Hepatitis C-Induced Hepatocellular Carcinoma in the Middle East

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1 Introduction

Hepatitis C virus (HCV) is a hepatotropic virus that belongs to the *Flaviviridae* family, discovered in 1989. It is a small, enveloped, positive-stranded RNA virus [1]. The virus has seven genotypes based on variations in the nucleotide sequence by >30% and 67 subtypes based on variations at the nucleotide sequence by less than 15% [2].

HCV is well-known to cause acute and chronic hepatitis. More than half of chronic liver disease around the globe is attributed to HCV [3]. Chronic viral hepatitis causes high mortality, and currently, they ranked the 7th leading cause of mortality around the world, with close to 50% of these deaths due to chronic hepatitis C (CHC) [4]. In 2013, 626,000 compensated cirrhosis, 137,000 decompensated cirrhosis, 16,100 hepatocellular carcinoma (HCC) cases, and 33,000 liver-related deaths were attributed to CHC. The number of deaths related to HCV complications has increased to around 399,000 deaths in 2015 [5].

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Based on the World Health Organization (WHO) reports in 2017, the estimated global number of patients with CHC was 71 million people [6]. Around one-third of these patients will progress to advanced fibrosis and cirrhosis, and close to 5% per year of those cirrhotic patients will develop HCC [5]. Not all patients infected with HCV will develop chronic hepatitis; up to 35% will clear the virus spontaneously, and the remaining 65% will progress to CHC, defined as persistent HCV RNA in the blood for more than 6 months [7]. Several studies have looked at factors associated with spontaneous clearance of acute HCV and identified age at acquiring the infection, female gender, ethnicity, and coinfection with other viruses such as HIV to be the most important factors [8–10]. Thomas et al. showed that the HCV clearance rate in non-black is higher with an odds ratio of 5 [8]. These ethnic differences in HCV clearance could be partly explained by the immune system response to different insults.

Genome-wide association (GWA) studies showed that HCV spontaneous clearance and treatment response are related to patients' genetic variations [11–14]. Different single-nucleotide polymorphisms (SNPs) in the IL28B gene in chromosome 19 coding for type III interferon INF-λ 3, as well as other SNPs in different chromosomes, were associated with HCV treatment response as well as HCV spontaneous clearance [15–17].

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There is marked variation in the natural history of CHC, ranging from minimal liver inflammation to progressive liver fibrosis and the development of complications such as decompensated cirrhosis and HCC [9, 18]. The natural history of CHC is affected by many factors, which can be divided into host-related factors such as age at acquiring HCV infection, coinfection with other viruses such as hepatitis B virus (HBV), human immune deficiency virus (HIV), presence of metabolic syndrome especially diabetes and non-alcoholic steatohepatitis (NASH), and concomitant alcohol abuse and to a less extent viral factors such as viral load and genotype [9, 18–22].

Despite the progression of CHC to advanced fibrosis, only a minority of CHC patients will develop HCC [23]. This progression is due to the complex interaction between HCV, the patient, and environmental factors that promote carcinogenesis. The mechanism of oncogenicity in HCV is different from HBV, where the viral DNA is integrated into the host chromosomal DNA. HCV is a cytopathic virus that replicates within the liver cell cytoplasm, promoting hepatocyte proliferation and inducing cellular inflammation. It also leads to mitochondrial damage and induces the production of reactive oxygen species (ROS). The induced inflammation and ROS production cause genomic mutations and instability, which is the nidus for the development of HCC [24].

HCC accounts for more than 85% of primary liver cancer (LC) [25]. In most cases, HCC develops on a background of liver cirrhosis except in chronic hepatitis B (CHB), where HCC can develop in non-cirrhotic liver. Liver cirrhosis due to chronic viral hepatitis is the leading risk factor for the development of HCC [26].

The risk of HCC is increased 15–20-fold in patients infected with CHC. Patients with liver cirrhosis due to CHC are at risk of developing complications such as decompensated cirrhosis at a rate of 3–6% per annum and development of HCC at 1–5% per annum [23].

Despite the availability of direct-acting antiviral agents (DAAs), HCV and its related complications will remain a significant global health issue in the coming years. This could be attributed to many newly discovered cases, a high number of unrecognized HCV-infected cases, and access to the new DAA [27].

2 HCV Epidemiology in ME

The Middle East (ME) is a transcontinental region that includes 18 countries from Asia and Africa (Fig. 1). The majority of those countries (13 out of 18) are part of the Arab world. The term "Middle East" may have originated in the 1850s in the British India Office. However, in 1902 the American naval strategist used the term the Middle East and it since then became widely known [28]. The ME has a total population of 371 million based on World Bank data in 2010.

The region demonstrates a wide range of anti-HCV and viremic prevalences and diversity in HCV genotype distributions. WHO estimates that there are at least 21.3 million HCV carriers in the Eastern Mediterranean countries, close to the number of carriers estimated in the Americas and Europe combined [29]. Country-level anti-HCV prevalence is classified into low (<1.5%), moderate (1.5–3.5%), and high (>3.5%) levels [29].

The reported prevalence of HCV in ME is affected by multiple factors. The reported prevalence in certain countries such as the Gulf Cooperation Council (GCC), a political and economic alliance of six Middle Eastern countries—Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman—is affected by the population demography of those countries. More than one-third of the population of the GCC countries are migrants. Based on 2015 population statistics, the number of temporary worker immigrants in certain countries such as Qatar and UAE was more than 80% [30, 31]. Modeling prevalence demonstrated a 10% increase in HCV prevalence since 2007 in Qatar and UAE due to foreign workforce from endemic countries [30, 31]. Therefore, any epidemiological data that does not differentiate between nationals and temporary worker migrants will be affected by the HCV epidemiology profiles of the migrants' countries of origin.

Fig. 1 Countries that constitute the ME

The prevalence data from other Middle Eastern countries such as Turkey, Egypt, Iraq, and Jordan are less affected by immigration. However, most studies looking at HCV prevalence from ME used non-homogenous populations such as blood donors, hemodialysis patients, and multi-transfused patients. Those groups of patients do not represent the entire country population, and in fact, they are a high-risk population for HCV infection. In addition to that, older studies used anti-HCV as a marker of infection. The characteristic performance of anti-HCV testing using first- and second-generation EIA was not optimal [32].

The prevalence of HCV infection in Middle Eastern countries varies geographically. A low prevalence of HCV (<1.5%) was reported in Kuwait, Oman, Qatar, Iran, and UAE. At the same time, Iraq, Lebanon, Saudi Arabia, Turkey, and Syria had moderate prevalence (1.5–3.5%) and a high majority (>3.5%) in Egypt and Yemen. Table 1 showed the prevalence of HCV and the most common genotype among Middle Eastern countries [33–39].

Egypt is considered to have the highest prevalence of HCV in the world. Based on the Egyptian Demographic Health Survey (EDHS) that was conducted in 2008 on a large country representative sample, the prevalence of HCV among the age group 15–59-year-old was found to be 14.7%, 10% of those found to have chronic infection and genotype 4 was found in 90% of the patients [40]. In another large Egyptian Health Issues Survey (EHIS) conducted in 2015, including the younger age group, the seroprevalence of HCV was found to be 6.3% among the age group 0–59 years old. The investigators reported a significant reduction of 32% and 29% in HCV antibody- and HCV RNA-positive people [41]. The reported prevalence of HCV in certain Middle Eastern countries varies between different regions within the same country. In a population-based study in Iran by Merat et al., the prevalence of HCV in Iran was 0.3% in Tehran, 1.6% in Hormozgan, and 1.0%

Table 1 Prevalence of HCV and the most common genotype among Middle Eastern countries

Country	Population	Prevalence	Common genotype
Afghanistan	32,527,000	0.5%	Genotype 3
Bahrain	1,377,000	1.2%	Genotype 1
Egypt	91,508,000	6.3%	Genotype 4
Iran	79,109,000	0.2%	Genotype 1
Iraq	36,423,000	0.2%	Genotype 4
Jordan	7,595,000	0.3%	Genotype 1
Kuwait	3,892,000	0.8%	Genotype 4
Lebanon	5,851,000	0.2%	Genotype 1
Oman	4,491,000	0.4%	Genotype 1
Palestinian	4,668,000	2.2%	Genotype 4
Qatar	2,235,000	1.6%	Genotype 4
Saudi Arabia	31,540,000	0.3%	Genotype 4
Syria	18,502,000	3.0%	Genotype 4
Turkey	84,181,300	0.6%	Genotype 1
United Arab Emirates	9,157,000	1.3%	Genotype 1
Yemen	29,710,300	0.8%	Genotype 4
Cyprus	1,189,000	0.46%	Genotype 1 and 4

in the Golestan provinces [42]. Other studies reported a prevalence of 15.6% in Fars, 44.3% in Kerman, 29.6% in Zahedan, 59.1% in Hamadan, 71.3% in Gilan, and 76.7% in the northwest of Iran, representing an overall prevalence rate of almost 50% [43]. Similar findings were also reported by different researchers from Saudi Arabia with different HCV prevalence in different regions of Saudi Arabia [44].

Looking at risk factors for HCV transmission, reports from different Middle Eastern countries showed that medical practice especially before the era of blood and blood product screening such as blood or blood product transfusion in cases of thalassemia or hemophilia, hemodialysis, hospital instrumentation, and invasive procedures played a significant role in HCV transmission [45]. Alnaamani et al. showed that 41% of multi-transfused thalassemia patients from Oman were positive for anti-HCV. The majority of those patients were transfused before 1990 [46]. Age and level of education were also associated with HCV infection in certain Middle Eastern countries such as Yemen and Syria [47, 48]. Other risk factors for HCV transmission, such as intravenous drug abuse, piercing, and tattooing, as well as a risky sexual practice, contributed further to the spread of HCV among Middle Eastern countries [49]. Perinatal transmission from HCV-infected mothers to their newborn babies played a less important role as the risk of transmission is less than 5% unless the mother is coinfected with HIV. Intravenous drug abuse (IVDA) was found to be a major risk factor for HCV transmission in many Middle Eastern countries, including but not limited to Egypt, Lebanon, Oman, Palestine, Saudi Arabia, and Syria. Certain community groups such as prisoners and female sex workers are at increased risk of acquiring HCV infections, especially HIV-positive prisoners. The prevalence of anti-HCV among female sex workers in Lebanon, Libya, and Syria was higher than the general population [49, 50].

