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Epidemiology, transmission, diagnosis, and outcome of Hepatitis C virus infection

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Abstract

Hepatitis C infection is one of the main causes of chronic liver disorders worldwide. Nearly three percent (3%) of the world population has an HCV infection. Prevalence of HCV infection was higher in some groups such as injected drug users (IDUs) and HIV positive populations. Acute hepatitis has proven asymptomatic in most cases, and delay of diagnosis might lead to late onset of hepatocellular carcinoma and cirrhosis. Some host characteristics such as age, gender, body mass index, and viral properties are associated with HCV outcome hepatitis. Although disease progression is typically slow, some risk factors such as alcohol abuse and coinfection of patients with HBV and HIV can worsen the disease. On the other hand, viral overload is one of the main causes of prediction of HCV infection outcome. Prevalence of HCV infection will increase if we do not consider means of transmission, virus behaviors, and immunologic responses. Rapid diagnostic tests can help us to create preventive strategies among undeveloped villages and prisoners. Screening and training of the high-risk population such as IV drug users, dialysis patients, and hemophiliacs must be one of main HCV preventive programs. The present review is intended to help health policymakers to design suitable preventive and management programs.

Keywords: Epidemiology; Hepatitis C; Outcome; Prevalence

1. Introduction

Hepatitis C virus (HCV) is a major health burden that affects more than 170 million people around the world (1). Unfortunately, most patients who are infected with Hepatitis C infection cannot clear the virus and progress to the chronic infection. This rate is higher in human immunodeficiency virus (HIV) infected patients and lower in women and children (2, 3). Cirrhosis, portal hypertension, hepatic decompensation, and hepatocellular carcinoma have been reported as results of chronic HCV infection, and it is estimated that more than 300,000 deaths have occurred annually due to HCV infection (4). More than 50% of hepatocellular carcinoma cases in endemic population have

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happened due to chronic HCV infection and consisted of more than 6% of cirrhosis causes around the world (5). The natural history of HCV infection among patients has been incompletely defined. Many cofounders can have an impact on HCV progression to hepatic fibrosis. According to retrospective studies and within 20 to 30 years of infection period, cirrhosis rate was between 17% and 55%, HCC rate between 1% and 23%, and liver death between 1% and 23% (6-8). Some factors such as one's age during infection, male gender, alcohol consumption, obesity, insulin resistance, and co-infection with Hepatitis B or HIV were reported as confounding factors, which have an impact on progression of HCV infection (9). Although much expenditures has been spent in research centers with different strategies on HCV pathogenesis, there is no acceptable vaccine for HCV infection. HCV infection has increased in IV drug abusers who freely share syringes. At the time of selecting the new therapeutic plane for patients, some factors such as viral genotype, age, and gender of patients and related disorders must be considered. It seems that we require some preventive activities for high-risk population. In the present review, we described most HCV-infection-related occurrences such as epidemiology, transmission, diagnosis, and outcome of patients with Hepatitis C infection. A narrative review search using the citation databases PubMed and Scopus was performed. Keywords included Hepatitis C epidemiology, transmission, virology, prevalence alone, and combinations. Also we searched the European Association for the Study of Liver Disease (EASLD) and the American Association for the Study of Liver Disease (AASLD).

2. Discussion

2.1. HCV virology

Although Hepatitis C is a hepatotropic virus, it can be proliferated in extrahepatic tissues, including peripheral blood mononuclear cell (PBMC) (3). Hepatitis C virus is a linear and a positive one-chain structure with around 9600 nucleotides. In patients with chronic Hepatitis, daily 10^{12} virus particles were produced (62). Hepatitis C virus is a single hepatotropic virus from the Hepacivirus strain and Flavivirideh family. Hepatitis C virion has a diameter of around 55–56 μm, and its genome consists of one long open reading frame (ORF), which end in the two untranslated regions at 5` and 3` (2), and its polyprotein is coded around 3015 amino acids (5). Presynthetic polyprotein is divided into 11 mature proteins and consists of three proteins: A) structural proteins and core protein B) two superficial glycoprotein E1, E2, and C) one Viroporin P7 and six nonstructural proteins, including (NS2), (NS3), (NS4B), and (NS5A). Two viral peptidases participated in the nonstructural process. NS2 is a zinc-dependent metaloproteinas, which break places between NS2 and NS3. NS3/4A is a serine proteinase, which is separated into relationships between other NS proteins. Protein NS5A has a main role in virus proliferation. (4, 6, 7). The Hepatitis C genome has high genetic divergence, and the superfacing E1 and E2 protein has the most changes (62). Hepatitis C is not a DNA virus, thus it cannot enter into the host genome, and it does not proliferate with DNA; its half-life is around 2.5 hours (5). The Hepatitis C virus can penetrate into the hepatocytes via cross-reaction of hepatic cell receptors such as CD8 and RLDL with tight junction protein claudin1 and occludin. Virus genome can escape from host immune system due to heterogeneity and lead to chronic infection (8).

