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Epidemiology of Liver Diseases Across the Levant and Egypt: A Review

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Abstract

Liver diseases constitute a major burden on the society worldwide in terms of morbidity and mortality. Common causes of liver disease include infectious causes (hepatitis A-E viruses) and non-infectious causes (most importantly is Non-alcoholic fatty liver disease). The recent studies have shown an increased prevalence and incidence of liver diseases in general and a change in trends in the leading etiologies across the years with a decrease in the reported viral hepatitis prevalence and an increase in the prevalence of non-alcoholic fatty liver disease. The Middle East shares similar trends with the world; however we show in our review the paucity of literature in this area and aim to highlight this deficiency in order to raise awareness and decrease the risk factors.

Keywords: Liver disease; Middle East; Levant; Hepatitis; Non-alcoholic fatty liver disease; Hepatocellular carcinoma; Epidemiology

Abbreviations

AVM: Acute Viral Hepatitis; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HDV: Hepatitis D Virus; HEV: Hepatitis E Virus; ME: Middle East; NAFLD: Non-Alcoholic Fatty Liver Disease; WHO: World Health Organization

Introduction

Liver diseases are a major cause of mortality and morbidity throughout the world, causing two million deaths per year worldwide (3.5% of all death); with 50% related to cirrhosis complications and 50% related to Hepatocellular Carcinoma (HCC) and viral hepatitis infections [1]. Liver disease incidence and prevalence have been increasing significantly over the years with varying evolutions of etiologies [2].

Among a variety of liver diseases that commonly affect individuals globally, Non-Alcoholic Fatty Liver Disease (NAFLD) and viral hepatitis present a serious health burden. NAFLD is a major cause of liver disease worldwide that affects around 25% of the global adult population with a prevalence of around 31.8% in the Middle East (ME) [3]. It is defined as a cytoplasmic accumulation of fat in more than 5% of hepatocytes with or without inflammation when other causes of steatosis such as excessive alcohol consumption, viral hepatitis, genetic disorders, and drugs are ruled out [4]. It is a metabolic disease and lies on a spectrum of histopathological features ranging from simple steatosis all the way up to HCC [5]. Another important cause of liver disease is viral hepatitis, which refers to inflammation of the liver due to a viral infection, namely hepatitis A, B, C, D, or E. According to the World Health Organization (WHO), 325 million people currently live with a hepatitis infection, with the ME showing high endemicity to particular types. In addition, alcoholic hepatitis is still considered a major etiology of liver disease, with it being the main cause of liver related deaths in countries like France and Spain (30 deaths per 10,000 per year) [6]. Other causes of liver diseases include cholestatic and autoimmune liver diseases in addition to metabolic hereditary causes and iatrogenic causes [6].

The ME for a very long time, has been a region of constant turmoil with conflicts taking place on a regular basis. These factors have imposed harmful consequences unto some aspects of the healthcare sector in the region and strained the development of particular screening programs in some countries. In this paper we aim to study, through a review, the epidemiology of liver diseases in various countries across the ME with a particular focus on Lebanon, Syria, Jordan, and Egypt.

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Hepatitis A

Hepatitis A Virus (HAV) is a major cause of enterically transmitted hepatitis causing a significant burden worldwide [7]. According to WHO, HAV caused approximately 7,134 deaths in 2016 (accounting for 0.5% of the mortality due to viral hepatitis) [8]. In Lebanon, a recent study conducted on HAV, reported an increase of HAV incidence between 2001 and 2017 [9]. The annual average for the number of reported HAV cases was 300 between 2001 and 2012, which then suddenly rose to 2,600 cases in 2014 [9]. This outbreak was attributed to the influx of Syrian refugees, most notably in the Beqaa and North Governorates, which were closest to the Syrian borders [9]. Subsequently, cases began to drop in the years that follow. Another recent study in Lebanon studied anti-HAV IgG seroprevalence in a cohort of 283 healthy blood donors and reported an overall prevalence of 72% amongst its participants [10]. Their data showed that anti-HAV seropositivity for the younger age group (19 to 29 years) and older adults (50 to 59 years) were 60% and 90%, respectively [10]. Moreover, Lebanon has carried a large burden on its healthcare system with the rise in HAV cases that followed the influx of Syrian refugees. On the other hand, no consistent info is reported from Syria. The last published account for HAV prevalence in Syria in 2000 and showed that 89% of 849 Syrians tested positive for anti HAV IgG, with 50% in the 1 to 5-year age group and 95% in the 11 to 15-year age group [11]. More recently, in 2018 a HAV outbreak was identified to have occurred among internally displaced Syrians as a result of the war. A total of 638 cases of suspected acute HAV infection had been reported, of which 98.59% were under 15 years of age and the rest were between 16 to 54 years old [12]. The high displacement rate, deteriorated health conditions, and lack of access to clean water likely resulted in the increase of HAV cases across the country. In Egypt, a surveillance study was conducted between 2014-2017 to describe the epidemiology of Acute Viral Hepatitis (AVH) in the country and compare it to the period 2001-2004. Out of the 8,362 participants that tested positive for AVH, 7,806 (93.4%) tested positive for HAV with most participants being 5 to 19 years of age (66.2%) and residents of urban regions (79.4%) [13]. These results showed a large increase in the proportion of HAV infection from the 2001-2004 surveillance study which reported 40.2% positive for HAV, and it was clear that HAV was the main causative agent for HAV in Egypt [13]. It is important to note, however, that the surveillance sites were within the largest few hospitals in Egypt, so they do not necessarily reflect accurately the population at large. Furthermore, the increase in HAV was attributed to poor sanitary conditions, particularly in preschools and nurseries, as studies showed that the youngest populations were most affected [13]. According to a cross-sectional study that was conducted in Jordan in 2008, HAV was classified as highly endemic to Jordan. In a study of 3,066 participants from all across Jordan, the seroprevalence rates among age categories 0 to 1 years, 2 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 19 years, and those above 20 years were 26%, 32%, 44%, 63%, 78%, and 94%, respectively [14]. Unfortunately, no further studies on HAV in Jordan were found in the literature.