The majority of patients with positive anti-HCV in ME are chronically infected with HCV. The overall pooled mean viremic rate (positive HCV RNA) is 67.6% (95% CI, 64.9–70.3%). This figure is similar to that found in large population-based and nationally representative surveys [51]. Studies looking at the viremic rate at certain Middle Eastern countries reported the viremic rate to be 51.6% in Saudi Arabia and approximately 70% in Egypt and the UAE [5].

2.1 HCV Genotype and Subtype

HCV has 7 genotypes and 67 sub-genotypes based on variations at the nucleotide sequence by >30% and less than 15%, respectively [52]. There are several methods used to determine HCV genotypes; all of the methods use direct sequencing of certain regions of the HCV genome mainly (NS5, core, E1, and 5' UTR regions) using polymerase chain reaction (PCR) in combination with the phylogenetic analysis [53–56].

The distribution of HCV genotype varies between different regions of the world. HCV genotype 1 is the most prevalent worldwide representing 49.1%, followed by genotype 3 (17.9%), 4 (16.8%), and 2 (11%). The differences in HCV worldwide distribution are attributed to ancient world trade and human migration [57]. Genotype 4 is the most common in the ME,

accounting for 71% of all HCV-infected patients, followed by genotype 1, since most HCV-infected patients are from Egypt, where 90% of infected people have genotype 4 (Table 1) [58].

Analysis of HCV reports from ME showed that there are two main patterns of HCV genotype distribution. The first pattern represents most Arab countries where genotype 4 is the most common genotype except Jordan, Oman, Lebanon, Bahrain, and UAE, where genotype 1 is the most common [59]. Al-Busafi et al. reported the most common genotype in Oman to be genotype 1, representing 44%, followed by genotype 3, representing 35% [50]. The second pattern represents non-Arab countries (Turkey and Iran), where genotype 1 is the most common [59]. In Iran, genotype 1a is predominant for HCV, followed by genotype 3a and 1b, in addition to mixed genotypes [60]. Similar findings were reported from Turkey, where genotype 1b is the most common genotype representing >70% of HCV-infected people, followed by 1a. This HCV genotype distribution pattern in Turkey is similar to that reported from Eastern and Southern European countries [61].

3 Epidemiology of HCC in the ME

With an incidence of one million LC cases in 2016, LC is ranked as the seventh most common cancer worldwide. The majority of LC (75%) are HCC, followed by cholangiocarcinoma in 1–20% of cases [25]. HCC represents a leading cause of cancer-related mortality. More than 800,000 patients died in 2016 due to HCC. This high number of death ranked HCC as the fourth deadliest cancer [62]. Despite recent marked improvements in treatment modalities, the prognosis for HCC patients remains poor, with an average 5-year survival rate of approximately 5–6% [63]. Unfortunately, this is mainly attributable to a lack of access to medical facilities in many underdeveloped countries [64].

HCC is more common among males than females. The gender-specific age-adjusted incident rate (AAIR) ratio ranges from 1.3 to 3.6 worldwide. In high prevalence regions, the incidence of HCC rises after the age of 20 and peaks at 50 years of age [65].

There is marked variation in the prevalence of HCC in different parts of the world, with more than two-thirds of cases reported from East and South Asia as well as sub-Saharan Africa [66]. This is mainly due to differences in the prevalence of viral hepatitis, particularly hepatitis B and C, the predominant causes of liver cirrhosis, a known risk factor for HCC [67, 68]. The introduction of hepatitis B vaccination schedules in many countries has led to a marked reduction in HCC cases, with improvements in medical facilities and the designated screening programs similarly expected to help increase the detection and, therefore, reduce the incidence of HCC in these regions [69, 70].

The estimated risk of developing HCC in patients with CHC is 15–20 times higher than healthy persons, and this risk is further increased if CHC patients progressed to cirrhosis [71]. The age-standardized incidence rate (ASIR) of HCC in the Eastern Mediterranean countries based on the Global Burden Disease (GBD) study (2015) was 8.1 per 100,000 men and 4.7 per 100,000 in women [72]. The incidence and mortality of HCC in the Middle Eastern countries have increased based on the GBD 2015 [72]. However, such data should be interpreted cautiously. We have to keep in mind that cancer registries are incomplete in most Middle Eastern countries, and therefore the true incidence of HCC is underestimated. The absence of infrastructure and widespread medical facilities in countries affected by wars such as Iraq and Afghanistan will decrease the number of diagnosed cases as well as reported cases. Higher incidence rate and mortality related to HCC in other Middle Eastern countries could be attributed partly to improved healthcare facilities in certain countries as GCC; therefore, more cases are diagnosed and reported.

Cancer registry reports from certain Middle Eastern countries such as Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, Bahrain, and Lebanon showed a lower incidence rate of HCC than high incidence countries in Southeast Asia and sub-Saharan Africa. The exception is Egypt,

where the incidence of HCC is considered high, most likely due to the high prevalence of HCV.

HCC is ranked the fourth most common cancer in Egypt and the second cause of cancer-related mortality in both genders [72]. The highest age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) of LC were observed in Egypt and Qatar in 1990 and 2017. There was a rise by close to 12% in the ASIR of LC in ME from 1990 to 2017. On the other hand, there was a decline in ASIR of LC in certain Middle Eastern countries such as Yemen, Lebanon, Oman, Syria, Turkey, Afghanistan, Bahrain, Iraq, and Qatar from 1990 to 2017 [73]. This decline in ASIR could be due to improvement in the health system in certain countries such as Oman, Bahrain, Qatar, and Turkey and underreporting in certain countries due to many factors such as wars in Yemen, Syria, and Afghanistan [73]. Based on the Saudi Cancer Registry (SCR) reported in 2014, LC was ranked the sixth most common cancer in Saudi men and the ninth in Saudi women [74]. The ASIR for LC was 4.5 per 100,000 populations, and the ASMR was 4.2 per 100,000 populations based on 2018 data from the International Agency for Research on Cancer (IARC). The ASIR of LC in Saudi Arabia and Kuwait was a bit higher compared to other GCC countries. The reported ASIR per 100,000 populations for Bahrain was 3.4, Qatar 4.1, United Arab Emirates 4.2, and for Oman 4.4 [75]. Alghamdi IG et al. looked at all the documented cases of LC from different regions of Saudi Arabia between 2004 and 2014 and reported 300 patients (9.1%) per year. Old age, mean age of 75 years old, Saudi males were commonly affected [76]. Al-Naamani et al. reported the characteristics of HCC among 284 patients from Oman and showed the mean age of presentation was 61.02 ± 11.41 years. Most of the patients (67.6%) were male. The majority had liver cirrhosis (79.9%), with the most common etiologies being CHC (46.5%) and CHB (43.2%) [77]. The highest ASIR and ASMR of LC among both genders were reported from Egypt at 49 and 3.8 per 100,000 populations, respectively [78].

HCC is not common in certain countries such as Lebanon, ranking 14th among both males and females with an ASIR of 3.5 and 2.2 per 100,000, in both males and females, respectively [79]. Different studies from Iran reported different incidence rates from other regions of Iran. This discrepancy in the incidence rate is most likely related to the prevalence of various risk factors and the accuracy of diagnosis and registration of cancer in different regions [80, 81]. In a meta-analysis by Hassanipour et al., LC's incidence rate among Iranian men and women was 1.66 and 1.2 per 100,000 populations, respectively. This incidence rate is lower when compared to Asian countries [82]. The Turkish ministry of health report in 2003 showed the incidence of HCC was 0.83 per 100,000 populations. There was no difference in the annual incidence of HCC in Turkey between 2000 and 2003 [83]. Based on the Turkish multicenter study of 222 patients with HCC, Alacacioglu et al. showed that the median age of HCC patients was 62 + 11.3 years. The majority of the patients (76.9%) were males with liver cirrhosis (74.2%) [84].

4 Risk Factors of HCC in ME

The main challenge still present in ME is the high prevalence of chronic viral hepatitis. Therefore, prevention of infection with hepatitis B and hepatitis C is the key to reduce the burden of viral hepatitis complications such as HCC in ME. The major risk factors for HCC are the presence of cirrhosis due to any etiology and HBV infection. Most HCC arises on the cirrhotic liver [85–87].

The marked improvement in the management of liver cirrhosis and screening for HCC over the last few decades has increased liver cirrhosis patients' survival and therefore increased the chance of development of HCC [88–90]. However, screening and diagnosis of early-stage HCC may lead to better treatment outcomes [91].

Other risk factors, such as aflatoxin B exposure, are important in certain parts of the world, especially Asia and Africa [92]. Liver cirrhosis due to hepatitis C and NASH are common risk factors for the development of HCC in the developed world [93, 94]. Studies and reports from ME showed marked variation in the etiology of

HCC. Chronic viral hepatitis is still the most common etiology of liver cirrhosis and HCC in the ME.

The ASIR of HBV-related HCC in ME decreased markedly from 1990 before the era of HBV vaccination to 2017; however, despite the marked reduction in HBV infection incidence, it remains the second common cause of HCC in ME. This is most likely due to the complications of HBV-infected people before the era of vaccination [73]. HBV-related liver cirrhosis is the most common etiology of HCC in Lebanon and Turkey, followed by HCV and alcohol-related cirrhosis, respectively.

CHB is associated with higher risks for HCC [95]. There is a closer relationship between HBV infection and the development of HCC. CHB patients can develop HCC at any stage of their disease; however, most develop HCC after reaching cirrhosis [96]. The risk of developing HCC is 100-fold higher for patients infected with HBV compared to those who are not infected [96]. Previous studies demonstrated that male gender, old age, high serum HBV DNA, pre-core and core promoter mutations, and the presence of cirrhosis are risk factors for the development of HCC among CHB patients [97–99].