2.2. Hepatitis C virus genotype

Hepatitis C virus is divided into the seven main genotypes and more than 100 different subtypes. Genotypes have more than 30% differences in their nucleotide sequences; in most similar species (Quasi-species) differences between nucleotide sequences is 20% (10). Prevalence and distribution of HCV genotyping is different in several geographic regions. Genotype -1 is more present in developed countries such as European or North American countries, for instance; HCV-1 (subtype A1-B1) is common in 60% to 70% of patients in USA. HCV-2 was more prevalent among middle and west of Africa, and HCV-3 is most prevalent in Far East countries and India. Genotypes 4, 5, and 6 have more prevalence in specific endemic geographical regions. HCV-4 is more prevalent in Egypt and sub-Sahara region, HCV-5 in South Africa and HCV-6 is more prevalent in China and Southeast Asian countries (11). On the other hand, HCV-1, HCV-2, and HCV-3 have global prevalence around the world, and HCV-4, HCV-5, and HCV-6 have limited prevalence; for example, HCV-4 is more prevalent in Arabic countries such as Saudi Arabia, Egypt, Syria, and recently in specific parts of Europe (12). HCV-5 is limited to South Africa, and HCV-6 is more prevalent in southeast countries, including China, Hong Kong, and Taiwan (13). HCV-3 in Pakistan and HCV-1 and HCV-3 in Iran were more common (14, 15). In one study on Iranian peoples in South of Iran, 1a (62.1%), 1b (23%), and 3a (14.9%) had more prevalence, respectively (16). genotype 7 HCV infection reported from Canada that isolated from central immigrant (17).

2.3. HCV Epidemiology

Hepatitis C infects nearly 3% of the world population; between 130 and 150 million people all over the world are infected with Hepatitis C virus, and annually between 350,000 and 500,000 people died due to Hepatitis-induced

hepatic disorders. The burden of Hepatitis C will reach the highest level in 2020 (3, 18). Recent studies reported that from 1990 to 2005 frequency of people with seropositive anti-HCV antibodies increased from 2.3% to 2.8% (19). The highest HCV prevalence (>3.5%) has been reported in East Asia, North Africa, and Middle East regions (19). Most of the available epidemiologic data for Hepatitis C virus were prevalent from population base studies (20), and, due to asymptomatic acute viral Hepatitis among patients, we cannot assess the incidence of Hepatitis C among patients. Developed countries such as United States (1.8%), Germany (0.6%), Canada (0.8%), France (1.1%), and Australia (1.1%) had lower HCV prevalence compared with East Asia or North Africa. China and India with one-fifth of world population had 3.2% and 0.9%, as HCV prevalence and HCV prevalence in Indonesia and Pakistan were 2.1% and 6.5%, respectively (21). Meraat et al., in their study on prevalence of Hepatitis C virus among the Iranian population, found that, in comparison with other neighbor countries such as Pakistan (5.1%), HCV infection in our country was low, and only 0.5% of the Iranian population suffered from HCV infection. According to noted studies, HCV infection had geographical variance and wide frequency around the world. Epidemiological assessment of HCV infection prevalence around the world has been really effectual for preventing the disease and treating the patients. This assessment will be also effective in controlling of the possible future transmission of HCV.

