Hepatitis C Virus Infection in Populations With Liver-Related Diseases in the Middle East and North Africa

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We investigated hepatitis C virus (HCV) epidemiology in populations with liver-related diseases (LRDs) in the Middle East and North Africa. The data source was standardized databases of HCV measures populated through systematic reviews. Random-effects meta-analyses and meta-regressions were performed, and genotype diversity was assessed. Analyses were based on 252 HCV antibody prevalence measures, eight viremic rate measures, and 30 genotype measures on 132,358 subjects. Pooled mean prevalence in LRD populations was 58.8% (95% confidence interval [CI], 51.5%-66.0%) in Egypt and 55.8% (95% CI, 49.1%-62.4%) in Pakistan; these values were higher than in other countries, which had a pooled prevalence of only 15.6% (95% CI, 12.4%-19.0%). Mean prevalence was highest in patients with hepatocellular carcinoma at 56.9% (95% CI, 50.2%-63.5%) and those with cirrhosis at 50.4% (95% CI, 40.8%-60.0%). Type of LRD population and country were the strongest predictors of prevalence, explaining 48.6% of the variation. No evidence for prevalence decline was found, but there was strong evidence for prevalence increase in Pakistan. A strong, positive association was identified between prevalence in the general population and that in LRD populations; the Pearson correlation coefficient ranged between 0.605 and 0.862. The pooled mean viremic rate was 75.5% (95% CI, 61.0%-87.6%). Genotype 4 was most common (44.2%), followed by genotype 3 (34.5%), genotype 1 (17.0%), genotype 2 (3.5%), genotype 6 (0.5%), and genotype 5 (0.3%). *Conclusion:* HCV appears to play a dominant role in liver diseases in Egypt and Pakistan and has a growing role in Pakistan. Testing and treatment of LRD populations are essential to reduce disease burden and transmission and to reach HCV elimination by 2030. (*Hepatology Communications* 2020;4:577-587).

Hepatitis C virus (HCV) is a bloodborne pathogen transmitted parenterally through use of contaminated injections, contaminated medical equipment, and blood transfusion.[1,2] Globally, there are an estimated 62 million to 79 million persons chronically infected with HCV.[3-5] Chronic HCV infection is a leading cause of several liver-related diseases (LRDs), such as liver fibrosis, cirrhosis, and cancer[2] and places a burden on health care systems.[6] In 2015 alone, HCV infection accounted for 21% of all liver cancer deaths worldwide.[7]

Approximately 20% of all chronically infected individuals reside in the Middle East and North Africa (MENA)[3-5] and mostly in the two countries

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LR, likelihood ratio; LRD, liver-related disease; MENA, Middle East and North Africa; PCC, Pearson correlation coefficient; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RNA, ribonucleic acid; SCC, Spearman's correlation coefficient; WHO, World Health Organization.

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most affected by HCV infection, Egypt[8,9] and Pakistan.[10,11] Direct-acting antivirals (DAAs), a highly effective treatment that was recently developed, has provided the opportunity to control HCV transmission and its disease burden.[12] Therefore, the World Health Organization (WHO) has set a goal to eliminate HCV globally by 2030.[5,13,14]

The objective of this study was to investigate HCV epidemiology in populations with LRDs in MENA by (1) estimating the population-specific pooled mean HCV antibody prevalence (henceforth, HCV prevalence) in populations with LRDs; (2) identifying the predictors and trends of HCV prevalence in these populations and sources of between-study heterogeneity; (3) assessing the correlation between HCV prevalence in the general population and in populations with LRDs; and (4) calculating the frequency and diversity of HCV genotypes in populations with LRDs. This study was performed as part of the MENA HCV Epidemiology Synthesis Project,[15] an ongoing project with the overarching goal of characterizing HCV epidemiology and informing public health research, policy, and programming in MENA.

Materials and Methods

DATA SOURCES

Studies reporting HCV measures in populations with LRDs in MENA were retrieved from the Synthesis Project database.[15] This database includes several subdatabases on different HCV epidemiological measures, as described in Table 1.