The majority of Middle Eastern countries have introduced HBV vaccination, reaching 90% coverage before the age of 1 year. Unfortunately, this is not complemented by highly viremic pregnant women's treatment neither administration of hepatitis B immunoglobulin to babies of HBV-infected mothers. Moreover, the rate of HBV diagnosis in ME is low (6%); besides, only 2% of HBV treatment-eligible patients were treated [100]. All of the above obstacles will reduce HBV elimination activities in Middle Eastern countries.

CHB patients coinfected with HDV are at higher risk of acceleration to cirrhosis and, therefore, developing HCC [101]. Coinfection with HDV leads to accelerated fibrosis and cirrhosis in more than 70% of cases [102]. The reported prevalence of hepatitis D virus (HDV) among CHB patients in Jordan was 23% [103]. The prevalence of HDV among patients with HCC differs between different Middle Eastern countries. The reported prevalence in Jordan was 67%; however, patients with HDV coinfection were older than those with HBV mono-infection [103]. The reported prevalence of HDV in Turkey ranges from 18.8% to 23.0% of HBsAg-positive HCC [104, 105]. These findings suggest an association between HDV and HCC.

Non-alcoholic fatty liver disease (NAFLD) is becoming the leading cause of cirrhosis and HCC worldwide. The world prevalence of NAFLD is estimated at around 25% [106]. The prevalence of NAFLD in ME is approximately 30%, which is considered one of the world's highest prevalence [106]. Despite the limitations of the studies quoted by Younossi et al., the high prevalence of DM, obesity, and metabolic syndrome is reported in multiple publications [107]. GCC states reported the highest prevalence of obesity in the world among the young age population. This population will most likely carry their obesity and their associated NAFLD into adulthood and develop complications such as liver cirrhosis and HCC [108]. NASH-related HCC had the highest ASIR in ME, and the development of HCC on the non-cirrhotic liver was also described in patients with NASH [109].

For a long time, CHC is the most common cause of HCC in ME, followed by CHB. Chronic viral hepatitis accounted for approximately 70% of all HCC in ME [6]. Studies looking at the epidemiology of HCC in ME reported that the majority (70%) of patients with HCC from Egypt, which has the highest prevalence of HCV worldwide, were found to have markers for HCV infection [110, 111]. Similarly, more than one-third (39.5%) of HCC patients from Saudi Arabia were found to be positive for anti-HCV [34, 76]. The pathogenesis of HCV-induced HCC will be discussed later in this chapter.

The mortality related to HCC in ME is declining in the young population, most likely due to HBV vaccination and the high cure rate of HCV associated with DAA treatment [100]. Thus, future trends in HCC in Middle Eastern countries are expected to come down and to have a favorable outcome than other parts of the world, such as East Asia and Africa [112].

4.1 Risk Factors of HCC Among HCV-Infected Patients

The incidence rate of HCC related to CHC in the ME has increased by 16% over 17 years, from 1990 to 2017 [73]. The interaction between CHC and the host immune system is complex. This interaction involves multiple factors leading to the development and growth of HCC. The vast majority of patients with CHC develop HCC on a background of cirrhosis. However, approximately 15% of CHC patients who develop HCC have no cirrhosis [113–116].

Multiple host and, to a lesser extent, viral factors play roles in developing liver cirrhosis and HCC. Host factors such as chronic excessive alcohol consumption, NASH, and coinfection with HBV and HIV play major roles in accelerating liver fibrosis [98]. Poynard et al. showed that patients with CHC who consume more than 50 g of alcohol daily had a 34% higher rate of progression to advanced fibrosis compared to non-drinkers regardless of the age and duration of infection [9]. Similar findings were reported by researchers from Japan who showed that patients with HCV who consume more than 65 g of alcohol daily for more than 5 years have RR, 3.04; 95% CI, 1.31–7.09; and $P < 0.01$ of developing HCC [117, 118]. Further evidence of the additive risk of development of HCC in patients with HCV who consume a large amount of alcohol for many years was shown in the Dionysos study by Donato et al. from Italy [71].

NASH is a common risk factor for the development of HCC among CHC patients. There is a complex relationship between NASH and CHC. CHC, especially genotype 3, is known to induce fatty liver through the direct cytopathic mechanism, and NASH tends to accelerate liver fibrosis progression in patients with CHC [119]. The prevalence of fatty liver among patients with CHC varies from 40% to 80% [120]. However, the reported prevalence of NASH among CHC patients is much lower, around 4–10% [121–124]. Bedossa et al. showed that patients with CHC and NASH tend to have advanced fibrosis compared to patients with CHC alone. A higher grade of fibrosis and cirrhosis will predispose CHC to the risk of HCC [123].

HBV is a carcinogenic virus. Patients with CHB are at risk of developing HCC at any stage of their liver fibrosis. CHC coinfected with CHB tends to have a higher incidence of HCC of 6.4% as compared with an incidence of 2% for CHB alone and 3.7% for HCV infection alone [125]. Zampino et al. evaluated the development of HCC among patients with viral hepatitis. They found that 14% of HCV coinfected with HBV developed HCC compared to 2% and 4% among HBV and HCV mono-infection, respectively [126]. A similar synergistic effect was reported by Bevegnu et al., who showed 36% of HCV coinfected with HBV patients developed HCC compared to only 6% of CHC patients and 11% of CHB patients [127]. This additive risk of development of HCC in coinfected patients was also demonstrated in Asian studies. Oh et al. reported a hazard ratio of 115 for developing HCC in coinfection, 17 in HBV mono-infection, and 10.4 in HCV mono-infection [128]. Certain factors such as alcohol consumption, genetic factors, and NASH presence could contribute to the higher risk of development of HCC in HBV/HCV coinfected patients [71, 129, 130].

HIV is common among CHC patients. Almost one-quarter of HIV patients are coinfected with HCV [131]. Liver disease is a major cause of non-AIDS-related deaths, accounting for 16% of mortality among HIV-infected patients [132]. The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s to treat HIV has markedly changed the natural history of HIV infection. The improvement in the survival of HIV patients led to a significant reduction in diseases related to the human immunodeficiency syndrome. Prior studies demonstrated accelerated liver injury in HIV mono-infection and HIV coinfected with HCV [133, 134]. Puoti et al. looked at an Italian cohort of 41 HIV patients who developed HCC and demonstrated an unfavorable association between HIV/HCV coinfection and HCC behavior (infiltrating tumors and/or extra-nodal metastasis at presentation (OR = 11.8; $P < 0.001$). HIV infection was independently associated with poor survival (hazard

ratio, 1.63; $P = 0.015$) [135]. Similar findings were reported by Beretta et al. in 2011, who demonstrated a shorter survival rate among young patients coinfected with HIV and HCV who develop HCC [136].

Most of the studies mentioned above were observational studies with a small number of patients, and there was no adjustment for other risk factors such as alcohol intake and the presence of NASH. In addition to that, these studies were performed before the era of DAA, where a significant number of patients were not treated for HCV using interferon-based therapy. The above findings were not demonstrated by Marcon et al., who looked at 399 Brazilian patients with HIV coinfected with HCV and compared them to 405 monoinfected with HBV or HCV. One-third of HIV-negative patients developed liver cirrhosis compared to 16.5% of coinfected ($P < 0.001$). HCC was diagnosed in 10 HIV-coinfected patients compared to 26 monoinfected with HBV or HCV [137].

One of the crucial factors for the development of HCC in patients with CHC is type 2 diabetes mellitus (DM-2). DM-2 is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance. DM-2 is becoming a major cause of morbidity and mortality around the globe. The prevalence of DM-2 in ME has increased enormously over the last few decades. DM-2 has been found to increase the risk of different types of malignancies, such as breast, endometrial, renal, and GI cancers such as colon, pancreatic, and liver cancers [138–142]. DM-2 may induce liver fibrosis and HCC through different mechanisms, including hyperglycemia, hyperinsulinemia, insulin resistance, and activation of insulin-like growth factor (IGF) signaling pathways. These mechanisms are known to have proliferative effects such as insulin and insulin-like growth factor 1 and oncogenic effects such as hyperglycemia [143]. In addition to that, DM-2 also predisposes patients to NASH, which may progress to cirrhosis in up to 5% of cases [144]. Rousseau et al. looked at the 3107 male cancer cases and 509 population controls, used information on diabetes and several covariates collected by interview, and found that the risk of HCC was increased among people with diabetes and adjusted OR was 3.1 (95% CI: 1.1, 8.8) [145]. Similar findings were reported by El-Serag et al., who performed a meta-analysis of 13 cohort studies and 13 case-control studies and found that DM is associated with an approximately 2.5-fold increased risk of HCC [146]. The risk of developing HCC is significant in the presence of other HCC risk factors, such as chronic viral hepatitis, high alcohol consumption, and liver cirrhosis.

5 Pathogenesis of HCV-Induced HCC

The exact mechanisms of development of HCC in patients with CHC are unknown despite the establishment of the relationship between CHC and the formation of HCC [147, 148]. Chronic viral hepatitis is the leading cause of HCC. HCV has become an important risk factor for HCC in regions with intermediate-incidence areas such as the ME [73]. More than half of HCV-infected patients will develop cirrhosis, and 14.4% are predicted to develop HCC [149]. Different mechanisms of HCC development have been postulated to explain the causal relationship between HCC and HCV. Since the discovery of HCV in 1989, multiple studies using animal models revealed that HCV changes many cell signaling pathways involved in cell proliferation, migration, and transformation. Many of these changes will ultimately lead to chronic inflammation and fibrosis. The interaction between the host, the virus, and other additive mechanisms leads to the development of HCC (Fig. 2).