2.4. HCV transmission

Most patients infected with HCV via blood transmission and HCV-RNA were detected at 7-21 days after blood transfusion (22). Most infected patients were asymptomatic in the acute phase and were not aware of their disorder (23). Spontaneous clearing occurred in 20% to 30% of infected patients (24). Many patients have not shown hepatic-specific symptoms for HCV infection diagnosis, and their disorder continued at a chronic phase (25). Blood transfusion is more important in patients who need a continuous blood transfusion due to their disorders such as patients with thalassemia, hemophilia, chronic renal failure and require hemodialysis, and many cancers (26). Unsafe injection, especially with multi-using syringes and needles is another HCV transmission pathway. It is predicted that, annually, 160,000 people had HIV and 4.7 million people infected with HCV infection and 16 million IV drug abusers existed in the world (27). Intravenous drug abuse (users) is another critical method of HCV transmission. Vertical transmission of HCV virus from mother to her fetus is limited up to 5% with HCV negative, but in between HIV co-infection is 5.8% to 10.8%. (28). Cesarean section does not increase HCV infection rate. Needle stick was reported as an important cause of HCV infection among health care workers (29). It is recommended that health care workers with occupational exposure to HIV and HCV infection must reconfirm their negative results six months after suspected infection due to late sero conversion (30). In one KAP study, 13.3% and 10% of health-care workers had low awareness rate for Hepatitis B and C, respectively (31). HCV infection can be transmitted with sexual contact and is increased among people with multiple sexual partners. It seems that co-infection with HIV can increase HCV transmission rate (32). Nosocomial transmission occurred due to using unsterile medical devices such as endoscopy, angiography, and surgical devices. Investigators have reported methods such as tattooing, piercing, and cupping as additional agent for HCV transmission. Medical procedures such as gynecology and cardiology operation, angiography, endoscopy, and colonoscopy can increase HCV infection rate due to use of unsterile devices (33, 34). Although near to 40% of causes of HCV among patients were not recognized, some risk factors such as receiving blood and its products, hemophilia, thalassemia, hemodialysis, tattooing were reported as recent risk factors of HCV transmission (35).

2.5. Hepatic manifestation

Acute phase of HCV infection lasted six months after the beginning of an HCV infection and was silent in most of the patients. HCV infection in 70% to 80% of patients changed into the chronic phase, and most symptoms in this phase were jaundice (40%), fatigue (80%), abdominal pain (50%), and dyspepsia (40%) (36). Diagnosis of HCV infection was on anti-HCV and HCV-RNA tests. HCV-RNA was positive in two weeks after infection and anti-HCV Ab was positive in eight weeks from the beginning of the HCV infection (37). Chronic phase of HCV infection began six months after infection. Among patients with chronic HCV infection, 15%-35% of patients lead to cirrhosis after 20 years and annually 1%-3% of them will have hepatocellular carcinoma. Hepatocellular carcinoma occurred 17 times more than patients with chronic HCV infection compared with others (38). Some factors such as male gender, coinfection with HBV, HIV, alcohol consumption, insulin resistance, and nonalcoholic fatty liver, obesity, and immunosuppression were determined as causes of progressive acute to chronic phase among patients who had HCV infection (39). Chronic Hepatitis infection can continuously injure the liver and lead to cirrhosis and hepatocellular carcinoma in infected patients who did not receive suitable treatment (40). After 20 years, untreated chronic Hepatitis C can increase the risk of hepatic cirrhosis in 15% to 30% patients, and risk of

hepatocellular carcinoma among cirrhotic patients is increased from 2% to 4% annually; their five years of survival rate among decompensated cirrhotic patients reaches up to 50% (41, 42).

2.6. Extrahepatic manifestation

Autoimmune presentations were common among patients with chronic HCV infection. Mixed cryoglobulinemia was common among 19% to 45% of patients. Sjögren syndrome occurred in 6% to 26% of patients. Autoimmune thyroid occurred with chronic HCV infection. Lichen planes, CREST syndrome, necrolytic acral erythema (43, 44). Metabolic syndrome, and diabetes types 2 were common extrahepatic symptoms, which had between 14% to 50% prevalence among patients with HCV infection.