Although these countries have all been headed towards an improved health sector and sanitary infrastructure over the years, they have all been subjected to similar circumstances that greatly governed how much they were able to invest in fighting HAV. As a result of the refugee crises, a recent HAV outbreak across these countries could have been likely observed, had there been more recent reporting on HAV cases in the past few years. This calls for more health measures and screening program to be implemented, in order to limit the transmission of HAV between refugees and the host communities.

Hepatitis B

Hepatitis-B (HBV) is a widespread human pathogen and one of the leading causes for chronic liver disease and HCC. According to the WHO, two billion people have been infected with HBV and more than 350 million have a chronic state, with a prevalence ranging from 1% to 20% according to geographic regions [15]. HBV in the ME predominantly occurs due to perinatal transmission, horizontal transfer between family members, and through injection use [16].

WHO's last statement on HBV in Lebanon estimated that its prevalence ranges between 1.6% and 2.2% in 2007 [15]. A more recent national cross-sectional study was conducted in Lebanon in the period between 2011 and 2012, where 31,147 participants were recruited from all over the country and blood samples from each were tested using PCR. After screening, 542 individuals tested positive, and results showed a 1.74% prevalence for HBV, which was consistent with the studies conducted back in 2007. Additional studies conducted across seven hemodialysis centers in Lebanon, found that the prevalence of HBV amongst hemodialysis patients was 1.6% [17]. Thus, it is evident that the prevalence of HBV in the Lebanese population is very low. In Syria, in 2004, a large serological survey on a random cluster sample with 528 clusters and 3,168 individuals reported that the seroprevalence for HBV was 5.6% [18]. Moreover, another serological survey was carried out in 2005-2006 with a random sample of 1,217 individuals from Hassakeh and 763 from Deir Zour and showed that HBV prevalence values of 32.2% and 37.4%, respectively [18]. Further screening in premarital clinics and blood banks in the years that follow, showed a great decreasing trend for HBV seropositivity amongst individuals with values that range from 0.54% to 2.54% depending on geographical location. That being said, HBV in Syria is classified as low-intermediate in level [18]. However, it is important to note that higher prevalence values are clustered in the northern and eastern parts of the country due to factors like less access to quality healthcare, inaccessibility of the MoH due to ongoing political conflict, and limited public awareness on the disease.

On the other hand, viral hepatitis in Egypt has been a major public health challenge and is currently ranked 5th for the burden of viral hepatitis worldwide [13]. A nationwide cross sectional analytical study in 2015 reported the prevalence of HBV to be 1.4% with a localization of the disease in the upper urban areas [19]. In a large surveillance study conducted between 2014 and 2017, 238 (2.8%) tested positive for HBV [19]. Compared to the same study conducted back in 2001-2004, the proportion of HBV had decreased from 30% to 2.8%. In Jordan, significant improvements have been made to reduce the HBV prevalence in the country. Historical records report the prevalence to be around 9.9% in the general population, whereas a recent modeling study done by Polaris observatory estimated the prevalence to be around 2.4% in 2016 [20]. Remaining studies on HBV in Jordan were all performed on specific populations that were not very reflective of the population at large.