The Synthesis Project database was built through systematic reviews for HCV measures across MENA.[8-10,16-21] These studies followed a standardized methodology, which can be found in each of these systematic reviews in more detail.[8-10,16-21] Briefly, the methodology was developed as informed by the Cochrane Collaboration Handbook,[22] and the findings were reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] Literature searches were performed in international databases (PubMed and Embase), national/regional databases (WHO Index Medicus for the Eastern Mediterranean Region database, Iraqi Academic Scientific Journals database, Iran's Scientific Information database, among others), MENA HIV/AIDS Epidemiology Synthesis Project database,[24,25] abstract archives of international conferences, and gray literature comprised of public health reports and routine data reporting. The literature searches used broad search criteria with no language restrictions in order to include all publications reporting HCV measures since 1989, the year in which the virus was discovered.[26]

In this project, the MENA region consisted of 24 countries, as outlined in Supporting Box S1. As relevant in this study, separate analyses were conducted for Egypt and Pakistan, given the unique nature of the HCV epidemics in these two countries[8-11,27-29] relative to the remaining MENA countries.[16-21]

POOLED MEAN HCV PREVALENCE

Meta-analyses were performed to pool HCV prevalence measures in populations with LRDs in Egypt, Pakistan, other MENA countries (excluding Egypt and Pakistan), and all MENA countries collectively. Meta-analyses were performed when there were three or more prevalence measures, each of which with a sample size of 25 participants at minimum. DerSimonian-Laird random-effects models[30] with inverse-variance weighting to pool measures[30] were used to perform

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TABLE 1. SUMMARY OF THE SUBDATABASES OF THE MENA HCV EPIDEMIOLOGY SYNTHESIS PROJECT DATABASE[20]

	All Populations		Populations With LRDs	
Subdatabase	Studies	Participants	Studies	Participants
HCV antibody prevalence	2,614	49,821,739	252	132,358
HCV genotype frequency	338	82,257	30	1,919
HCV RNA	179	19,680	8	3,768

Abbreviations: HCV, hepatitis C virus; LRDs, liver-related diseases; MENA, Middle East and North Africa; RNA, ribonucleic acid.

the meta-analyses. Stabilization of the variance of each measure was performed using the Freeman-Tukey type arcsine square-root transformation.[31,32] Statistical measures were used to assess heterogeneity.[30,33] Forest plots were examined, and Cochran's Q test was conducted where statistical significance was indicated by $P < 0.10$.[30,33] The percentage of variance explained by true differences across studies rather than chance, I^2, and its confidence interval (CI) were calculated.[30] Prediction intervals were also determined to estimate with 95% confidence the range in which HCV prevalence in a future study will fall.[30,34]

Meta-analyses were also performed to pool all HCV RNA-positive measures among HCV antibody-positive populations with LRDs to determine the viremic rate[35,36] or the proportion of those antibody-positive individuals that are chronically infected. Statistical analyses were performed using R version 3.4.3.

PREDICTORS, TRENDS, AND SOURCES OF BETWEEN-STUDY HETEROGENEITY FOR HCV PREVALENCE

Univariable and multivariable random-effects meta-regressions were performed based on established methodology[22] to assess predictors of HCV prevalence in populations with LRDs, trend in prevalence over time, and sources of between-study heterogeneity. *A priori* relevant independent variables included type of population with LRDs, country, sample size (<100 or ≥10 to investigate a small-study effect[37,38]), year of data collection, and year of publication. The country variable included Egypt, Pakistan, and other MENA countries. The likelihood ratio (LR) test was performed where variables with an LR test $P < 0.1$ qualified for inclusion in the final multivariable model. An adjusted odds ratio (AOR) $P < 0.05$ in the multivariable model was considered to provide strong evidence for an association. Separate meta-regressions were conducted for Egypt and Pakistan to assess the trend in HCV prevalence in each of these two countries.

In studies in which the year of data collection variable was missing, the missing observations were imputed by deducting the year of data collection from the year of publication for each study and using the median of these values. Meta-regressions were performed on STATA 13, using the metan command.