5.1 Viral-Related Mechanism

An extensive network of tubules and flattened sacs within the hepatocyte cytosol called the endoplasmic reticulum (ER) plays an essential role in lipids and protein biosynthesis, therefore maintaining hepatocyte function in the liver. CHC infection poses significant stress on the ER through alterations of protein synthesis, degrada-

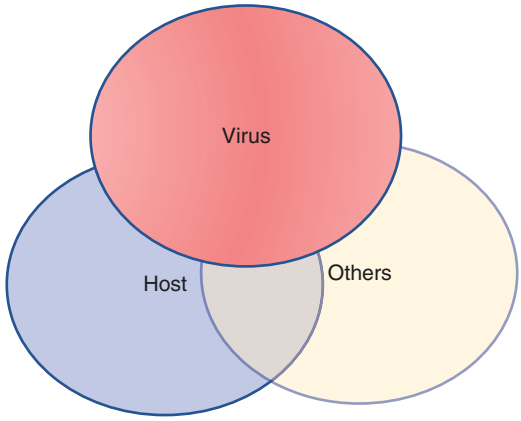

Fig. 2 Interaction between viral, host, and other additive mechanisms

tion, or folding. CHC infection, especially genotype 3, is associated with fatty liver. The accumulation of fatty acids and cholesterol within the infected hepatocyte may inhibit protein degradation, adding more stress to the ER. Due to these reasons, the stressed ER can activate specific signaling pathways leading to inflammation, cellular injury, fibrosis, and cirrhosis [150–152]. In addition to the stress imposed by CHC on ER, continuous viral replication increases hepatocyte's DNA damage, genomic instability, and ultimately death of hepatocytes through different forms such as apoptosis, necrosis, and autophagy [153].

Autophagy is the process by which the cells remove misfolded or aggregated proteins and clear damaged organelles and eliminate intracellular pathogens. Autophagy is essential for maintaining the cellular source of energy during extreme cellular stress. Uncontrolled autophagy has been linked to the development of HCC [154].

The stress produced by HCV infection is maintained and amplified by certain inflammatory cytokines and interferon (IFN). Infected liver cells respond to continuous stress imposed by CHC through unfolded protein response, antioxidant response, and induction of integrated stress response that enhances the transcription of many genes required for survival [155]. Analysis of whole-exome sequencing of HCV-related HCC tumors demonstrated downregulation of many suppressor genes, mutations in cancer driver genes, and genomic instability in the majority of cases [156, 157].

5.2 Host-Related Mechanisms

The innate and adaptive immune responses are both activated during HCV infection. Activation of both responses leads to the recruitment of many inflammatory cells. Production of interferons (IFNs) and certain cytokines by the immune system during HCV infection is a characteristic of early host immune responses [158]. HCV develops different mechanisms that impair the cytotoxic and immunoregulatory activities of immune cells to avoid early host immune responses and develop chronic infection [159].

CHC infection is characterized by immune-mediated inflammation with the production of chemokines, metabolites, and growth factors that promotes liver regeneration and fibrosis. The repeated cycles of liver cell death and regeneration could drive the formation of HCC [160, 161].

5.3 Additive Mechanisms

More than one etiology of liver cirrhosis can be found in the same patients leading to accelerated fibrosis, cirrhosis, and finally development of HCC. Coinfection with hepatitis B doubles the risk of development of HCC compared to each virus alone [162]. Similarly, patients with HCV and HIV coinfection are at higher risk of developing liver cirrhosis and HCC [163].

Components of metabolic syndrome such as obesity, type 2 diabetes, and associated NASH have been found to accelerate HCV-induced liver cirrhosis and HCC [164, 165].

The mechanisms involved in the HCV-induced HCC are similar to other etiologies leading to liver fibrosis, cirrhosis, and HCC. ER stress leads to chronic inflammation, cell death and regeneration, fibrosis, and the development of HCC. Activation of oncogenes and loss of tumor suppressor can play some role in the development of HCC; however, the development of HCC

post-HCV eradication is not fully explained by the previously mentioned mechanisms.

Multiple studies demonstrated different immune-related changes post-HCV treatment using interferon-free therapy. A rapid decline in HCV RNA leads to memory re-differentiation and reduced lymphocyte activation, restoration of HCV-specific CD8+ T cell function, modulation, and normalization of NK cell function [166–168]. These changes lead to loss of immune response to neoplastic cells and therefore HCC recurrence after DAA treatment.

6 Strategies to Prevent HCV-Induced HCC

Many patients with HCC are asymptomatic when tumors are at an early stage. Therefore, unfortunately, the majority are diagnosed at advanced stages, which is associated with a dismal prognosis [169]. One study from KSA showed that most of the patients were diagnosed at an advanced stage (53% had cancer of the Liver Italian Program score (CLIP) of 4–6 (advanced stage), and 55% had large multinodular tumors) [170]. A similar finding was shown in other country-specific reports from Qatar [171] and Oman [77]. Despite advancements in the treatment modalities of different types of cancers, HCC is considered a highly refractory cancer to therapeutic interventions [172]. It is well-known that prevention and early detection are the most rational and effective ways to substantially impact cancer-related outcomes rather than starting treatment at an advanced stage [173]. This highly supports the importance of considering prevention and early detection of HCC in high-risk patients [172]. Like any other preventive diseases or cancers, HCC prevention constitutes three levels of interventions (Table 2). The primary prevention focuses on preventing and eliminating exposure to HCC-related risk factors at an early stage using lifestyle and dietary changes, vaccination (under research), and avoiding exposure to environmental factors or carcinogens in an etiology-specific manner. Next is secondary prevention, which focuses on early detection or chemoprevention of HCC in high-risk patients. Lastly, tertiary prevention focuses on the prevention of the progression or recurrence of HCC [174].

Table 2 Levels of prevention against HCV-related HCC

Level	Description	Examples
Primary prevention	Prevention of new HCV infection	Screening blood products Universal precautions to prevent blood contamination in healthcare settings Education programs for high-risk patients Treatment of HCV-infected patients
	Prevention of fibrosis progression to cirrhosis	Treatment of HCV-infected patients Modifications of other related factors (i.e., treatment of HBV, HIV, lifestyle modifications in NASH)
Secondary prevention	Prevention of progression of cirrhosis or regression of cirrhosis	Treatment of HCV-infected patients Chemoprevention
	Early detection of HCC to improve treatment outcomes	HCC screening (liver ultrasonography with/without alpha-fetoprotein)
Tertiary prevention	Prevention of tumor progression or recurrence after curative treatment	Antiviral therapy for HCV Locoregional therapies Chemoprevention Close monitoring

Modified from Hoshida et al. [174]

6.1 Primary Prevention

Primary prevention of HCV-related HCC includes prevention of new HCV infection either through vaccination (under research) or prevention of transmission. Although research efforts are still ongoing, unlike HBV infection, vaccines for HCV infection are currently unavailable. The development of an effective HCV vaccine is challenged by several viral factors, including the lack of a neutralizing antibody and the diversity of the viral genome [175, 176]. Therefore, the primary

prevention against HCV transmission depends mainly on universal precautions, especially through contaminated blood or blood product transfusion, sterilization of medical instruments, and intravenous injection use (Table 2).

As we mentioned earlier, several reports from different Middle Eastern countries showed that healthcare-related exposures were most frequently reported, followed by exposure to intravenous drug use [177]. Blood and blood product transfusion, hemodialysis, surgical and other invasive medical procedures, dental practice, and medical injections were identified as key healthcare-related exposures [177]. The other important primary prevention method is eradicating HCV infection using antiviral therapies. Effective treatment of HCV is associated with preventing transmission of the virus as well as preventing progression to advanced fibrosis/cirrhosis and development of HCC [178]. Apart from Egypt, most Middle Eastern countries have not yet implemented a national HCV screening program [179]. In 2018, the Egyptian Government initiated a national HCV screening campaign, and all those with confirmed HCV infection are enrolled in government-subsidized treatment program using DAA regimen [180]. In Saudi Arabia, premarital screening for HCV is mandatory for all nationals [181]. However, one pooled analysis of 2500 prevalence measures, including 49 million tests, in the MENA region showed that the population risk of HCV exposure depends on whether the type of epidemic is generalized (like Egypt and Pakistan) or concentrated (like the rest of the countries). This study demonstrated that major gains could be achieved through targeted, cost-effective screening programs that factor in the epidemic type and are tailored to each country [182].

6.2 Secondary Prevention

Secondary prevention of HCV-related HCC aims at preventing HCC development in high-risk patients through direct anti-HCV therapy, treatment of additive factors such as HBV and HIV, lifestyle modifications in NASH patients, and elimination of alcohol intake. Over the last decades, there were several trials, including phase III trials, on chemoprevention therapies targeting inflammation, fibrogenesis, and carcinogenesis. Unfortunately, these trials have demonstrated limited efficacy and utility of those therapies [183–185]. In addition, conducting clinical trials of those identified candidate chemopreventive agents, such as statins, anti-diabetic drugs, aspirin, and dietary agents such as coffee, vitamin E, and fish oil, is limited by the long duration of cancer development that requires long-term, costly studies [176]. Thus, well-designed, prospective, population-based cohort studies might overcome those obstacles and provide the best evidence for the chemo-preventive effectiveness.

The eradication of HCV in patients using anti-HCV treatment lowers but does not eliminate HCC risk in already established advanced fibrosis or cirrhosis [172, 176, 186–190]. More data from IFN-based therapy demonstrated a beneficent long-term clinical effect in patients who achieve SVR, including a reduction in the risk of HCC [191–194]. One recent large population study from Canada included more than 8000 patients treated with older IFN-based therapy between 1990 and 2013 and showed that SVR prevents HCC. However, those with cirrhosis and age ≥50 years remain at higher HCC risk and will require continued monitoring for HCC [186]. Furthermore, different studies using post-therapy liver biopsy have observed that HCV eradication can lead to long-term histological regression of the grade of fibrosis or reduction in the rate of fibrosis progression in more than 50% of the patients [193, 195, 196]. Although we can believe that the same will happen in patients treated with DAA therapy, more studies have to be demonstrated [197]. A recent real-world cohort study from Portugal showed DAA-induced SVR is associated with a low risk (but does not prevent) HCC occurrence or disease progression [189]. In the same study, using post-SVR transient elastography to assess fibrosis improvement, there was an improvement in liver stiffness after SVR. This improvement may result from a decrease in necro-inflammatory activity after SVR, which may lead to overesti-

mation of fibrosis regression [198–200], a fact that has also been demonstrated by matched elastography-biopsy comparison [201].