2.7. Diagnosis of HCV infection

Diagnosis of HCV infection was performed by direct and indirect methods. In indirect methods, antibodies such as Anti-HCV IgM for recent infection and Anti-HCV IgG for old infection, in which secretions against Hepatitis viruses were measured. In the direct method, virus antigens were purified and detected by nucleoid acid. Overall, rapid immunoassay tests were used for screening and recombinant immunoblot tests in order to confirm HCV infection. Primarily HCV infection was diagnosed by detection of anti-HCV antibodies. The HCV-RNA test is positive in patients with at least 50 international units of HCV, and HCV-RNA can diagnose infection at one to two weeks after HCV exposure. Serum levels of Alanine transferase was increased within two to eight weeks after exposure and reaches up to 10 times normal value (39). Laboratory assessments were used for the diagnosis and follow-up of HCV infection among patients. Serologic tests were used for detecting HCV antibodies, and molecular tests were used for detection and assessment of HCV-RNA (45). Screening of the general population was not recommended for all of people, and only high-risk patients must be screened (46). The American Association for the Study of Liver Disease (AASLD) recommends HCV screening for specific groups such as people who received blood and blood products, IV drug abusers, dialysis patients, thalassemic and hemophilic patients, and people with abnormal liver enzymes, infants of mothers with HCV infected and needle stick in health-care workers (47). Serologic assays had been known as enzyme immunoassay (EIA) for anti-HCV immunoglobulin, which had three generations: first generation had 80% sensitivity, and the second generation had 95% sensitivity and 30 to 90 days after HCV entrance can be determined. The third generation of tests showed an unstructured protein (NS5), which was added to second-generation antigens and had near 97% sensitivity (48). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used to assess of liver condition. Decrease in platelet and ALT/AST ratio and prolonged prothrombin time (PT) can show cirrhosis and people with chronic HCV, liver cirrhosis, and fibrosis must use for hepatocellular carcinoma. Suspected patients for HCV infection must assess with anti HCV with EIA antibodies and HCV-RNA with sensitive test (49). Presence of HCV-RNA in patients without anti-HCV antibodies strongly detected acute Hepatitis C (49). Among patients with clinical and biological symptoms of chronic Hepatitis C, both of anti-HCV antibody and HCV-RNA were needed for diagnosis of HCV infection. Enzymatic immunoassay screening included rapid diagnosis tests and recombinant immunoblot assay (RIBA) was confirmatory laboratory tests. Quantity and quality of Hepatitis C virus were checked by recognition of viral RNA according to nucleic and amplification tests (NATs). Viral core antigens as laboratory diagnosis and genotyping with serologic and molecular methods are other diagnostic methods for Hepatitis C infection.

2.7.1. *Recombinant immunoblot assay (RIBA)*

This test can detect viral antigens and is performed for confirmation of specific serological test.

2.7.2. *Polymerase chain reaction (PCR)*

Different molecular techniques such as real-time PCR, reverse transcriptase PCR, transcription mediated amplification (TMA), and branched DNA can detect HCV RNA among serum or plasma of patients. This diagnostic method was more useful in cases in which virus counts are low. Determine of HCV genotype is performed with 5` noncoding sequence and Trugene 5/ NC and it is useful to predict the patient's outcome (49).

2.7.3. *Liver biopsy and fibroscan*

This diagnostic method was performed for assessment of inflammation and cirrhosis, and its grading and scoring were performed according to histological activity index (HAI) and ISHK and METAVIR, respectively. Although, liver biopsy with histological assessment was a gold standard method for hepatic fibrosis assessment, it has proven to be a painful and invasive method for patients and, in rare cases, might lea50to hemorrhage and misdiagnosis. New methods with noninvasive devices that can assess liver stiffness have been replaced with liver biopsies. One of these methods is fibroscan with an ultrasound probe that utilizes 5 MHZ power, which estimates liver stiffness in one cylinder, 4 cm long and 1 cm wide, and presented from F0 to F4 with kpa. Sensitivity of fibroscan in F2, F3 was more than serological tests. The liver biopsy, according to METAVIR scoring system, presents five stages: F0 =

without fibrosis; F1= fibrosis around the port; F2 = fibrosis port and port septum; F3 = fibrosis of port with lobular twist; F4 = hepatic cirrhosis (51).