ASSOCIATION BETWEEN HCV PREVALENCE IN THE GENERAL POPULATION AND IN POPULATIONS WITH LRDs

The Pearson and Spearman's rank correlation coefficients (PCC and SCC, respectively) were calculated to estimate the correlation between HCV prevalence in the general population of each country and in populations with LRDs of each country. $P < 0.05$ was considered to provide strong evidence for an association. HCV prevalence in the general population of each country was provided through meta-analyses of prevalence in each MENA country.[8-10,16-21] Statistical analyses were performed using STATA 13.[39]

GENOTYPE DIVERSITY

Using the genotype subdatabase from the Synthesis Project database (Table 1), we determined the frequency of each genotype in populations with LRDs. Individuals with untypeable genotypes were excluded. Individuals with mixed genotypes contributed separately to each genotype frequency. The Shannon Diversity Index was used to evaluate the diversity of genotypes.[40] Assuming maximal genotype diversity (i.e., equal contribution of all seven genotypes[41,42]) provides the largest Shannon Diversity Index score at 1.95.

Results

OVERVIEW OF EVIDENCE

Analyses were based on studies retrieved from the Synthesis Project database, as described in Table 1. All

studies on HCV prevalence are reported in Supporting Table S1. HCV prevalence measures in populations with LRDs were available for 16 of the 24 MENA countries. The number of HCV prevalence measures varied by country (Fig. 1), with Pakistan contributing the largest number (n = 76), followed by Egypt (n = 53). HCV RNA positivity measures (Supporting Table S2) were available for only six countries. Genotype frequency measures (Supporting Table S3) were available for only nine countries, with most data being from Egypt and Pakistan.

HCV PREVALENCE IN POPULATIONS WITH LRDs

The estimated pooled mean HCV prevalence in populations with LRDs across MENA is presented in Table 2. Forest plots are shown in Supporting Figs. S1-S4.

Egypt

HCV prevalence in Egypt ranged from 4.3% to 100%, with a median of 66.2%. The pooled mean prevalence in all populations with LRDs was 58.8% (95% CI, 51.5%-66.0%). The pooled mean prevalence was lowest in patients with viral hepatitis (17.6%; 95% CI, 10.4%-26.1%) and highest in patients with liver disease (74.9%; 95% CI, 67.3%-81.8%), followed closely by patients with hepatocellular carcinoma (HCC) (74.8%; 95% CI, 68.2%-80.9%).

Pakistan

HCV prevalence in Pakistan ranged from 3.0% to 100%, with a median of 63.0%. The pooled mean prevalence in all populations with LRDs was 55.8% (95% CI, 49.1%-62.4%). The pooled mean prevalence was lowest in patients suspected of having an LRD (20.7%; 95% CI, 13.5%-28.9%) and highest in patients with HCC (72.4%; 95% CI, 64.2%-79.9%).

Other MENA Countries

HCV prevalence in the other MENA countries (excluding Egypt and Pakistan) ranged from 0.0% to 76.2%, with a median of 11.5%. The pooled mean prevalence in all populations with LRDs was 15.6% (95% CI, 12.4%-19.0%). The pooled mean prevalence was lowest in patients suspected of having an LRD (2.9%; 95% CI, 0.0%-9.4%) and highest in patients with cirrhosis (25.9%; 95% CI, 17.3%-35.6%).