Regarding patients with fibrosis stage 4 (F4), those with an "early regression" (decrease in hepatic stiffness ≥30% 24 weeks after the end of therapy) had higher baseline elastography values, which supports the role of inflammatory activity reduction in this context [202]. Another recent study using the FIB-4 index also showed that achieving SVR post-DAA therapy is associated with decreased fibrosis progression in more than half of the patients [203]. Different studies showed that SVR might lead to sustained progressive improvement in the degree of portal hypertension and, probably, in the degree of liver fibrosis through either direct (reduction in hepatic venous pressure gradient (HVPG)) or indirect measurement (improvement in platelet counts) [199, 200, 204].

Secondary prevention also includes early detection of HCC and therefore increasing the likelihood of curative treatment. Screening using a "one-size-fits-all" approach, i.e., regular 6-monthly ultrasound with or without a-fetoprotein (AFP), in populations with HCC risk is recommended by all current international societies [205–207], including the Saudi Gastroenterology Association [208]. A series of studies and reports indicate that HCC screening is cost-effective and associated with improved early tumor detection, curative treatment rates, and overall survival when available to more than 34% of patients at risk [209–211]. HCC screening is practically challenging to implement in clinical practice as only one in five patients received surveillance before HCC diagnosis (low application rate of <20%) [172, 212, 213]. The low utilization rate of HCC screening was not shown to be related to patient adherence, as one study showed only 3% of patients with HCC failed to complete surveillance despite orders [213]. Provider-related factors, including failure to recognize liver disease or cirrhosis, failure to order screening tests, and time constraints, were identified as more influential factors compared to patient adherence [213, 214]. HCC surveillance was more likely among patients seen by hepatologists compared to non-specialists (odds ratio of 6.1) [213]. Population-based interventions such as mailed outreach invitations could improve the surveillance rate to approximately 45% [215]. With the currently available resources, the large number of the target population is another limitation, given that cirrhosis is estimated to affect around 1–2% of the world population [216]. The extent of HCC risk for emerging populations, such as NAFLD without cirrhosis and HCV patients post-sustained virologic response (SVR), is yet to be determined. The most proper screening methods and surveillance internals for these populations will need to be clearly defined [212]. All of the above issues highlight the limitations of the current one-size-fits-all HCC surveillance strategy, which assumes a similar risk of HCC across all patients with the same clinical condition (e.g., HCV-related cirrhosis). This strategy may result in an over- or underestimation of HCC risk for each patient [217, 218]. Thus, a more precise determination of individual HCC risk is critical for implementing practical and feasible HCC screening and to enable optimal allocation of the limited resources, as detailed below.

6.3 Tertiary Prevention

The tertiary prevention aims to prevent HCC progression or recurrence after curative therapy of initial HCC, such as surgical resection, ablative treatment, or liver transplantation. However, despite the advances in surgical techniques and ablation technologies, the 5-year survival rate and recurrence rate are around 50% and 70%, respectively [219, 220]. The incidence of post-curative therapy HCC recurrence in cirrhosis is approximately three times more frequent than the first HCC. Therefore, it is vital to identify effective tertiary prevention interventions rather than secondary prevention [221].

HCC recurrence post-curative therapy has been classified as early (within 2 years of curative treatment) or late (>2 years after curative treatment) [222–224]. Early recurrence has been attributed to undetected micrometastasis and is associated with both tumor and surgical factors,

such as large tumor size, macroscopic vascular invasion, multinodularity, and close resection margins. On the other hand, late recurrence has been attributed to de novo second primary tumor development and is associated with host factors, such as background liver diseases, hepatitis virus load, and cirrhosis status.

To date, similar to secondary prevention, adjuvant chemoprevention therapies have not proven effective as tertiary prevention [224–226]. Although several early studies, including randomized control trials, explored the potential benefit of vitamin K2, retinoid, different systemic chemotherapy agents, and lately sorafenib, none of the studies reported successful [226].

Like primary and secondary prevention, tertiary prevention could also theoretically be achieved through anti-HCV therapies. One may expect that effective anti-HCV therapies may only reduce late HCC recurrence, as demonstrated by the Italian randomized control trial using adjuvant IFN-α therapy in HCV-related HCC [224]. However, IFN-α plus ribavirin therapy also reduced early recurrence within 1 year in another Taiwanese nationwide cohort study [227]. In another randomized control trial performed in Japan, 49 patients with HCV-related HCC were administered IFN-α therapy after complete ethanol ablation. Among the treated patients, 14 (29%) demonstrated SVR. Compared with the 25 patients who did not receive adjuvant IFN-α therapy, the rates of first recurrence were similar, but the rates of second and third recurrence were lower in those receiving adjuvant IFN-α treatment [225]. Therefore, IFN-based therapy has been shown to improve outcomes following curative HCC therapy.

Whether the high rates of SVR achieved with DAA regimens have a beneficial or deleterious effect on the risk of recurrence following resection or ablation of HCC has been debated, following the publication of a large number of generally small-scale, retrospective studies with contradictory results [228–237]. Systematic review and meta-analysis of Waziry et al. in 2017, including 13,875 patients to assess HCC occurrence (26 studies) and recurrence (15 studies) post-IFN therapy versus DAA-based SVR, found no evidence to support the higher rate of occurrence and recurrence of HCC post-DAA compared to IFN therapy [238]. In addition, a retrospective US cohort study including 797 patients with HCV-related HCC who achieved a complete response to resection, local ablation, transarterial chemo- or radio-embolization, or radiation therapy has shown that DAA therapy was associated with a significant reduction in the overall risk of death [239]. Therefore, there are no conclusive data that DAA therapy is associated with increased or decreased risk, differential time to recurrence, or aggressiveness of recurrent HCC in patients with a complete response to HCC therapy. Thus, DAA therapy should not be withheld from such patients. According to the recent EASL guidelines, DAA therapy can conveniently be deferred 4–6 months in patients without cirrhosis or with compensated, Child-Pugh A, cirrhosis to consolidate treatment and confirm a response to HCC therapy in patients treated with curative intent [240].

Treatment of patients awaiting or post-liver transplantation (LT) has also been controversial. The impact of DAA on delisting for HCC progression or recurrent HCC post-LT has not been well characterized. In a retrospective cohort study of 149 LT candidates with HCV infection and HCC at a single center, patients treated with DAAs for their HCV infection had a lower risk of waitlist dropout due to tumor progression or death compared to the patients who had not been treated [228]. Post-LT treatment of HCV was reported to be cost-effective in patients with HCC [241]. In patients with HCC, without cirrhosis, or with compensated cirrhosis, with an indication for LT, pre- or post-LT antiviral treatment indications are similar to those in patients who do not have HCC [240, 241]. In patients with HCC awaiting liver transplantation with an HCV infection in centers with long waiting times, HCV treatment should be initiated before liver transplantation to facilitate locoregional therapies to reduce waiting list dropouts due to tumor progression.

7 HCC Risk Prediction Models

HCC risk scores are used to enable precise HCC risk prediction. Such scores could identify a subgroup of individuals at high risk, maximizing the cost-effectiveness of screening tools and concentrating the efforts and resources, especially in resources-limited countries [172], in other words, applying HCC risk scores to those who are most likely to benefit from prevention and early detection, i.e., individual personalized risk-based HCC screening [172].

HCV-related HCC is previously discussed in this chapter. The risk of developing HCV-related HCC was shown in different studies to be significantly associated with the presence of cirrhosis, older age, male gender, excessive alcohol consumption [117, 118], coinfection with HBV [125–127, 129] and HIV [131–136], presence of obesity [164, 242, 243], diabetes status [139, 141, 143, 144, 146], and NASH [119–124].

Other epidemiologic and clinical studies have reported more demographic, clinical, lifestyle, genetic, and pharmacological factors that further affect or modify the likelihood of HCC [212]. The combination of different readily available clinical risk factors has been evaluated by various trials to develop HCC risk-predictive scores. However, their performance is somewhat limited, and they are yet to be adopted in clinical practice (Table 3) [212]. Molecular biomarkers have also been actively explored like AFP "a-fetoprotein," AFP-13, and DCP "des gamma-carboxy prothrombin," and some of them were combined with the clinical scoring systems to improve their HCC risk prediction [172, 244]. While the promise of these candidate molecular biomarkers is clear, some significant challenges and obstacles limit their clinical translation, like assay development and implementation and regulatory approval.

8 Antiviral Therapy and HCC

Before 2011, IFN-based therapy, with or without concomitant ribavirin, was the mainstay of treatment for those infected with HCV, with success rates ranging between 5% and 50%, depending on the genotype, stage of liver disease, and duration of therapy [259–261]. The addition of ribavirin improved outcomes but was poorly tolerated by most patients due to severe adverse effects. The management of HCV has transformed over the past decade, with SVR rates above 90% following the introduction of an IFN-free DAA-based regimen even in patients with cirrhosis [262–264].

Before using DAAs, IFN-based regimens were used in specific subgroups of patients, with significant histopathological improvements seen following successful treatment. Nowadays, it is harder to assess post-SVR histopathological changes as we are no longer required to perform pre-treatment biopsies as we were within the IFN era. However, when evaluating histopathology within 2 years of treatment, though there is a suggestion of fibrosis regression, persistent inflammatory activity has been observed despite the absence of the virus [265]. IFN-based therapies have shown that SVR is consistently associated with gradual regression of fibrosis and lower risk of HCC in retrospective studies [266, 267].

