

Viral Hepatitis Among Somali Immigrants in Minnesota: Association of Hepatitis C With Hepatocellular Carcinoma

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Abstract

Objective: To study the frequencies of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, and their associations with hepatocellular carcinoma (HCC) in immigrant Somalis seen at Mayo Clinic in Rochester, Minnesota. **Patients and Methods:** We determined the frequencies of HBV and HCV infection and HCC in immigrant Somalis seen at Mayo Clinic from July 1, 1996, through October 31, 2009. Non-Somali Olmsted County residents served as controls. **Results:** For Somali males and females, age-adjusted proportions (per 1000 population) were 209 and 123 for hepatitis B surface antigen (HBsAg), 644 and 541 for hepatitis B core antibody (HBcAb), and 99 and 66 for anti-HCV. The comparative proportions in non-Somalis were 20 and 9 for HBsAg, 126 and 97 for HBcAb, and 32 and 17 for anti-HCV. Hepatitis C virus RNA confirmed that 68 of 73 Somalis (93.2%) and 261 of 282 non-Somalis (92.6%) with positive anti-HCV test results had active HCV infection. Of 30 Somali patients with HCC, 22 (73.3%) tested anti-HCV positive (odds ratio [OR], 31.3; 95% confidence interval [CI], 13.0-75.5; *P*<.001; compared with anti-HCV-negative Somalis), 5 (16.7%) were HBsAg positive (OR, 1.4; 95% CI, 0.5-3.7; *P*=.53), and 18 (60.0%) were HBcAb positive (OR, 1.8; 95% CI, 0.8-4.2; *P*=.16). Viral hepatitis was diagnosed coincident with HCC in 9 of 20 patients (45.0%) with HCV-associated HCCs. Only 4 of 24 cases of HCC (16.7%) were detected during surveillance.

Conclusion: Both HBV and HCV occurred frequently in this sample of Somali immigrants. However, HCV was the major risk factor for HCC. Screening Somali immigrants for HCV infection may enhance the prevention, early detection, and optimal treatment of HCC.

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nfections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common risk factors for hepatocellular carcinoma (HCC) worldwide, with up to 78% of HCCs attributable to HBV (53%) or HCV (25%).1 In the United States, HCV has contributed to a significant proportion of the increase in HCC incidence and HCC-related mortality in the past 30 years.²⁻⁷ The overall prevalence of hepatitis B surface antigen (HBsAg) carriers in the United States is 0.2%,8 whereas the prevalence of HCV exposure as detected by anti-HCV antibody is approximately 1.6%, and active infection as detected by HCV RNA is approximately 1.3%.9 In contrast, the HBsAg prevalence in sub-Saharan Africa ranges from 8% to 15%, 10,11 whereas the prevalence of HCV in sub-Saharan Africa ranges from 0.1% to 13.8%.12

Since 1990 immigration from sub-Saharan Africa to the United States has increased substantially. The 2000 US Census estimated the number of immigrant Somalis in Minnesota at 25,000. However, current estimates now approach 50,000. Somalia is

in a high prevalence region for HBV but has not been reported to have a high prevalence of HCV infection. No studies on the epidemiology of viral hepatitis in Somalia have been reported since 1992, and few data are available on HBV and HCV prevalence among Somalis who have immigrated to Europe and North America. A 1992 study of the prevalence of serologic markers for HBV and HCV in 596 children in a residential institution in Somalia reported a prevalence of 16% for HBsAg and 1.5% for anti-HCV.13 Another study of 62 Somali patients with chronic liver disease, including primary HCC, showed prevalences of 37.1% for HBsAg and 40.3% for anti-HCV.14 With regard to Somali immigrants, a survey of Somalis in Liverpool, England, found prevalences of 5.7% and 27.5% for HBsAg and hepatitis B core antibody (HBcAb), respectively. 15 A population-based study using the Rochester Epidemiology Project found 191 residents of Olmsted County, Minnesota, with chronic HBV infection, of whom 55 (28.8%) were African immigrants. 16 Al-



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though country of origin was not ascertained in this study, on the basis of the county demographics, the African immigrants were presumably mostly Somalis. Another study of the seroepidemiology of HBV among 12,505 new refugee immigrants to Minnesota between 1998 and 2001 found a prevalence of chronic HBV infection of 7.1%. Africans were 3 times more likely and Asians 2.4 times more likely to be infected than European immigrants. ¹⁷