2.8. Pathogenesis

HCV cannot directly enter into the genome of host cells; it can attack to immune system and infected hepatocytes and lead to cellular inflammation and necrosis and finally fibrosis and hepatocellular carcinoma. In patients with coinfection of Hepatitis C and HIV, hepatic fibrosis progression is more rapid in infection with each of them separately. HCV interferes with defense mechanisms and interferon signaling pathways. HCV is responsible for supplying of antigen to the MCH-1 cell class and is the cause of chronic Hepatitis c. Nonstructural protein NS5 can interfere in cellular regularity, and core protein can prevent apoptosis (52).

2.9. Viral responses

Most patients with chronic Hepatitis C infection require antiviral drugs. The first goal of therapy is to cure infection, and the final goal of therapy is sustained virological response (SVR). In this phase, HCV-RNA counts will reach to less than 50 international units per milliliter; six months after the beginning of treatment can demonstrate sustained treatment and that recurrence is only in 5% of patients (53). Other definitions of SVR is undetection of HCV-RNA in patients' serum with diagnostic test with diagnostic ranges less than 50,000 international units per milliliters (IU/ML) or loss of HCV RNA in less than 44 weeks after ending the treatment (54). Early virological response (EVR) is another therapeutic index that estimates therapeutic response after 12 weeks from the beginning of the therapy. EVR definition is negative HCV RNA after 12 weeks (complete EVR) or decreasing RNA into the 2log10 (EVR partial). EVR is increasingly used to determine of 12 or 48 weeks therapeutic regimens. Rapid virological response (RVP) is another therapeutic index and is defined as undetection of HCV-RNA into serum samples (<25 IU/ml) or negative HCV-RNA (<50 IU/ml) (55). It is necessary that genotype of HCV is determined before beginning of the treatment. On the other hand, HCV genotypes can determine drug dosage and treatment time. HCV genotype is an important factor for viral tolerance and reaching sustained therapeutic or viral responses (56). In recent years, the most important factors in automate clearance of acute Hepatitis C virus is related to host factors, especially polymorphism in location near the IL.28B gene on the chromosome 19 (57).

2.10. HCV treatment according virus genotype

Patients with less than 75 kg weight infected with HCV-1 genotype require a therapeutic regimen with daily high doses of ribavirin (1000–1200 mg); in patients with more than 75 kg weight, drug dosage is increased to 1600 milligram per day. Therapeutic period conducted for patients lasted 48 weeks. In patients with HCV-1, European hepatic association recommended that 48 weeks therapy with interferon and ribavirin were required for patients with high viral loads (> 800,000 IU/ml) before treatment and only 24 weeks for patients with viral load less than 800,000 IU/ml (58). In one case study to assess of the effectiveness of a lower dose of ribavirin (400 milligram) or shorter treatment period (less than 16 weeks), 89 patients with HCV-2 as group C and 31 patients with HCV-3 as group D were included in the study. Patients in group C received a peg iterferon containing 180 mg interferon alpha a2 with 800 mg ribavirin, and patients in group D received 400 mg ribavirin. Treatment period and ribavirin dosage have important roles in optimum outcome in patients with HCV-2 and HCV-3. If short-term therapy is selected based on the patients' age, the therapeutic regimen must last for 24 weeks. One therapeutic regimen with low dose of ribavirin and shorter therapeutic period is related to low SVR and it increases HCV recurrence. Patients in both groups had a more rapid response to interferon, thus SVR is 90% and 70% in patients with in HCV-2 and HCV-3, respectively. In similar studies, patients with HCV-2 and HCV-3 required less drug dosage comparing with HCV-1 (59).