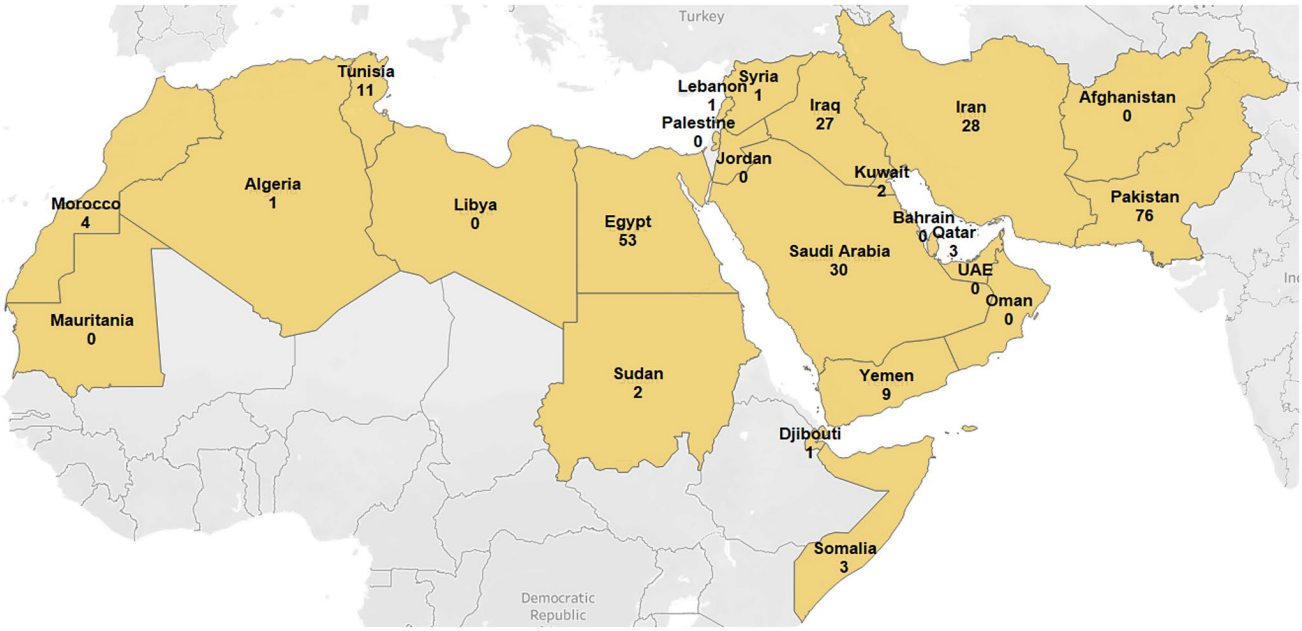

FIG. 1. Map of the Middle East and North Africa region showing the number of included studies for HCV antibody prevalence in populations with LRDs for each country. Abbreviation: UAE, United Arab Emirates.

TABLE 2. RESULTS OF THE META-ANALYSES FOR HCV ANTIBODY PREVALENCE IN POPULATIONS WITH LRDs ACROSS MENA

	Studies	Samples	HCV Prevalence		Pooled HCV Prevalence Estimate		Heterogeneity Measures		
Population (Patients)	Total (n)	Total (n)	Range (%)	Median (%)	Mean (%)	95% CI	Q (*P* Value)*	I^2 (95% CI)†	Prediction Interval (%)‡
Egypt									
Hepatocellular carcinoma	23	5,701	28.6-95.2	78.0	74.8	68.2-80.9	519.3 ($P < 0.01$)	95.8 (94.6-96.7)	40.7-97.4
Cirrhosis	2	130	56.0-75.4	65.7	66.0§	45.9-83.6	—	—	—
Liver disease	13	26,087	38.6-100	79.1	74.9	67.3-81.8	591.9 ($P < 0.01$)	98.0 (97.4-98.4)	42.2-96.8
Viral hepatitis	12	1,603	4.3-78.7	14.1	17.6	10.4-26.1	183.0 ($P < 0.01$)	94.0 (91.2-95.9)	0.0-55.6
Multiple LRDs	0	—	—	—	—	—	—	—	—
Suspected of having an LRD	3	4,509	13.0-43.2	29.8	27.6	15.2-42.1	43.2 ($P < 0.01$)	95.4 (89.7-97.9)	0.0-100
All populations	53	38,030	4.3-100	66.2	58.8	51.5-66.0	6,844.1 ($P < 0.01$)	99.2 (99.2-99.3)	10.3-98.0
Pakistan									
Hepatocellular carcinoma	19	3,908	33.3-92.2	76.5	72.4	64.2-79.9	529.1 ($P < 0.01$)	96.6 (95.6-97.3)	32.2-98.3
Cirrhosis	23	4,731	13.2-100	68.0	65.7	58.1-72.9	572.8 ($P < 0.01$)	96.2 (95.1-97.0)	27.6-94.8
Liver disease	25	6,616	3.0-78.4	40.0	42.2	31.9-52.8	1,694.7 ($P < 0.01$)	98.6 (98.3-98.8)	1.7-91.4
Viral hepatitis	6	1,660	6.4-93.3	25.8	34.4	10.2-64.0	679.6 ($P < 0.01$)	99.3 (99.0-99.4)	0.0-100
Multiple LRDs	1	205	—	40.0	40.0	28.8-48.1	—	—	—
Suspected of having an LRD	2	6,834	17.0-24.8	20.9	20.7§	13.5-28.9	—	—	—
All populations	76	23,854	3.0-100	63.0	55.8	49.1-62.4	7,630.6 ($P < 0.01$)	99.0 (98.9-99.1)	5.9-98.5
Other MENA countries‖									
Hepatocellular carcinoma	23	2,512	0.0-62.0	26.2	25.8	17.7-34.8	515.7 ($P < 0.01$)	95.7 (94.6-96.7)	0.0-73.2
Cirrhosis	16	3,225	1.7-73.3	24.5	25.9	17.3-35.6	336.8 ($P < 0.01$)	95.5 (94.0-96.7)	0.2-69.6
Liver disease	15	3,675	0.8-65.0	21.5	20.2	13.0-28.6	397.1 ($P < 0.01$)	96.5 (95.3-97.3)	0.0-59.1
Viral hepatitis	60	55,514	0.0-76.2	5.4	10.6	6.6-15.5	5,832.0 ($P < 0.01$)	97.6 (97.2-97.9)	0.0-60.5
Multiple LRDs	4	162	2.7-18.8	9.9	9.6	3.6-17.5	6.2 ($P = 0.10$)	51.4 (0.0-83.9)	0.0-47.1
Suspected of having an LRD	5	5,386	0.5-13.5	1.2	2.9	0.0-9.4	405.0 ($P < 0.01$)	99.0 (98.6-99.3)	0.0-44.5
All populations	123	70,474	0.0-76.2	11.5	15.6	12.4-19.0	10,157.5 ($P < 0.01$)	98.8 (98.7-98.9)	0.0-61.3
All MENA countries¶									
Hepatocellular carcinoma	65	12,121	0.0-95.2	61.0	56.9	50.2-63.5	3,362.1 ($P < 0.01$)	98.1 (97.9-98.3)	9.0-97.5
Cirrhosis	41	8,086	1.7-100	59.4	50.4	40.8-60.0	2,764.9 ($P < 0.01$)	98.6 (98.4-98.7)	2.0-98.2
Liver disease	53	36,378	0.8-100	40.3	44.2	34.8-53.7	10,811.2 ($P < 0.01$)	99.5 (99.5-99.6)	0.0-98.6
Viral hepatitis	78	58,777	0.0-93.3	8.6	13.2	9.3-17.6	6,961.3 ($P < 0.01$)	98.9 (98.8-99.0)	0.0-62.2
Multiple LRDs	5	267	2.7-40.0	12.0	14.9	3.6-31.4	38.2 ($P < 0.01$)	89.5 (78.3-94.9)	0.0-82.7
Suspected of having an LRD	10	16,729	0.5-43.2	13.3	11.4	5.0-20.1	1,911.7 ($P < 0.01$)	99.5 (99.4-99.6)	0.0-52.4
All populations	252	132,358	0.0-100	30.8	35.5	31.7-39.5	46,908.6 ($P < 0.01$)	99.5 (99.4-99.5)	0.0-92.0