Immigrants from high prevalence areas are at risk for the complications of HBV and HCV infections, including HCC, and may face health disparities in the diagnosis and management of these infections and complications. Therefore, we studied a sample of Somali immigrants in Minnesota to determine the proportions with chronic HBV infection or prior exposure (as determined by HbsAg and HBcAb serologic testing) and with chronic HCV infection (as determined by anti-HCV serologic testing and HCV RNA testing) and the associations of these infections with HCC. We also investigated the proportion of patients who were diagnosed as having viral hepatitis at the time of HCC diagnosis and the proportion of patients who were in a surveillance program at the time of diagnosis of HCC. The goals of the study were (1) to estimate the proportion of Somali immigrants seen at Mayo Clinic in Rochester, MN, who had positive HBV and HCV test results and (2) to determine the association of HBV and HCV infection with HCC in Somali immigrants and the timing of HBV, HCV, and HCC diagnosis among HCC patients in the Somali immigrant population.

PATIENTS AND METHODS

Identification of Study Participants

We searched the Mayo Clinic Life Sciences System (MCLSS) database from July 1, 1996, through October 31, 2009, to identify all Somali patients seen at Mayo Clinic who had tests performed for HBV or HCV infection or who were diagnosed as having HCC during the study period. We used Boolean combinations, namely conjunction (AND), disjunction (OR), and negation (NOT), to detect the different combinations of the International Classification of Diseases, Ninth Revision codes for HBsAg, HBcAb, anti-HCV, and HCC. The MCLSS was then used to query the medical record database to detect the words Somali, Somalian, or Somalia in the patients' clinical notes. The medical records of patients included in this study were compiled by 3 of the authors (A.M.S., J.K.K., and D.S.S.). To further confirm the ethnicity of identified patients, medical records of these patients were screened by 2 authors (A.M.S. and N.H.G.), who are both of Somali heritage. Individuals from Olmsted County, Minnesota, who were confirmed as not being Somali (nonSomalis) were used for the comparison group. Olmsted County has 90% white residents.

Validation of HCC

The information on HCC determined from the MCLSS was complemented and verified using data from the Mayo Clinic Cancer Registry and the Mayo Hepatobiliary Neoplasia Registry. Hepatocellular carcinoma was diagnosed on the basis of histopathologic or noninvasive criteria. The following criteria were used for the noninvasive diagnosis of HCC: (1) a newly developed, enhancing lesion larger than 2 cm identified by 2 or more of the following 3 imaging modalities in a patient with cirrhosis: contrast computed tomography (CT), contrast magnetic resonance imaging (MRI), or hepatic angiography; or (2) a newly developed, enhancing lesion larger than 2 cm identified by the presence of a serum α -fetoprotein level greater than 200 ng/mL (to convert to μ g/L, multiply by 10) and 1 of the following 3 imaging modalities in a patient with cirrhosis: contrast CT, contrast MRI, or hepatic angiography.

Medical records of patients with HCC were reviewed for confirmation of HCC diagnosis and mode of HCV, HBV, and HCC diagnosis. Hepatocellular carcinoma was considered to be detected during surveillance if imaging such as abdominal ultrasonography, CT, or MRI was obtained within 1 year before the diagnosis of HCC.

Statistical Analyses

The overall age distribution of the Somali and non-Somali Olmsted County residents (used as controls) was expected to differ. Hence, the primary summarization of rates is as age-adjusted values, using the US 2000 total population as the reference distribution. ^{18,19} Briefly, the overall rate is a weighted mean of the observed rates in each group, weighted by the fraction of the US population at that age rather than by the fraction of the sample who were of that age. Because of the small number of study participants at the oldest and youngest ages, we standardized to the 20- to 70-year-old cross-section. To avoid potential referral bias, the reference group was limited to patients from southeastern Minnesota.

RESULTS

Proportion of Somalis and Non-Somalis With HBV and HCV Infections

For Somalis, the rates for each age and sex group are given in Table 1 along with the age-adjusted rate for each test. The age-adjusted positive rate for HBsAg was 20.9% in males compared with 12.3% in females, the age-adjusted positive rate for HBcAb (evidence of prior HBV exposure) was 64.4% in males