2.11. Micro RNAs

Micro RNAs is one small ribonucleotide that cannot codding RNA had important role in control of biological process such as cellular metabolism, cellular development, cellular proliferation, and apoptosis. Several studies showed that micro RNAs were associated with clinical and pathological presentation of hepatic disorders such as cirrhosis, co-infection of Hepatitis B and C and HCC metastasis, recurrence, and prognosis. HCV-RNA proliferation was related to specific micro RNA (mir-122). Results of the noted study showed that SVR in patients with PBMC micro RNA had a reverse association with therapeutic response in HCV-1 patients. Results of the noted study can guide in pretreatment decisions and synthesis process of the new drugs (60). Hepatic micro RNA acts as biomarkers in predicting therapeutic response in patients with chronic Hepatitis C. Peripheral blood mononuclear cells (PBMC) play an important role in HCV progression. Recent studies showed several disorders with micro RNA in PBMC; recently, induction of mir-155 was seen in PBMC of patients with chronic HCV (61).

2.12. New drugs

Combination therapy with ribavirin and pegylated interferon in patients with chronic Hepatitis was preferred to treatment with interferon without pegylated ribavirin. It is important for patients and clinician to have different choices to select of antiviral drugs. In 2011 some drugs such as inhibitors of Hepatitis C enzymes were entered into the second and third phases of clinical trials after the drugs dosage got the final approval and these drugs might be useful in the future. Treatment with boceprevir or telaprevir in combination with pegylated interferon and ribavirin in HCV-1 can significantly decrease SVR rate. Treatment with sofosbuvir and ribavirin with/without interferon in HCV-1, HCV-2, and HCV-3 patients were prefered, especially in patients who were not able to tolerate interferon. Simeprevir was recommended in treatment of patients with 1a and 1b genotypes. These drugs can be used in patients with significant fibrosis (metavir > F2) or sever fibrosis with compensated cirrhosis or in patients that did not respond to standard treatment of had recurrence and patients with hepatic transplantation and Cryoglobulinemia (62). New therapeutic recommendations in 2015 suggested that close collaboration between patient and physician is required to achieve high-efficacy treatment. New drugs that have been used since 2011 in European countries are known as direct acting antivirals (DASS) and can decrease SVR rate among different group of patients with different risk factors and genotypes. In the next years' role of interleukin, 28B might be neglected in determination of final therapeutic response, and the main role in predicting final treatment will be performed by these new enzymatic drugs. Although these drugs will be replaced with previous drugs, some countries may not have the sufficient financial sources for buying these drugs for several years; but, new drugs such as Ledipasvir (LDV), Sofosbuvir (SOF), Daclatasvir (DCV) are currently avialble in many countries

2.13. Outcome of HCV infection

Different factors such as the patient's race or treatment according to alpha interferon, fibrosis, liver cirrhosis, high age, male, and metabolic disorders and level of AST and ALT have been effective in predicting the outcome of patients with HCV infection (63). Several studies have shown that factors such as age, sex, race, host immune response, and genetic susceptibility had a role in outcome of HCV infection. Polymorphism of IL-28B was one of the powerful causes of therapeutic response to HCV infection (64, 65). Serum level of ALT showed a level of liver lesions caused by HCV, and high level of GGT was known as an independent predictor of treatment failure. High levels of GGT have been associated with fibrosis progression, steatosis, and insulin resistance, which are more in common in nonresponsive patients (66). Everhat et al. reported that GGT was an oxidative stress and must be considered as a marker of disorder function (67). Liver biopsies and fibroscans were used for assessment of inflammation and fibrosis progression. Liver biopsy was a gold standard method for liver fibrosis assessment and due to the invasive nature of liver fibrosis. Calcium metabolism and vitamin D have played a role in regulation of the immune system (68). In another study, researchers found considerable association between low grades of 25-hydroxy vitamin D being lower than 15 ng per milliliter and outcome of patients with HCV infection (69).

