in North Africa lives in an urban area compared with <40% of the population in East Africa.[25] Understanding the burden of HBV-related HCC among rural populations compared with urban populations in Africa is an important epidemiologic consideration.[26] Rural areas in Africa may experience higher rates of HBV because of a number of possible factors, including limited access to HBV vaccination, screening, and awareness campaigns compared with urban areas. Communities in rural areas may also experience an increased risk of HBV infection through unsafe injection equipment reuse in resource-limited settings and more frequent exposure to aflatoxin and dietary iron overload compared with communities in urban areas.[27-29] Evidence of these differences in risk factors has been found in studies showing that rural-born and rural-residing patients with HCC are diagnosed with HCC earlier than urban-born and urban-residing patients with HCC.[30]

These findings underscore the importance of investing resources to increase hepatitis B awareness, testing, and vaccination in rural areas where access may be limited and the burden of HBV-related HCC may be particularly high. Unfortunately, in regions where HBV programs exist, the majority are in urban settings, leaving rural communities underserved.[19] While communities living in rural areas may traditionally be more difficult to reach, it is imperative that rural communities are not overlooked and that these communities are specifically targeted for life-saving HBV vaccination, screening, and awareness campaigns. Initiatives should be tailored to meet the needs of rural communities. Awareness campaigns should be designed carefully with culturally sensitive messages that align with the knowledge levels of communities.[31] Mobile clinics for point-of-care testing and vaccination can reach communities that might not otherwise have access to health care facilities.[32] Education and empowering community health workers can help bridge gaps, particularly for pregnant women in rural areas who may give birth at home.[33]

Further research is needed to understand the burden of HBV-related HCC in Africa across rural and urban areas. Future research should include primary data collection with patient-level variables—such as patient residence, vaccination status, and other HCC risk factors—to validate and extend the results of this pooled analysis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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