Generally speaking, there is a common trend of decreased HBV prevalence in the ME. The reduction in HBV among infected patients was a result of enhanced infection prevention, improved control measures, and expanded coverage of HBV vaccination in health facilities across the nations [13]. This evolution towards enhanced healthcare should focus more on the rural areas across the ME, as

these tend to be much more neglected than the average rural area worldwide.

Hepatitis C

Hepatitis C Virus (HCV) infection is amongst the major causes of mortality and morbidity worldwide and is the prominent cause of chronic liver disease, HCC and liver transplantation in developing countries [21]. The WHO has estimated a 1% worldwide prevalence of the virus affecting more than 170 million people globally [21]. The ME continues to be a region that is impacted by this disease, though geographical locations show significant differences in its distribution.

Lebanon, for example, is considered to have low endemicity for HCV. A national cross-sectional study conducted between 2011 and 2012, showed that amongst 31,147 participants enrolled for the study, 64 (0.2%) tested positive for HCV with majority from the South of Lebanon [15]. The higher prevalence for HCV in the south could be attributed to the lower standard of care in that area, nonetheless; HCV infections currently does not contribute much of a burden on the Lebanese government as prevalence values are low. Another cross-sectional study in 2012, showed prevalence rates of 0.01%, 0.18%, 0.37%, and 0.55% for 0 to 19 years, 20 to 39 years, 40 to 59 years, and greater than 60 years old, respectively [22]. According to the global review of HBV and HCV in 2013, Syria was classified to have a low prevalence for HCV [18]. However, more recent studies indicate the contrary with prevalence less than 1% with variations among specific populations [18]. For example, HCV prevalence was reported to range from 48.9% to 75% among hemodialysis patients [23]. Meanwhile, prevalence among drug users and hemophilia patients were measured to be 21% and 20.5%, respectively [23]. Despite these high values amongst populations of high risk, for the general population, HCV prevalence ranged between 0.3% to 0.9% among blood donors [23]. Egypt, on the other hand, has a high endemicity for HCV and is considered to have the highest prevalence rate in the world. Since it can take many years (up to 40) for the clinical symptoms of HCV to show up, it was not until relatively recently that the problem in Egypt became apparent. In an attempt to treat all HCV infected individuals, a screening of 62.5 million people across the country was done in 2018 [24]. Among the 48345,948 that were tested, HCV seroprevalence was found to be 4.61%, with some variations across states, highest being in the middle of the Nile Delta [24]. Compared to studies conducted in 2015 a decrease in seroprevalence was found across all states [24]. The decline in seroprevalence positively reflects the impact direct acting anti-viral agents had on the disease, when they were introduced by the government in 2014 reducing the burden of disease [24]. With regards to Jordan, limited data was found on HCV epidemiology in the country. Among populations of high risk, HCV seroprevalence ranged from 21% to 49.8% in hemodialysis patients and 32.8% in thalassemic patients, whereas, for the general population prevalence values less than 1% was observed for blood donors and people attending public hospitals [23].

In summary, HCV prevalence amongst these countries, excluding Egypt, show a general trend for low prevalence of less than 1% in the general population. Despite the low prevalence, findings show on going transmission amongst specific population groups in hospital settings, such as hemodialysis patients. Through effective government intervention, Egypt seems to be on the track to successful recovery from high HCV prevalence, although it is still considered to be the country mostly affected by the disease. Since these countries all face potential political turmoil and instability, routine screening and infection control measures should be carried out, as these factors can fluctuate prevalence rates over a short period of time.

Hepatitis D

Hepatitis D (HDV) is a virus that requires the presence of HBV for infection. According to the WHO, nearly 5% people who have a chronic infection with HBV are also infected with HDV [25]. Since the 1980s there has been a trend towards global decline for the virus, though there has been a lack of sufficient data on HDV across the ME. Therefore, the true status of the virus in the region cannot be determined. After a thorough review of the literature, we found a very limited number of papers that discussed the epidemiology of HDV in the region.

The last study conducted in Lebanon was in 2004, in which only 3 out of 258 patients tested positive for HDV antibodies from 10 medical centers in the country [26]. In Egypt, studies conducted in 1990 demonstrated HDV antibodies in 23.53% of patients with chronic HBV, and in 2003 showed anti-HDV in 20% of HBsAg positive patients [27,28]. The latest study available, conducted from between 2009 and 2011, showed that 32/216 patients were positive for anti-HDV, resulting in a prevalence of 14.8% amongst HBsAg positive patients [29]. The only information on HDV in Jordan was from a single study between 1978 to 1985. Prevalence of HDV in patients with chronic liver disease, acute hepatitis, and HBsAg carriers were 23%, 16%, and 2%, respectively [30]. Unfortunately, no available data was found for Syria.