2.14. Hepatocellular carcinoma and cirrhosis (HCC)

HCC is the fifth most common type of cancer around the world. Annually more than 600,000 new cases are diagnosed. Most patients have shown one causative factor such as chronic liver disorder (cirrhosis, for example) that is caused by chronic Hepatitis B or C and excessive alcohol consumption. In industrial countries, Hepatitis C infection and alcohol abuse typically lead to cirrhosis and HCC. Recently, industrial countries paid more attention to HCC owing to increasing rate of HCC incidence. In Asian and African countries this problem arises because of poor health services (70, 71). Almost all HCC related to HCV occurred among cirrhotic patients and cirrhosis pre-canceric situations before carcinoma. HCV is a carcinogenic defect in humans, and experimental models showed that core protein and NS3 had an oncogenic impact (72). More than 85% of HCC cases occur in developing countries. Incidence rate of HCC in the USA has increased three times (73). In Japan HCV is the main cause of HCC in more than 70% of the population. In some countries such as France and Belgium, alcoholic drinks plays a significant role in HCC (45, 71). Tactless use of alcohol also plays a major role in cirrhosis (more than 60%) and in 25% to 35% of HCC cases (74). HCC incidence rate among Asian countries, especially in the East regions, was higher than in industrial countries. It appears that this high rate is due to exposure of HBV with aflatoxin. HCC causes an increase in financial burden for patients, and almost of patients with HCC related to HCV had cirrhosis in the diagnosis time. In recent decades HCC incidence was duplicated and increased HCC related mortality rate, and a five-year survival rate of HCC patients in America was less than 13%. Rapid diagnosis can help patients have prompt effect on their outcome (75). Current radiological methods have been cross-sectional imaging and biopsy. Biopsy is used in cases that imaging cannot help with diagnostic criteria. It is predicted that the most common and highest HCC risk factors re cirrhosis and chronic Hepatitis C, which can increase risk ratio 15 to 20 times more than in current situations. Detecting of powerful markers for diagnosis and screening of Hepatitis C among patients with

chronic Hepatitis C and diagnosis of target molecules for treatment is important for patients who have HCC with HCV (76). Inflammation of the liver in chronic patients can progress into cirrhosis. Cirrhosis is presented in two forms: compensated (liver function isn't impaired) and decompensated (liver function is impaired). Compensated cirrhosis has complications such as ascites, hemorrhage, and hepatic encephalopathy, which can cause impairment in hepatic function (77). Patients with decompensated cirrhosis typically require liver transplantation. According to prevalence of Hepatitis C in some East Asian countries, more than 32.3 million people are suffering from Hepatitis C, and one-third of these patients has experienced cirrhosis and complications that lead to main morbidities and finally the need for liver transplantation (78). In recent years, the guidelines of the American Association of Study of Liver (ASSLD) recommended that patients with decompensated cirrhosis related to HCV might refer to liver transplantation, and low dose of interferon therapy had not curative impacts. More than 50% of patients with HCV-related decompensated cirrhosis in five years died without liver transplantation. These patients required suitable treatment after liver transplantation for the prevention of disease progression, improvement of liver function, and prevention of hepatitis recurrence. Interferon in these patients suppressed bone marrow and increased the chance of systemic infections and impaired anemia and hepatic function. Patients with decompensated cirrhosis with HCV-1 had lower SVR in comparison with other patients. Most studies recommended a combination of PEG interferon and ribavirin, which had one viral response rate range between 0 and 38%; the highest response was related to HCV-3 genotype (79).

3. Conclusions

HCV had seven genotypes and more than 100 subtypes and is known as one of the causes of increased morbidity and mortality. Early diagnosis and suitable treatment of HCV patients are important. Development of new techniques with the ability of rapid diagnosis, genotyping, and quantitative assessment of HCV infection can decline HCV burden. Although much expenditures have been spent in research centers with different strategies on HCV pathogenesis, there is no acceptable vaccine for HCV infection. HCV infection is increased in IV drug abusers who freely shared each other's syringes. At the time of selecting a new therapeutic plane for patients, some factors such as viral genotype, age, and gender of patients and related disorders must be considered. It seems that we need some preventive activities for a high-risk population and raise general awareness about HCV infection and transmission ways. One-time diagnosis of HCV infection, especially in the acute phase, can help us prevent its progression to the chronic type and hepatocellular carcinoma and cirrhosis. Some genetic factors of patients and some virological factors such as viral genotype play a significant role in the final outcome of the patients. Screening and training of high-risk populations such as injected-drug abusers and hemodialysis and hemophilic patients are critical and top agenda of health policymakers in the world.

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There is no conflict of interest to be declared.

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All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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