Age group (y)	HBsAg-positive/ total males (No.)	HBsAg-positive/ total females (No.)	HBcAb-positive/ total males (No.)	HBcAb-positive/ total females (No.)	Anti-HCV-positive/ total males (No.)	Anti-HCV-positive/total females (No.)
≤20	7/90	4/74	12/54	7/32	0/63	0/41
21-30	21/115	20/158	48/88	36/90	1/97	0/101
31-40	13/67	18/196	36/60	40/85	0/67	0/99
41-50	12/62	11/102	36/53	33/63	6/58	3/75
51-60	16/55	6/49	38/50	31/42	11/55	11/49
61-70	3/23	10/38	14/19	26/32	11/24	6/42
>70	7/44	3/36	33/39	18/28	20/49	9/34
Total	79/456	72/653	217/363	191/372	49/413	29/441
Age-adjusted frequency (per						
1000 population)	209	123	644	541	99	66

compared with 54.1% in females, and the age-adjusted positive rate for anti-HCV was 9.9% in males compared with 6.6% in females. Of 78 Somali patients with positive anti-HCV serologic test results, 73 had been tested for HCV RNA. Of the 73 patients tested, 68 (93.2%) had positive HCV RNA test results. Of the 68 Somali patients with positive HCV RNA, 22 (32.4%) of them gave a history of receiving a blood transfusion, surgery, or both in Somalia or Kenya (a country in which most Somalis immigrating to the United States spent time as refugees).

Data from non-Somali Olmsted County residents who were tested during the same period were used for comparison. The age-adjusted rates for HBV and HCV infection in the non-Somali population (Table 2) were substantially lower than for the Somalis. The age-adjusted positive rate for HBsAg

was 2.0% and 0.9% in male and female controls (vs 20.9% and 12.3% in Somalis), whereas the age-adjusted positive rate for HBcAb was 12.6% and 9.7% in male and female controls (vs 64.4% and 54.1% in Somalis). The age-adjusted positive rate for anti-HCV was 3.2% and 1.7% in male and female controls (vs 9.9% and 6.6% in Somalis). Of 282 non-Somali patients with positive anti-HCV serologic test results, all had been tested for HCV RNA. Of these 282 patients tested, 261 (92.6%) had positive HCV RNA test results.

Age and Sex Group Characteristics of HBV and HCV Infections in Somalis and Non-Somalis

Age- and sex-specific rates showed differences across the range of ages for both the male-female and

TABLE 2. Frequency of HBV- and HCV-Positive Test Results in Non-Somali Patients from Olmsted County, Minnesota						
Age group (y)	HBsAg-positive/ total males (No.)	HBsAg-positive/ total females (No.)	HBcAb-positive/ total males (No.)	HBcAb-positive/ total females (No.)	Anti-HCV-positive/ total males (No.)	Anti-HCV-positive/ total females (No.)
≤20	7/254	4/718	16/153	11/278	1/243	4/419
21-30	15/960	26/3821	43/506	58/907	10/1113	12/1912
31-40	43/1401	25/3519	114/815	103/878	32/1485	27/1616
41-50	31/1209	11/1252	112/772	77/745	73/1245	42/1265
51-60	8/883	14/870	81/615	54/577	48/883	12/938
61-70	4/509	3/453	40/350	40/329	9/494	5/445
>70	0/285	3/321	24/180	23/218	2/276	5/320
Total	108/5501	86/10,954	430/3391	366/3932	175/5739	107/6915
Age-adjusted frequency (per						
1000 population)	20	9	126	97	32	17
HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.						