Although not much can be inferred on HDV from the following data, there does seem to be potential for endemicity of the virus in this region today. New screening programs in this regard are highly advised among high-risk populations, and major campaigns for HBV vaccines and injections safety could be a major way to minimize the prevalence and burden of HBV.

Hepatitis E

Hepatitis E (HEV) is considered the most common cause of acute viral hepatitis and jaundice worldwide [31]. The WHO estimates that on average of 20 million people are infected with HEV per year with 3.3 million displaying symptomatic symptoms [32].

In Lebanon, one cross sectional study conducted in northern Lebanon in 2015 showed that 1/450 pregnant women was positive for anti-HEV IgG antibodies. In another study among 171 hemodialysis patients from three hospitals in Northern Lebanon, seropositivity was observed in 37/171 (21.63%) [33]. Further studies in Lebanon are needed to clarify the epidemiology of HEV, as these studies do not reflect the general population. Egypt has long been known to have a high seroprevalence for HEV antibodies, and multiple studies have been conducted in this regard, but all-in specific contexts and populations. A study from 2000 collected samples from two rural villages in Egypt, one in upper Egypt and the other along the southern Nile Delta, and it reported anti-HEV prevalence of over 60% in both populations (amongst the highest in the world) [34]. Years later, a large multicenter prospective study in 2008 reported that 33/123 (26.8%) of admitted children between 2 to 18 years of age had an HEV infection [35]. More recently, a prospective cohort study between July 2015 and March 2016, reported that among the HCV-infected villagers, HEV-IgG was found to be positive in 71.4% of the chronic hepatitis patients and 96.1% of the advanced liver disease patients [36]. Lastly, a cross sectional study from 2016 reported HEV seroprevalence in 27.15% of

children suffering from beta-thalassemia [37]. Although more recent and representative samples are required to make inferences on HEV epidemiology in the country as a whole, collectively these results do suggest a good likelihood for high endemicity of HEV in Egypt today. As for Jordan, the first and only report on HEV prevalence showed a high exposure to HEV Between 2015 and 2016. Out of 450 blood samples that were screened, 139 tested positive for anti-HEV IgG with a prevalence of 30.89% with males and the elderly (60 to 80 years) at higher odds for HEV [38]. Additional statistics from the study report that eating undercooked meat and owning animals (camels) is significantly associated with an increased odd for HEV seropositivity [38]. Surprisingly, the place of residence and source of drinking water in Jordan showed no association with HEV prevalence [38]. No literature from Syria was available.

It is important to note, that the role of HEV in the region is under investigated and more data is necessary to assess its epidemiology. However, given the current data obtained, it is very probable that HEV poses a serious threat in the region today. Therefore, at the present time there should be serious consideration by public health authorities to impose routine surveillance screening programs for HEV to reduce disease burden, especially in patients at risk of being infected or developing serious complications as a result of infection.

Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is a spectrum of liver disease that can range from simple fatty infiltration in the absence of fibrosis all the way up to steatohepatitis, eventually leading to liver cirrhosis, fulminant hepatitis and HCC [39]. Obesity, type II diabetes mellitus (insulin resistance), and metabolic comorbidities have been established to be associated risk factors for NAFLD; a strong complicated and bidirectional relationship links NAFLD with the metabolic syndrome and insulin resistance. In fact, NAFLD have proposed to be the hepatic manifestation of the metabolic syndrome.

With the world assuming a more sedentary lifestyle and unhealthy eating habits, obesity and diabetes have become leading public health problems globally, with high prevalence values across the globe. Consequently, NAFLD is recognized as a rising pandemic.

Over the past years, recent changes in lifestyle have radically changed health priorities in most areas of the world [40]. Today, NAFLD has been regarded amongst the most fast-growing liver diseases in the world and the global prevalence is estimated to be around 24% [39,41].

Due to variations in lifestyle and risk factors amongst the different countries, NAFLD epidemiology differs accordingly. No studies are currently available to directly describe the prevalence of NAFLD in the ME and North Africa region, however taking into consideration its risk factors, one can develop an estimate about the seriousness and the widespread of this disorder in the area.

Overall, the prevalence of obesity in the ME is currently considered higher than the Caribbean and European regions, it ranges from the lowest of 6.6% (Yemen) to the highest 41.0% (Qatar) [42]. Multiple theories could explain this high prevalence on the ME hypothesize by the lifestyle and economic changes. The sedentary lifestyle and office work, the change to unhealthy diet, the low physical activity and the high prevalence of pediatric obesity are all factors in play.