*Q, Cochran Q statistic assessing the existence of heterogeneity in HCV prevalence measures.
†I^2, a measure assessing the magnitude of between-study variation that is due to true differences in HCV prevalence measures across studies rather than chance.
‡Prediction interval, a measure estimating the 95% interval of the distribution of HCV prevalence measures around the estimated mean.
§Weighted average calculated as there were too few studies (less than three) to perform a meta-analysis.
‖All MENA countries, excluding Egypt and Pakistan.
¶All MENA countries, including Egypt and Pakistan.
Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LRDs, liver-related diseases; MENA, Middle East and North Africa.

All MENA Countries

HCV prevalence in all MENA countries ranged very broadly from 0.0% to 100%, with a median of 30.8%. The pooled mean prevalence in all populations with LRDs was 35.5% (95% CI, 31.7%-39.5%). The pooled mean prevalence was lowest in patients suspected of having an LRD (11.4%; 95% CI, 5.0%-20.1%) and highest in patients with HCC (56.9%; 95% CI, 50.2%-63.5%).

Strong evidence for heterogeneity in HCV prevalence was found in all meta-analyses ($P < 0.01$). The vast majority of the variation was due to true variation in prevalence across studies rather than chance ($I^2 > 51.4\%$). Considerable variation in prevalence was confirmed by the prediction intervals.

HCV VIREMIC RATE IN POPULATIONS WITH LRDs

The HCV viremic rate varied across studies (Supporting Table S2), ranging from 43.5% to 93.0%, with a median of 70.2%. The pooled mean estimate for the viremic rate across MENA was 75.5% (95% CI, 61.0%-87.6%), indicating that three quarters of those antibody-positive individuals are chronically infected. There was evidence for heterogeneity in viremic rate measures ($P < 0.01$), with nearly all heterogeneity being due to true variation in viremic rate across studies ($I^2 = 96.0\%$).