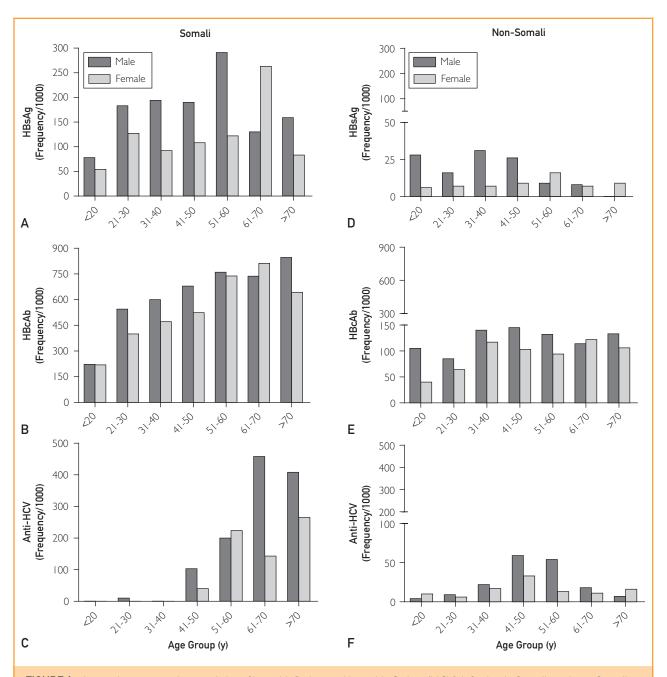


FIGURE 1. Age and sex group characteristics of hepatitis B virus and hepatitis C virus (HCV) infection in Somalis and non-Somalis. Both Somalis and non-Somalis were divided into 10-year age groups by sex. A and D, Hepatitis B surface antigen (HBsAg) frequency for Somalis and non-Somalis, respectively. B and E, Hepatitis B core antibody (HBcAb) frequency for Somalis and non-Somalis, respectively. C and F, Anti-HCV frequency for Somalis and non-Somalis, respectively.

Somali-control comparisons (Figure 1). The highest proportion of HBsAg (29.1%) in Somalis was in 51-to 60-year-old men; in females the highest proportion (26.3%) was in the 61- to 70-year age group. The peaks of HBsAg positivity in non-Somalis were in the 31- to 40-year age group for males (3.1%) and

in the 51- to 60-year age group for females (1.6%). For all non-Somali age groups except the 51- to 60-year age group, males had higher HBsAg positivity than females (Figure 1D). There were no HBsAg positive men in the older than 70-year age group. For HBcAb, the peak in Somali males (84.6%) oc-

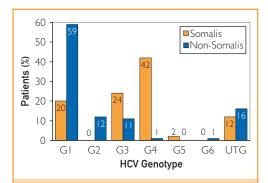


FIGURE 2. Hepatitis C virus (HCV) genotypes found in Somalis and non-Somalis. Significant differences were observed in the HCV genotype distribution pattern among Somalis vs non-Somalis. UTG = unable to genotype.

curred in the older than 70-year age group and for Somali females (81.3%) in the 61- to 70-year age group (Figure 1B). For HBcAb in non-Somalis, the highest proportions were seen in the 41- to 50-year age group for males (14.5%) and in the 61- to 70-year age group for females (12.2%) (Figure 1E). For anti-HCV in Somalis, only 1 individual (a male) had a positive test result in the first 4 decades. Anti-HCV positivity peaked in the 61- to 70-year age group for males (45.8%) and in the older than 70-year age group for females (26.5%) (Figure 1C). For anti-HCV in non-Somalis, the proportions in both sexes peaked in the 41- to 50-year age group, at 5.9% for males and 3.3% for females (Figure 1F).

HCV Genotypes of Somalis and Non-Somalis

We found significant differences in the HCV genotype distributions between Somalis and non-Somalis (Figure 2). In Somalis, genotype 4 was the most frequent HCV genotype (17/41; 41.5%), followed by genotype 3 (10/41; 24.4%), genotype 1 (8/41; 19.5%), and genotype 5 (1/41; 2.4%). Five (12.2%) of 41 viruses could not be genotyped and were designated as unable to genotype (UTG) (P<.001 between Somalis and non-Somalis when comparing genotype 4 to all other genotypes and the UTG group; χ^2 test). In non-Somalis, genotype 1 was the most frequent genotype (186/314; 59.2%), followed by genotype 2 (38/314; 12.1%), genotype 3 (34/ 314; 10.8%), genotype 6 (3/314; 0.9%), and genotype 4 (2/314; 0.6%). Fifty-one (16.2%) of 314 were UTG (P<.001 between Somalis and non-Somalis when comparing genotype 1 with all other genotypes and the UTG group; χ^2 test). None of the Somalis had HCV of genotype 2 or 6, and none of the non-Somalis had HCV of genotype 5.

Risk Factors for HCC in Somalis

We investigated the association of HBsAg, HBcAb, and anti-HCV positive test results with the development of HCC in the 30 Somali patients with HCC (Table 3). Somali patients with a negative result for each marker were used as the reference group. Not all of the 30 Somali HCC patients had complete results for all 3 markers: 28 had an HBsAg result, 26 had an HBcAb result, and 29 had an anti-HCV result. The strongest association with HCC was observed with HCV infection, with an odds ratio (OR) of 31.3 (95% confidence interval [CI], 13.0-75.5; P<.001). The OR for HCC in HBsAg-positive individuals was 1.4 (95% CI, 0.5-3.7; P=.53), and for HBcAb-positive individuals the OR was 1.8 (95% CI, 0.8-4.2; P=.16). Of the 22 HCC patients with HCV infection, only 8 had an HCV genotyping result; 6 of the 8 (75.0% of the available HCV genotypes in HCC patients) were genotype 4, whereas 2 (25.0% of the HCV genotypes in HCC patients) were genotype 3.