There is a serious paucity of data on NAFLD in the ME. Given the high prevalence values of the associated risk factors in the region, it is highly recommended that initiatives take place to investigate the prevalence of NAFLD. It is essential to understand the burden of the disease in the ME in order to create large collaborative interventions in the region to further investigate and minimize the burden of NAFLD.

Hepatocellular Cancer

HCC is the most common neoplasm in the liver, accounting to >80% of all primary liver cancers worldwide [43]. It is reported to be the 4th common cause of cancer related death that has a poor prognosis with a 5-year survival rate of 6.9% [44]. There is great global variation in the prevalence of HCC worldwide, with the highest prevalence reported to be in Eastern Asia and Sub-Saharan Africa (almost 85% of cases) [45].

Despite the ME having a lower prevalence of HCC than other regions in the world, it still represents a major public health concern since a significant proportion of highly prevalent HBC and HCV cases eventually progresses to HCC, particularly in Egypt and Saudi Arabia. According to a study in 2010, the incidence per 100,000 for HCC in Lebanon was 3.5 for men and 2.2 in women [46]. It is a relatively rare cancer in Lebanon, ranking 14th in both males and females [46]. Other studies show that the majority of cases arise from HBV-related liver cirrhosis, followed by HCV and alcohol abuse [46]. In Jordan, the incidence per 100,000 for HCC was reported to be 1.9 and 1.3, for men and women, respectively [46]. Only one study was found which studied the association between HDV and HCC, reporting the prevalence of HDV in HCC patients to be 67% [46]. In Egypt, HCC is the fourth most common cancer in the population, and second cause of cancer mortality in both sexes [47]. Men showed a much higher incidence than women, with the incidence per 1000,000 in men and women, 21.9 and 4.5, respectively. In the past decades, there has been an alarming rise in the number of HCC cases in the country, and this is mostly attributed to high seroprevalence of HCV antibodies in the population due to a high use of contaminated injections in the past [44]. In Syria, according to data extracted from the Global Burden of Disease (GBD), the incidence rate per 100,000 was reported to be 3.61 in 2017 [45].

HCC is a major contributor to cancer related death in the region, and this result in a high burden of disease, given the limited resources available [45]. Prevention and treatment of its two most important risk factors, namely HBV and HCV, is crucial in decreasing the burden of disease in these countries [45]. However, given the lack of developed registry and surveillance systems in the region, there is a limited understanding of the exact epidemiology of the disease. Moreover, with the presence of political, social, and economical turbulence in the region, it is likely to see an increased incidence of hepatic viral infections. There is a need for prompt public health interference in this regard, particularly with HCC surveillance programs that could lead to earlier detection of the disease and improved overall survival.

Other Diseases

A number of other liver diseases exist in the region, such as Alcoholic Liver Disease (ALD), hemochromatosis, Wilson's disease, and autoimmune hepatitis (among others), which are poorly investigated in the literature. A thorough search on the web confirmed that there is a paucity of data for these diseases. With regards to alcoholic fatty liver disease and autoimmune hepatitis, only one study conducted in a tertiary care center in Lebanon reported that 3.3% and 2.9% had ALD and autoimmune hepatitis, respectively, out of 620

patients that presented for Fibroscan [48]. That being said, it is likely alcoholic liver disease does not represent a serious health concern in the region due to low alcohol consumption patterns. According to WHO, the ME and North Africa have amongst the lowest alcohol consumption per capita globally, in contrast to European counties like Czech Republic where alcohol consumption is very high [49]. Reasons for this include cultural, religious, and economical factors that greatly impact alcohol intake. Whilst we acknowledge the presence of the other liver diseases in the region, no additional data was found.

Conclusion

The burden of liver diseases in the region has been of substantial importance, impacting millions of people over the years. The distribution of the various etiologies for these diseases has been changing gradually, with the proportion of virus induced hepatitis infections declining, while the proportion of NAFLD increasing. This is, in part, a result of major progress and knowledge in disease diagnosis, therapies, and disease prevention. Implementation of vaccination programs has greatly diminished the prevalence of hepatitis infections and resultant HCC in the region. However, we witnessed the opposite trend with regards to NAFLD. Although there has been an improvement in living standards in the recent years, the growing epidemic of obesity and type II diabetes mellitus has led to a surge in NAFLD prevalence in the region, and across the globe at large. It will likely continue as the leading cause of end-stage liver disease in the years to come. Our results warrant a need for increased awareness of the public on such diseases, in addition to implementation of active policies that improve the overall management of liver diseases, given that most causes of these diseases are preventable.

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