HCV PREVALENCE PREDICTORS, TREND, AND SOURCES OF BETWEEN-STUDY HETEROGENEITY

Results of the univariable and multivariable meta-regressions are shown in Table 3. In the univariable analysis, there was evidence for both population type and country as predictors of HCV prevalence ($P < 0.1$), and these were included in the final multivariable analysis. Year of data collection or year of publication had no effect on observed prevalence. Similarly, no small-study effect was found; study sample size did not have an effect on observed prevalence.

In the multivariable analysis, the strong evidence for population type and country as predictors was confirmed ($P < 0.05$). Relative to patients with viral hepatitis, patients with HCC, cirrhosis, or liver disease were all found to have a higher AOR at 6.1 (95% CI, 3.7-10.2), 5.7 (95% CI, 3.1-10.2), and 3.2 (95% CI, 1.9-5.6), respectively. Relative to other MENA countries, Egypt and Pakistan both had a higher AOR at 8.1 (95% CI, 4.9-13.2) and 5.3 (95% CI, 3.4-8.5), respectively. The model explained 48.6% of the variability in HCV prevalence.

In separate univariable and multivariable meta-regressions conducted for Egypt (Supporting Table S4) and Pakistan (Supporting Table S5), no evidence was found for a trend in HCV prevalence over time in Egypt; however, a trend of increasing HCV prevalence was observed in Pakistan (AOR, 1.1; 95% CI, 1.0-1.1; $P < 0.05$). A sensitivity analysis was conducted in which the imputed observations were excluded, but the results were invariable.

ASSOCIATION BETWEEN HCV PREVALENCE IN THE GENERAL POPULATION AND IN POPULATIONS WITH LRDs

The pooled mean HCV prevalence measures in the general population across MENA countries are shown in Supporting Table S6, and results of the correlation analyses are presented in Table 4. There were positive strong correlations between HCV prevalence in the general population of each country and HCV prevalence in each LRD population of each country; the PCC was 0.862 for patients with multiple LRDs, 0.816 for patients suspected of having an LRD, 0.727 for patients with HCC, 0.628 for patients with liver disease, and 0.605 for patients with cirrhosis. The only exception was that of patients with viral hepatitis, who had a PCC of 0.147 and a nonsignificant association ($P = 0.198$). Overall, correlation analysis using the SCC confirmed the PCC findings and ranged between 0.448 for patients with viral hepatitis and 0.819 for patients suspected of having an LRD.

HCV GENOTYPE DISTRIBUTION AND DIVERSITY

In populations with LRDs in MENA (Supporting Table S3), genotype 4 was the most common (44.2%), largely because of Egypt. This was followed by genotype 3 (34.5%), largely because of Pakistan; genotype

TABLE 3. UNIVARIABLE AND MULTIVARIABLE META-REGRESSION MODELS FOR HCV ANTIBODY PREVALENCE IN POPULATIONS WITH LRDs IN MENA

	Studies	Samples	Univariable Analysis				Multivariable Analysis*	
	Total (n)	Total (n)	OR (95% CI)	*P* Value	LR Test *P* Value	Variance Explained Adjusted R^2 (%)	AOR (95% CI)	*P* Value
Populations (Patients)								
Viral hepatitis	78	58,777	1.0	—			1.0	—
Hepatocellular carcinoma	65	12,121	13.4 (7.6-23.3)	<0.001			6.1 (3.7-10.2)	<0.001
Cirrhosis	41	8,086	10.2 (5.4-19.4)	<0.001			5.7 (3.1-10.2)	<0.001
Liver disease	53	36,378	7.6 (4.2-13.7)	<0.001			3.2 (1.9-5.6)	<0.001
Multiple LRDs	5	267	1.6 (0.3-7.4)	0.545			1.8 (0.5-6.7)	0.382
Suspected of having an LRD	10	16,729	0.8 (0.3-2.6)	0.757	<0.001	30.6	0.5 (0.2-1.3)	0.162
Country								
Other MENA countries	123	70,474	1.0	—			1.0	—
Egypt	53	38,030	12.1 (7.1-20.5)	<0.001			8.1 (4.9-13.2)	<0.001
Pakistan	76	23,854	10.3 (6.4-16.4)	<0.001	<0.001	34.7	5.3 (3.4-8.5)	<0.001
Sample size								
<100	117	6,344	1.0	—			—	—
≥100	135	126,014	1.1 (0.7-1.8)	0.726	0.726	0.0	—	—
Year of data collection	252	132,358	1.0 (1.0-1.0)	0.729	0.687	0.0	—	—
Year of publication	252	132,358	1.0 (1.0-1.0)	0.811	0.847	0.0	—	—