TABLE 3. Risk Factors Associated With Hepatocellular Carcinoma in Somali Patients Treated at Mayo Clinic						
Risk factor	Cases, No. (%)	Controls, No. (%)	OR (95% CI)	P value		
HBsAg positive	5 (17.9)	151 (13.6)	1.38 (0.52-3.69)	.53		
HBsAg negative	23 (82.1)	959 (86.4)	I (Reference)			
HBcAb positive	18 (69.2)	408 (55.5)	1.80 (0.77-4.20)	.16		
HBcAb negative	8 (30.8)	327 (44.5)	I (Reference)			
Anti-HCV positive	22 (75.9)	78 (9.1)	31.3 (12.95-75.52)	<.001		
Anti-HCV negative	7 (24.1)	776 (90.9)	I (Reference)			

TABLE 4. Time of Diagnosis of HBV, HCV, and HCC in Somali Patients						
Time of diagnosis	HCV, No. (%) (n=23)	HBV, No. (%) (n=5)	Total, No. (%)			
Diagnosis of HBV or HCV before HCC assessment	11/20 (55.0)	3/4 (75.0)	14/24 (58.3)			
Diagnosis of HBV or HCV on HCC assessment	9/20 (45.0)	1/4 (25.0)	10/24 (41.7)			
Diagnosis of HCC during surveillance	4/20 (20.0)	0/4 (0)	4/24 (16.7)			
HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus.						

Mode of Diagnosis of HBV, HCV, and HCC in Somalis

Of the 30 Somali patients with HCC, 3 were both HBsAg and anti-HCV negative and were not included in Table 4. One patient who was both HBsAg and anti-HCV positive was included in both the HCV and HBV groups. More than 40% of patients were diagnosed as having viral hepatitis at the time of HCC diagnosis; this proportion was higher in patients with HCV (45.0%) than with HBV (25.0%). For HCV patients, HCC was diagnosed during surveillance in 20.0% of patients, whereas none of the HBV patients was diagnosed as having HCC during surveillance (Table 4). None of these HBV patients had been treated before presenting to the clinic, and all were at terminal stages when seen at the clinic.

DISCUSSION

Analyses of the global distribution of chronic HBV infection have categorized regions based on HBsAg prevalence into low (<2%), intermediate (2%-7%), and high (≥8%) prevalence regions.²⁰ Following Centers for Disease Control and Prevention (CDC) and American Association for the Study of Liver Diseases guidelines, the Minnesota Department of Health screens immigrants arriving from intermediate and high HBV prevalence countries for HBV infection. Hepatitis B virus testing of sub-Saharan African primary refugees arriving in Minnesota between 2004 and 2009, a substantial proportion of whom are Somalis, showed a mean HBV prevalence of 7% (www.health.state.mn.us). Our finding of high adjusted HBsAg proportions in a sample of Somali immigrants is consistent with this. Importantly, we also found high proportions of anti-HCV positive test results among Somalis (10.3% in males and 6.7% in females). Hepatitis C virus RNA testing confirmed that 93% of Somalis with positive anti-HCV serologic test results had active HCV infection. The high anti-HCV positive rate found in Somali males is within the high prevalence category (>10%) of the global HCV distribution; however, in the global HCV distribution maps, Somalia is currently placed in the low prevalence category (1%-2.5%). ²¹ Given the reported low HCV prevalence in Somalia and sub-Saharan Africa, unlike the recommendations for HBV testing, there has been no formal recommendation for screening immigrants from this region for HCV infection.

For both Somalis and non-Somalis, males almost always have higher proportions of both HBV and HCV infection than females. For all 3 markers, HBsAg, HBcAb, and anti-HCV, peak frequencies were in later age groups in Somalis compared with the control group. This may be due to several factors, including the epidemiology of these infections (mode of transmission and viral characteristics), biologic differences among races, and health disparities between Somalis and the control group. We found 11 individuals with chronic HBV who were 20 years or younger; it is plausible that these individuals were born outside the United States and did not receive HBV vaccination at birth. Although differences have been shown in chronic HBV rates among immigrants compared with Olmsted County residents, more work is needed to understand the extent of the HBV and HCV disparities in this immigrant population. 16 Strategies designed to prevent and control viral hepatitis and its complications must also address significant disparities in morbidity and mortality associated with chronic HBV and HCV infections among different subpopulations in the United States.