One of the goals of achieving SVR is a reduction in the incidence rate of HCC. Studies from the era of IFN-based therapy demonstrated clearly that attaining SVR was associated with a lower rate of development of HCC in 0.5–1% per year [186–188]. There was an increasing number of reports in 2016 describing a higher incidence rate of HCC post-DAA compared to old treatment with interferon-based therapy [229, 230, 268, 269]. However, one has to keep in mind that most of these studies were observational studies, including a small number of patients, with a short period of follow-up and no control arm. In addition to that and with the high safety profile of DAA compared to interferon, older patients with cirrhosis and other risk factors for HCC that were not eligible for treatment with IFN were included in most of those observational studies using DAA. The meta-analysis by Morgan et al. in 2013, including 30 observational studies, of which 18 studies had adjusted effect estimates, found that SVR after HCV therapy at any stage of fibrosis was associated with reduced risk for

Table 3 Clinical risk prediction models for HCV-related HCC

Risk models	Study design	No. subjects	Race/ethnicity	Cirrhosis	Variables	Validation
Singal et al. [245]	Prospective-retrospective, cohort	442 + 1050[a]	White, black, Hispanic	100% + 41%[a]	23 clinical variables	External
REVEAL-HCV [246]	Prospective-retrospective, cohort	1095 + 572[a]	Asian	1.4% + 7.0%[a]	Age, ALT, AST/ALT, HCV RNA, cirrhosis, HCV genotype	External
Ganne-Carrie et al. [247]	Prospective-retrospective, cohort	720 + 360[a]	n.a.	100%	Age, past alcohol abuse, platelet, GGT, SVR	Internal
Lok et al. [248]	Prospective-retrospective, cohort	1005	White, black, Hispanic	40% (Ishak 5/6)	Age, race, platelet, ALP, esophageal varices, smoking	No
El-Serag et al. [249]	Retrospective, cohort	5586 + 5760[a]	White, black	100%	AFP, ALT, platelet, age	Internal
Motosugi et al. [250]	Retrospective, case-control	66:66[b]	Asian	n.a.	LSM by MRE	
Chang et al. [251]	Retrospective, cohort	1252 + 627[a]	Asian	45% (F3/4)	Age, sex, platelet, AFP, advanced fibrosis, HCV genotype 1b, SVR	Internal
Ikeda et al. [252]	Retrospective, cohort	1056	Asian	10%	Age, AST, platelet before IFN treatment	No
scoreHCC [253]	Retrospective, cohort	871	Asian	30%	Age, AFP, platelet, advanced fibrosis	No
Wang et al. [254]	Retrospective, case-control	21:355[b]	Asian	33.8% (F3/4)	LSM, advanced fibrosis, diabetes	No
ADRESS-HCC [255]	Retrospective, cohort	17,124 + 17,808[a]	White, Hispanic	100%	Age, diabetes, race, etiology, sex, Child-Pugh score	External
Velazquez et al. [256]	Prospective, cohort	295 + 168[a]	n.a.	100%	Age, HCV, prothrombin time, platelet	Internal
VFMAP [257]	Retrospective, cohort	1808	Asian	13%	LSM, fast plasma glucose, sex, age, AFP	No

n.a. not available/applicable. *"Prospective-retrospective"* indicates the retrospective analysis of prospectively collected cohort in the past [258]. *ADRESS-HCC* age, diabetes, race, etiology of cirrhosis, sex, and severity of liver dysfunction-HCC, *AFP* a-fetoprotein, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CPA* collagen proportionate area, *GGT* c-glutamyltransferase, *HbA1c* glycated hemoglobin, type A1c, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *IFN* interferon, *LSM* liver stiffness measurement, *MRE* magnetic resonance elastography, *REVEAL-HCV* Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HCV, *SVR* sustained virologic response, *VFMAP* virtual touch quantification, fast plasma glucose, sex, age, and AFP

[a]Training + validation

[b]Case-control

HCC (relative risk for all, 0.24 [95% CI, 0.18 to 0.31]) [270]. The second systematic review and meta-analysis of Waziry et al. in 2017, including a total of 13,875 patients to assess HCC occurrence (26 studies) and recurrence (15 studies) post-IFN therapy versus DAA-based SVR, found no evidence to support the higher rate of occurrence and recurrence of HCC post-DAA compared to IFN therapy [238]. A third and recent 2019 meta-analysis by Rutledge et al. includes 138 studies with many patients (n = 177,512) looking at the development of HCC post-DAA compared to those of IFN-treated and untreated populations. This study also showed no evidence of increased HCC in patients who achieved SVR by DAAs than those treated with IFN [271].

Multiple other studies and meta-analyses showed similar evidence to the above-quoted studies. Therefore, achieving SVR will reduce the risk of HCC development but will not eliminate it. Patients with advanced fibrosis and liver cirrhosis will be at risk of developing HCC, and continuous surveillance for early HCC detection is highly recommended.

8.1 Post-SVR Surveillance

HCC recurrence is exceptionally high, reaching up to 70% after 5 years of resection. HCC can occur even quite 10 years after SVR. The 1–4% yearly incidence of HCC post-SVR is higher than other cancers [176]. Therefore, prevention of HCC development in patients with liver cirrhosis could represent the foremost effective way of improving patient survival [174]. Retrospective evaluation of patients who developed HCC post-SVR showed several HCC-associated risk factors, most of which are similar to the risk factors in patients with active HCV infection. The foremost important risk factor for HCC development post-SVR is the presence of advanced liver fibrosis [252]. Other important risk factors that might lead to the development of HCC post-SVR are old age, high alcohol intake, coinfection with HBV or HIV, and the presence of metabolic syndrome [272]. Viral factors resulting in irreversible changes in cellular signaling due to epigenetic activation or imprinting continue to drive carcinogenesis even after achieving SVR [273, 274]. Hassany et al. from Egypt prospectively have analyzed the occurrence of HCC in patients with liver cirrhosis who have achieved an SVR after IFN-free treatment with no history of HCC, and they have found that the HCC occurrence rate is 6.3% within the first 2 years [275]. Due to the continuous risk of HCC formation among patients with liver cirrhosis despite SVR, a regular, twice-yearly screening using ultrasound abdomen is highly suggested by all international guidelines, including the Saudi Association for the Study of Liver Diseases and Transplantation [276–279].

9 Management of HCV in Patients with HCC

9.1 DAAs in HCV-Related HCC

The use of DAAs has improved the disease outcomes among HCV-infected patients with SVR rates surpassing 95%. Nonetheless, recent studies on the efficacy of DAAs in patients with HCC demonstrated lower SVR rates at 60–90% than those without HCC [280, 281]. This might be explained by different possible mechanisms [280, 282–284]. For example, it has been proposed that there is a suboptimal penetration of DAAs to the HCV-infected tumor cells due to altered morphology and the nature of the tumor blood supply, which is, for the most part, the hepatic arterial branches when compared to the portal venous system [283]. However, the data to assess the efficacy of DAAs among the HCC cohort is limited because the initial DAA studies have excluded patients with HCC [285]. Other factors such as the DAA treatment regimens (e.g., SOF/RBV) used or inadequate duration of therapy may explain the suboptimal result report among patients with HCC. Hence, further trials are needed to evaluate SVR rates in this cohort of patients with the new generation of DAAs, prolonged duration of therapy, and treatment combinations.

10 HCV Treatment Considerations Based on HCC Therapy

10.1 DAAs and Locoregional Therapies

Locoregional therapies (LRTs) (e.g., percutaneous radiofrequency ablation, microwave thermal ablation, and ethanol injection) are used as curative interventions in the early stages of HCC and as palliative interventions (e.g., Transarterial chemoembolization (TACE) and Transarterial radioembolization (TARE)) in the intermediate to advanced-stage HCC [206]. There is limited evidence on the best HCV treatment approach in

patients with HCC that is amenable to LRT, and more research is required. Based on the little available evidence, several important points may be considered when deciding whether or not to treat those patients with DAAs and when. Initially, since LRTs are mainly used in patients with well-compensated liver disease, achieving SVR may significantly improve the liver function in those with decompensated liver disease and increase the eligibility for LRT [286]. Besides, as we referenced above, since SVR rates are decreased in patients with HCC, it is preferred in those with compensated liver disease to treat the HCC with LRTs before treating with DAA therapy [281, 287, 288].

10.2 DAAs and Liver Transplantation

There is much speculation regarding timing and the likely effect of HCV treatment in patients with HCC, especially in those under consideration for liver transplantation [283]. Based on the available data, there are undoubtedly several advantages and disadvantages of treating HCV before or after liver transplantation for HCC, which ought to be considered on an individual basis (Table 4) [282, 283, 285].

10.3 DAAs and Systemic Therapies

There are few available studies on using the DAAs in HCV patients with advanced HCC on systemic therapies. Sorafenib, an oral multi-kinase inhibitor, was the first breakthrough targeted therapy used to treat advanced HCC. Although sorafenib's impact on median overall survival does not extend life expectancy beyond 1 year, it is yet to be superseded a decade after the landmark SHARP trial [205, 206, 289]. Sorafenib was shown in vitro to effectively block HCV replication through different mechanisms [290–293], which has not yet been demonstrated in human studies [289, 294]. One study has shown that HCV infection is predictive of a more significant overall survival benefit with sorafenib than other liver disease causes [295]. Another interesting study by Kawaoka et al. has reported that HCV eradication before sorafenib treatment for HCV-related advanced HCC could improve the median time to treatment failure, post-progression survival, and overall survival [296]. However, a recent single-center study by Lin et al. has shown that untreated HCV patients, i.e., no DAA group, were more likely to have advanced-stage HCC and more likely to be treated with sorafenib [234]. A study by Beste et al. showed a remarkably lower rate of SVR in patients treated with sorafenib (59%) compared to patients who underwent surgical resection (78.9%) [284]. The favorable response to DAA therapy in the post-resection group could be explained by the inactive nature of HCC in this group who are more likely to have compensated liver disease.