*The adjusted R^2 for the full model was 48.6%.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; LR, likelihood ratio; LRDs, liver-related diseases; MENA, Middle East and North Africa; OR, odds ratio.

TABLE 4. PCC AND SCC BETWEEN HCV ANTIBODY PREVALENCE IN THE GENERAL POPULATION OF EACH COUNTRY AND HCV ANTIBODY PREVALENCE IN POPULATIONS WITH LRDs IN EACH COUNTRY

Population (Patients)	PCC	*P* Value	SCC	*P* Value
Cirrhosis	0.605	<0.001	0.624	<0.001
Hepatocellular carcinoma	0.727	<0.001	0.720	<0.001
Liver disease	0.628	<0.001	0.622	<0.001
with multiple LRDs	0.862	0.013	0.739	0.058
Suspected of having an LRD	0.816	0.004	0.819	0.004
Viral hepatitis	0.147	0.198	0.448	<0.001
All populations	0.564	<0.001	0.628	<0.001

Abbreviations: HCV, hepatitis C virus; LRDs, liver-related diseases; PCC, Pearson correlation coefficient; SCC, Spearman's rank correlation coefficient.

1 (17.0%); genotype 2 (3.5%); genotype 6 (0.5%); and genotype 5 (0.3%). Genotype 7 was not found in any LRD population. Genotype diversity was moderate for MENA as a whole (Shannon Diversity Index, 1.19 out of 1.95 [61.1%]).

Discussion

We provided a detailed analysis of HCV epidemiology in populations with LRDs in MENA. To our knowledge, this is the first such analysis for any region. HCV infection appeared to play a major, if not dominant, role in different liver disease forms in Egypt and Pakistan but much less so for the other MENA countries (Table 2). The majority of cases of HCC, cirrhosis, and other liver disease forms were found to be exposed to HCV infection in these two countries, suggesting that this infection is the main driver of this disease burden as opposed to other causes (such as hepatitis B virus infection). The role of HCV in liver diseases was found to be 8-fold higher in Egypt and 5-fold higher in Pakistan compared to the other countries (Table 3). These findings should not be surprising given the high HCV prevalence and unique nature of epidemics in these two countries[8-11,27-29,43] relative to the rest of MENA.[16-21,43,44]

HCV antibody positivity in liver diseases was found to be highest for HCC, followed closely by cirrhosis (Table 2). No evidence was found for a decline in HCV prevalence in LRD populations over time in MENA as a whole or in Egypt, the country with the highest prevalence[8,9,27] (Table 3 and Supporting Table S4). However, there was strong evidence for increasing prevalence in Pakistan (Supporting Table S5), strikingly indicating a steadily growing role for this infection in liver diseases in this nation. Remarkably, there was a strong association between HCV prevalence in the general population of any country and the prevalence in LRD populations, highlighting how the role of this infection in liver diseases is a reflection of its background level in the general population. Moderate genotype diversity was observed in MENA as a whole. The most common genotypes were genotype 4 (44%) and genotype 3 (35%), which reflect the major epidemics in Egypt and Pakistan, respectively.[42,45]

The lack of evidence of a decline in prevalence over time with an increasing prevalence in Pakistan indicates that the recent introduction of DAA treatment has not yet demonstrated an impact on liver disease burden in the region. Evidence attributes the rapid growth of the epidemic in Pakistan to lower quality health care practices, such as insufficient blood screening, unnecessary therapeutic injections, and reuse of medical needles and syringes.[10,11,45] Progress in DAA rollout in Pakistan is markedly slow, with most patients being treated in the private sector.[46] Despite having the second largest epidemic in the world,[10,11,28,29] an estimated cumulative total of only 311,000 people have been treated since 2013.[28]