In this study, we had expected to find that HBV infection was the major risk factor for HCC in Somalis, as is typically the case in sub-Saharan Africa. Indeed, the proportion of HBsAg in Somalis was higher than that of anti-HCV positivity (14% vs 10.0%), but the chronic HBV seropositivity rate in HCC patients was lower than that of HCV. Consequently, HCV seropositivity was found to have the strongest association with HCC in Somalis (OR, 31.3), making HCV the primary viral cause of HCC in this Somali sample. Although the OR had wide CIs due to the relatively small number of HCC cases, the association is so strong that it is likely to be

validated in larger studies. Because of unavailability of HCV genotype in all 30 Somali HCC patients, it could not be conclusively determined whether a particular HCV genotype was more closely associated with HCC in Somalis. However, 6 of the 22 HCC patients with HCV infection had HCV genotype 4 infection and 2 had HCV genotype 3.

In addition to a high proportion of HBsAg-positive individuals, our study showed high rates of anti-HCV positivity in Somalis, confirmed by HCV RNA testing. The possible explanations for the high HCV infection rates are (1) transfusion of blood not screened for HCV, (2) hospital procedures performed without standard infection precautions, and (3) reuse of syringes and needles by paramedical workers. Epidemiologic studies in Egypt have shown an association between a history of receiving injections for the treatment of schistosomiasis and HCV infection.²² Similar risk factors may explain the spread of HCV infection in Somalia because during the 1970s and 1980s many people were vaccinated with the BCG vaccine, and needles and syringes may have been reused during the vaccination campaign.

In 2008, the CDC published recommendations for screening individuals for HBV infection,²³ but there are no specific policies from the CDC, American Association for the Study of Liver Diseases, Minnesota Department of Health, or any other relevant agencies for HCV screening of immigrants. Although the significance of chronic HBV and HCV infections among at-risk people and different subpopulations in the United States has been recognized,^{24,25} immigrants or refugees are not yet specifically identified as being in a high-risk category requiring screening for HCV. Our new data show a high proportion of anti-HCV positivity, confirmed by HCV RNA, in Somali immigrants in Minnesota and a strong association with HCC in this population. In a substantial proportion of cases the diagnosis of HCV infection was made at the time of HCC diagnosis, and the opportunity to enroll patients in a surveillance program to allow detection of HCC at an early stage was missed. Consequently, only a few HCCs were detected during surveillance in this population. Significant differences were also observed in the HCV genotypes isolated from Somalis vs non-Somalis. Because there are a growing number of newly identified chronic HCV cases each year in Minnesota, it is important to confirm our observations in additional studies. In particular, this study is subject to potential selection bias because of the likelihood that individuals with clinically concerning elevations in levels of liver enzymes would preferentially be subject to screening. These individuals would also be more likely to have severe disease and a higher risk of HCC. It is important to perform

population-based studies with random screening of the immigrant Somali population using both anti-HCV and HCV RNA testing to determine the true prevalence of HCV infection in the population. These additional studies could address other potentially significant factors not addressed in this study, including the relevance of time spent in Somalia or in refugee camps in neighboring states in determining the risk of HCV infection and the importance of aflatoxin exposure in determining risk of HCC. The Institute of Medicine also made 4 major recommendations to address the persistent transmission of HBV and HCV within the population and the incomplete identification and medical treatment of individuals with chronic viral hepatitis: (1) improvements in surveillance for HBV and HCV infections; (2) programs to improve knowledge and awareness, especially for at-risk individuals; (3) improvements in HBV vaccine coverage; and (4) improvements in access to services for viral hepatitis patients.²⁴ If our findings are confirmed, it would be appropriate to recommend that immigrants and refugees from high-risk regions be screened for HCV on entry into the United States and that appropriate therapy for anti-HCV-positive individuals and/or regular surveillance for those at risk for HCC be instituted to reduce the long-term morbidity and mortality due to this virus.

CONCLUSION

This retrospective, clinic- and hospital-based pilot study of HBV and HCV infection among Somalis conducted at Mayo Clinic produced important evidence of high frequencies of chronic HBV and HCV among this new immigrant population to the United States. Somalis showed higher frequencies of HBV and HCV than non-Somali residents of Olmsted County. Genotype 4 was the predominant HCV genotype in Somalis, and HCV was significantly associated with HCC in this population.

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