Newer drugs like lenvatinib, a multi-kinase inhibitor, in the first-line and regorafenib, cabo-

Table 4 Advantages and disadvantages of treating HCV before or after liver transplantation for HCC

	Advantages	Disadvantages
HCV treatment pre-transplantation	May improve liver function Prevention of recurrence post-transplantation Prevention of post-transplant complications such as fibrosing cholestatic hepatitis May prevent the need for transplantation	Improved liver function may affect list priority in deceased donor liver transplantation (the majority of Middle Eastern countries use liver donor liver transplantation) Lower SVR rates Possible resistance-associated variants HCV- positive donors less favorable post-SVR Speculative DAA associated with HCC recurrence
HCV treatment post-transplantation	Improved SVR rates HCV-positive donors considered with improved wait times No concern for DAA and HCC recurrence	Worsening of pre-transplant liver function Fibrosing cholestatic HCV post-transplant (<5%)

zantinib (both multi-kinase inhibitors), and ramucirumab (an anti-VEGF mAb) within the second-line are incorporated into new guidelines [205, 206] and are started to be used in practice; however, the evidence about their potential interactions with DAA agents is still minimal. Although two small studies have shown no adverse effects of combining DAAs with sorafenib, either in terms of SVR rate or antineoplastic effect, more well-designed studies are required to assess the interaction between targeted DAAs and systemic therapies [297, 298].

10.4 Timing of HCV Treatment in Advanced HCC

As previously discussed, the timing of HCV treatment when considering curative options has been the source of some debate. The decreased efficacy of DAAs seen in the context of HCC offers a compelling argument for treating HCV after treatment of the tumor. In advanced HCC, the possibility of a cure is marginal, and then delaying HCV treatment is not practical. In patients where life expectancy is significantly limited, the risk/benefit ratio of treating HCV must be considered. The AASLD guidelines recommend palliative measures in patients with limited life expectancy within 12 months as those patients are unlikely to benefit from HCV eradication [205]. This includes patients with decompensated liver disease and advanced HCC. HCV eradication is the preferred option for those with a better prognosis before initiating sorafenib treatment in advanced HCC patients. This approach has better outcomes, including better overall survival, as mentioned above [296]. Therefore, the decision concerning the management of concomitant HCV and advanced HCC should be made on a case-by-case basis, considering the overall prognosis and potential benefit.

Advanced stages of HCC occur commonly and with increasing frequency in developing countries, including Middle Eastern countries, where it is also associated with a bad prognosis. This increasing burden of HCC could be explained by different factors, including the absence of exiting HCC screening programs, delayed presentation, delayed referral to a specialist, the limited number of specialists, and the limited treatment options offered in most countries [299]. Therefore, the timing of HCV treatment in advanced stages in resource-limited countries will also be factored into the presence of the different treatment options for HCC and the availability of DAA therapy, among other factors.

11 HCV Elimination in the ME: Opportunities and Challenges

HCV is one of the main etiological factors of HCC worldwide, and hence an effective control of this infection may reduce the disease burden of HCC. In October 2003, a national viral hepatitis therapy program was launched in Taiwan. This program has been shown to significantly reduce the burden of end-stage liver disease [300]. A total of 157,570 patients with CHB and 61,823 patients with CHC were treated with antiviral therapy from 2004 to 2011. There was a 22% reduction in mortality from chronic liver diseases and cirrhosis, a 24% reduction in HCC mortality, and a 14% reduction in HCC incidence in 2008–2011 compared with the 4 years before launching the program, 2000–2003 [300].

In 2015, only 20% of HCV infections were diagnosed globally, and only 7% of CHC eligible patients were treated [301]. In 2016, the 69th World Health Assembly endorsed the Global Health Sector Strategy (GHSS) for the elimination of viral hepatitis worldwide by 2030 [302]. This was followed by the WHO global service coverage targets using five key interventions in prevention and treatment to eliminate viral hepatitis as public health threats by 2030. The WHO target is a 90% reduction in the incidence of chronic HBV and HCV infections and a 65% reduction in mortality by 2030 (Table 5) [302]. Implementation of this strategy would prevent 7.1 million deaths globally between 2015 and 2030 [301].

Table 5 WHO's targets for the elimination of viral hepatitis [302]

	Target area	Baseline 2015	2020 targets	2030 targets
Impact targets leading to elimination	Incidence: new cases of chronic HBV and HCV infections	6 and 10 million infections	30% reduction	90% reduction (900,000 infections)
	Mortality: HBV and HCV deaths	1.46 million deaths	10% reduction	65% reduction (500,000 deaths)
Service coverage targets	*Prevention*			
	Three-dose HBV vaccine for infants (coverage %)	81%	90%	90%
	Prevention of mother-to-child transmission of HBV: HBV birth dose vaccination or other approaches (coverage %)	38%	50%	90%
	Blood safety: donations screened with quality assurance	89%	95%	100%
	Safe injections: percentage of injections administered with safety-engineered devices in and out of health facilities	5%	50%	90%
	Harm reduction: number of sterile syringes provided per person who injects drugs per year (coverage%)	20	200 (50% coverage)	300 (75% coverage)
	Treatment			
	HBV and HCV diagnosis	<5% of chronic hepatitis infections diagnosed	30%	90%
	HBV and HCV treatment	<1% receiving treatment	5 million people will be receiving the HBV treatment	80% of eligible persons with chronic HBV infection treated
		<1% receiving treatment	3 million people have received HCV treatment	80% of eligible persons with CHC infection treated

Abbreviations: *HBV* hepatitis B virus, *HCV* hepatitis C virus

The estimated incidence of acute HCV in ME based on the dataset used for the WHO 2017 Global Hepatitis Report [301] provided by the Center for Disease Analysis (CDA) Foundation's Polaris Observatory is 18.5 per 100,000 patients. As of 2015, only around 20% of HCV infections in the ME were diagnosed, and less than 10% of those diagnosed patients were treated (Fig. 3). Meanwhile, the estimated daily death due to HCV is more than 14 deaths, with nearly 7000 patients progressing to decompensated cirrhosis or HCC every year [179]. To achieve the WHO elimination 2030 targets (90% diagnosed and 80% treated), almost 100,000 people would need to be diagnosed and treated each year from 2016 to 2030 [179]. Therefore, more efforts are urgently required to achieve the goals for eliminating viral hepatitis and HCC in the ME.

Each country of the ME region should have its elimination plans and strategies tailored to meet its need to achieve high efficacy and cost-effectiveness of HCV eradication [303]. There are different ME country-based characteristics concerning HCV epidemiology, clinical practice, healthcare system, availability, and accessibility of diagnostic and treatment methods. For example, the screening of patients with CHC is considered appropriate only for high-risk rather than the general population in Saudi Arabia, where the prevalence of the viral infection is low in the general population [181]. Also, the simple aspartate aminotransferase-to-platelet ratio index (APRI)

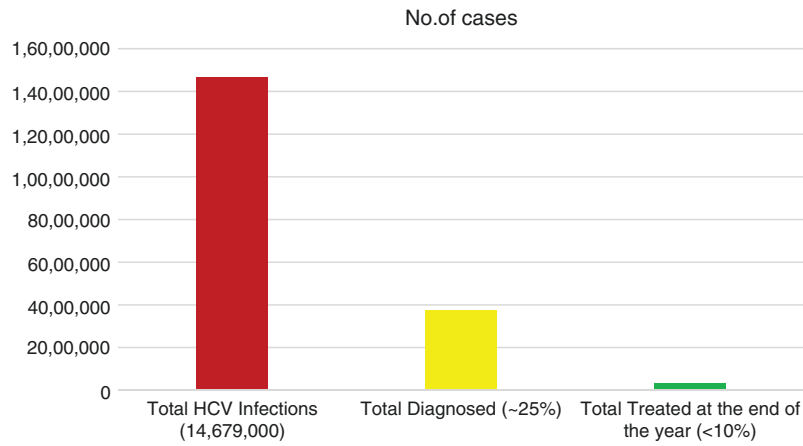

Fig. 3 Hepatitis C cascade of care in the ME in 2015. HCV hepatitis C virus

is considered as an alternative noninvasive test to assess the presence of cirrhosis in resource-limited countries. In contrast, transient elastography may be the preferred method in areas where they are available, and the cost is not a major constraint. Clinical guidelines for prevention, diagnosis, and treatment of CHC have been published by many national and international organizations, including the American Association for the Study of Liver Diseases [276], Asian Pacific Association for the Study of the Liver [304], and European Association for the Study of the Liver [277]. WHO has also published the guidelines with specific recommendations for low-income and middle-income countries [305].

There are different approaches to WHO's targets for viral hepatitis elimination across the ME [179]. These include steps such as the establishment of local strategies for viral hepatitis elimination, the building of databases, implementation of screening programs, starting awareness campaigns, and micro-elimination programs in selected high-risk groups such as hemodialysis patients, patients with thalassemia and sickle cell disease, and intravenous drug users and prisoners.

Certain Middle Eastern countries such as Qatar and Egypt are becoming role models to achieve the WHO's hepatitis C elimination goals by 2030 [306, 307]. Qatar, which is considered one of the low HCV prevalence countries, started a national program for HCV control and elimination in December 2014. This program's main goal was to prioritize and proactively manage HCV with the ultimate aim of viral hepatitis elimination by 2030. The program was based on four main pillars: primary prevention, early detection, clinical management, and continuous monitoring [307]. It was accompanied by a strong political will toward universal access to viral hepatitis-related services for all nationals and non-nationals. Important outcomes of this program were the improvement of HCV information systems, epidemiological surveillance, and patient registration. In 2016, a follow-up screening campaign was conducted, which included 7665 participants (21% were Qataris). The prevalence showed a reduction from 2% to 0.82% among the total population and from 0.8% to 0.2% among Qataris [307].