The launch of the national treatment program in Egypt in 2014 has put this country on track for HCV elimination by 2030, if not earlier, with a cumulative total of at least 1.5 million people being treated.[46] It will probably be several years before the impact of this program on the course of the epidemic in Egypt will be clearly visible. This is the largest HCV epidemic worldwide; it became generalized at a high level following decades of population-wide parenteral antischistosomal therapy campaigns and other health care practices[8,9,45,47-50] (also, Ayoub H, Chemaitelly H, Kouyoumjian SP, Abu-Raddad LJ, under review). HCV treatment remains largely limited in the other MENA countries. As treatment is scaled up in MENA, both HCV antibody prevalence and viremic rate in LRD populations could be used as proxies to track the progress in treatment coverage.[35,36]

The presence of HCV infection in patients with viral hepatitis in Pakistan was found to be higher than

that in Egypt (Table 2), despite higher HCV prevalence in all other LRD populations in Egypt (Tables 2 and 3). This finding may be explained by the fact that HCV prevalence in patients with viral hepatitis may reflect recent HCV incidence rather than older prevalent infections and incidence has been declining rapidly in Egypt[27] but persists at high levels in Pakistan.[11,28] This finding also supports recent evidence of a rapid decline in the role of HCV in acute hepatitis in Egypt[51] but the persistence of this role in Pakistan.[52] The weaker association between HCV prevalence in the general population and that in patients with viral hepatitis (Table 4), unlike other LRD populations, attests to prevalence in this population reflecting incidence rather than prevalence.

This study identified several gaps in evidence. The number of studies varied by country, with no studies identified for eight out of 24 MENA countries (Supporting Table S1). There was large heterogeneity across identified studies. Sample size of studies varied, but there was no evidence of a small-study effect that would affect our findings (Table 3). The comparison of HCV prevalence in populations with LRDs to that in the general population was assumed indicative of the etiological role of HCV in the LRDs. The latter may better apply to some LRDs, such as liver cancer, rather than others, such as liver disease, where additional factors could be cofounding the association. The study is overall of a descriptive nature with the clinical implications of some of its findings being straightforward, such as the need for LRD screening in specific settings, while others, such as the scale of required health intervention, are less evident and require further evidence. We based our population classification on how authors described the populations in their original studies, therefore overlap across LRD categories cannot be ruled out in the case of misclassification (for example, suspected viral hepatitis versus acute viral hepatitis). Only eight HCV RNA studies were identified, all of which were before the launch of DAA treatment programs (Supporting Table S2), and the viremic rate was similar to that in different populations in MENA.[35] Accordingly, the estimated viremic rate may not be representative of the rate currently in populations with LRDs in the region.

Despite these limitations, a large volume of studies were identified on HCV infection in populations with LRDs, and this enabled diverse analyses and informative inferences. Notably, the meta-regression analysis explained 49% of prevalence variation, highlighting that country (reflecting background HCV prevalence) and liver disease form (reflecting the role of HCV infection in each disease-specific etiology) were strong predictors of HCV antibody positivity in LRD populations (Table 3). Nonetheless, further research is critical to address the identified gaps in evidence, such as expanding surveillance in populations with LRDs, particularly in countries with little to no data.

HCV appears to play a major, if not dominant, role in different liver disease forms in Egypt and Pakistan but much less so in the other MENA countries. HCV infection appears to be the main driver of HCC, cirrhosis, and other liver disease forms, reflecting the severe nature of the epidemics that have affected these two nations. Despite the rollout of interventions since the discovery of this virus, there is no evidence for a decline in HCV prevalence in LRD populations in MENA, but there is evidence of an increasing role for this infection in liver diseases in Pakistan. Of the different disease forms, the role of HCV infection appears highest for HCC and cirrhosis. Remarkably, we identified a strong association between HCV prevalence in the general population and HCV prevalence in LRD populations.

The presented evidence attests to the immediate need for prioritizing LRD populations in HCV testing and treatment programs. Recent evidence has also highlighted the program efficiency of this prioritization.[53,54] It is also clear that interventions, such as testing and treatment, have not yet reached sufficient effectiveness, coverage, and reach to impact HCV epidemiology (apart from Egypt). Without timely and effective interventions, elimination of HCV infection and its disease burden by 2030 will not be possible.

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