Egypt is considered at the top of the countries with the highest prevalence of HCV infection worldwide [306]. The economic burden of HCV in Egypt in 2015 was estimated to be 3.81 billion. This is expected to increase exponentially as HCV-infected individuals progress to more advanced diseases, i.e., decompensated cirrhosis, HCC, and liver-related mortality [306]. In response to this major issue, through its National Committee for the Control of Viral Hepatitis (NCCVH), Egypt started a national treatment program for Egyptian HCV-infected patients in 2007. Mass HCV treatment program had started using IFN-based therapy between 2007 and 2014 and then shifted to DAA therapy from 2014 to date. By September 2018, about 2.5 million

patients had been tested and treated with different combinations of DAAs [180]. In October 2018, the Egyptian Ministry of Health began a national population-based screening program. By September 2019, around 52 million adult individuals will be screened after excluding those treated or tested before [180]. The NCCVH anticipates that 2.5–3.0 million newly diagnosed HCV individuals will be eligible for free treatment. Therefore, Egypt has taken a great step toward HCV elimination. The Egypt HCV elimination strategy is considered a care model for other high HCV prevalence countries to use in their battle against HCV [180].

Despite this progress, and with only 10 years to go until the 2030 deadline is reached, more commitment from most Middle Eastern countries is required to achieve HCV elimination. The diagnosis and treatment of HCV infection are still not up to the ME region level to be considered on track for elimination. As per a report from the CDA foundation, no Middle Eastern countries in 2017 were considered "on track" for achieving the WHO elimination targets. However, after 2017, most countries started to treat all HCV patients regardless of their fibrosis stage, which is an essential step toward improving patient access to treatment. Furthermore, there are ongoing efforts to implement national strategies in some countries, like Saudi Arabia, Qatar, the United Arab Emirates, and Kuwait.

There are significant barriers to HCV elimination in ME. These barriers vary between the countries of the ME and need to be addressed to achieve HCV elimination. A major gap in response to the epidemic remains the lack of reliable prevalence data in many countries and regions, including Middle Eastern countries [6]. The availability of those accurate and verifiable HCV prevalence data for the region and each country allows the establishment of better elimination strategies. These strategies must be tailored to the population's needs and allow easy monitor of progress and impact of interventions.

Moreover, budget limitations and low HCV awareness among the general population are major challenges for HCV elimination in low- to middle-income countries like Egypt [306]. The HCV diagnosis rates depend on the cost of the investigations and HCV awareness among the general population [306]. In many countries worldwide, including Middle Eastern countries, most known HCV cases have been treated and cured, and there are no more new HCV patients to treat [308]. Most of the cases in many Middle Eastern countries, including Saudi Arabia, are unfortunately still undiagnosed. Therefore, there is an urgent need for a screening program to increase diagnosed patients [181]. Diagnostic resources, including the capacity to process large volumes of screening tests and the availability of confirmatory tests, remain obstacles for elimination in many countries globally. In several Middle Eastern countries, including Egypt, Saudi Arabia, and Oman, access to affordable low-cost generic DAAs has been supported and successfully incorporated within their national treatment plans [179, 181, 306, 309].

Furthermore, challenges for successful implementation still exist even when elimination strategies have been established within national healthcare plans. In most countries, HCV treatment is provided by specialists, which may increase the waiting list and decrease treatment access for many patients. This was justified in the IFN-based therapy era when the treatment was associated with long therapy duration, severe adverse effects, and low cure rates. However, the current therapies are easy to prescribe and administer and of short period with almost few if any side effects and high cure rates. Many studies have shown that general practitioners can successfully treat most patients without compromising SVR [310, 311].

HCV elimination has been proven to be highly cost-effective and cost-saving across various health settings [312]. The WHO 2030 deadline for eliminating HCV, which has been deemed ambitious by many, is achievable, provided strong global support and commitment. The Middle Eastern countries need more expanded efforts to increase screening, diagnosis, and treatment. These efforts must be matched with firm political intention, sustainable funding, improved linkage to care and access to cheap high effective generic DAAs, raising awareness, eliminating stigma, and improved point-of-care access to

include general practitioners [313, 314]. Perhaps then the region can get firmly on track toward HCV elimination.

After 5 years of progress and assessment, the recent CDA foundation 2020 report on tracking countries' progress toward WHO global targets has raised concerns about the limitations of the existing targets [315]. These impact targets compare a country's progress relative to its 2015 baseline when most countries did not have existing hepatitis epidemiology data. These targets also penalize those countries that started their programs before 2015 and those with a young population or a low HCV prevalence. Therefore, the Polaris Observatory collaborators have proposed that WHO simplify the exiting hepatitis elimination targets and change to absolute targets, shown in Table 6 [315]. They also recommend allowing countries to achieve these targets with their service coverage initiatives that will have the maximum impact. Using this proposed model, more countries are expected to achieve all the new targets relative to the existing ones (Table 7).

12 Projection of Future HCV-Related HCC Trends in ME

The projections of the future burden of HCV-related HCC can inform prevention strategies aimed toward reducing HCC occurrence. With the ambitious WHO 2030 elimination targets, in

Table 6 Simplified hepatitis elimination targets using absolute targets [315]

Primary objective	Reduce the incidence		Reduce mortality	
2030 target	Reduce HCV new chronic cases to ≤5 per 100,000 (excluding the new cases from immigration)	Reduce HBsAg prevalence among 1-year-olds to ≤0.1%	Reduce HBV and HCV mortality to ≤5 per 100,000	Demonstrate HBV and HCV year-to-year decrease in new HCV- and HBV-related HCC cases
Measure options	Conduct two national surveys (minimum 1 year apart) and estimate incidence between the two by age group	Conduct HBsAg surveys in 1-year-olds in multiple regions in the country and maintain prophylaxis measures	Establish/use the national registry for HCC, decompensated cirrhosis linked to patient and death registries attributed cause, and adjust for underreporting	Establish/use the national registry for HCC, decompensated cirrhosis linked to patient and death registries attributed cause, and adjust for underreporting
	Conduct two surveys (minimum 1 year apart) in high-risk groups accounting for >80% of new infections and estimate incidence rate	Conduct HBsAg surveys among 1-year-olds in high prevalence regions/populations and maintain prophylaxis measures	Establish/use the national HCC registry. Estimate annual decompensated cirrhosis to HCC incident ratio in ≥1 major center. Use HCC and cirrhosis survival studies to estimate overall mortality by year	Establish/use the national HCC registry. Estimate annual decompensated cirrhosis to HCC incident ratio in ≥1 major center. Use HCC and cirrhosis survival studies to estimate overall mortality by year
	Use modeling to estimate incidence	Use modeling that considers the impact of prophylaxis to estimate the incidence and maintain prophylaxis measures	Use modeling to estimate HBV- and HCV-related HCC and cirrhosis mortality	Use modeling to estimate HBV- and HCV-related HCC and cirrhosis mortality over time

Abbreviations: *HBsAg* HBV surface antigen, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus

Table 7 Comparison between existing WHO elimination targets and the recently proposed absolute targets by 2030 [315]

Middle Eastern countries reaching the existing WHO elimination targets by 2030						
HBV 90% reduction in incidence	HBV ≤0.1% prevalence among 5-year-olds	HBV 65%reduction mortality	Countries meeting all HBV targets	HCV 90% reduction in incidence	HCV 65% reduction in mortality	Countries meeting all HCV targets
None	Egypt	None	None	Egypt	Egypt	Egypt
	Iran					
	Kuwait					
	Lebanon					
	Oman					
	Qatar					
	Saudi Arabia					
	Turkey					
	UAE					
Middle Eastern countries reaching the absolute HBV and HCV elimination targets by 2030						
HBV _0.1% HBsAg prevalence among 1-year-olds		HBV reduces mortality to ≤5 per 100,000 and decreases in new HCC cases	Countries meeting all HBV targets	HCV reduces new chronic infections to ≤5 per 100,000	HCV reduces mortality to ≤5 per 100,000 and decreases in new HCC cases	Countries meeting all HCV targets
Egypt		None	None	Egypt	Egypt	Egypt
Iran				Saudi Arabia	Turkey	Turkey
Kuwait				Turkey		
Lebanon						
Oman						
Qatar						
Saudi Arabia						
Turkey						
UAE						

Note: Blue countries/regions—those not achieving the absolute targets for a similar category in Table 4; only countries/regions analyzed by Polaris Observatory are listed; *UAE* United Arab Emirates, *UK* United Kingdom

most countries, the incidence and prevalence of HCV case are expected to decrease due to a combination of a prevalent aging population, availability of treatment, and a reduction in risk factors secondary to improvements in the safety of blood products and harm reduction programs for injection drug users [316, 317]. However, the morbidity and mortality attributable to HCV are expected to increase as the current infected population progresses to advanced stages of liver fibrosis. In most countries, the increased disease burden will likely not be controlled without significant changes in the overall treatment paradigm, including increases in screening, diagnosis, and treatment. This suggests that countries should assess different strategies to help decide how to manage the expected increase in their HCV-related disease burden, including HCC.

13 Future Research Needs

There are significant needs for more epidemiologic and clinical research on HCC worldwide. In the DAA treatment era, HCV-related HCC remains a major health problem in the coming one to two decades. The development of a vaccine remains an essential target for achieving global control and eradication of HCV. There is also a critical need for more basic research on carcinogenesis in CHC and identifying more risk factors, i.e., viral, cellular, immune, and host-genetic factors that add to the development of HCC. Identification of the steps leading to the progression of CHC infection to cancer would help develop means of prevention, early detection, and treatment. Focusing on ME, more population-based studies are needed to understand

the current and future contribution of HCV to HCC in the region. These studies should examine known and suspected risk factors and collect appropriate biologic samples to assess HCC markers that help early detection of HCC. Such studies could additionally provide essential data on the risk factors for the progression of CHC to HCC. The relationship between HCV and other conditions like obesity, diabetes, and NAFLD needs further research, particularly given the high prevalence of these conditions in the region and the large number of HCC cases in which no specific risk factor can be identified. Post-SVR HCC is an important emerging issue, with pressing unmet needs for the clinical strategy of early tumor detection and intervention and identifying HCC molecular mechanisms for therapeutic target and biomarker discovery. Long-term clinical trials on the impact of post-DAA SVR on HCC development and recurrence are also required.

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