*Review Article*

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# Hepatitis C Virus and its Relation to Hepatocellular Carcinoma

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**Abstract**

Hepatocellular carcinoma is the world's sixth leading cause of death due to its quick progression. It has a poor prognosis and a low survival rate. Though there are several factors leading to malignancy, some of them are not yet fully understood. For example HCV. Hepatitis C virus is known to cause hepatocellular carcinoma and clearing the viral load of HCV from the body using DAAs has helped in improved prognosis and prevention of HCC but there is no concrete evidence to prove the direct carcinogenic effects of HCV in causing HCC. The argument is that HCV does not directly causes HCC but its chronic effects in the liver eventually lead up to HCC.

**Keywords:** Carcinoma, Vascularity; Ribavirin; Hemolytic anemia; Tactile.

## Introduction

HCV prevalence in India is 0.5% to 1.5% and varies across different geographical regions. The tracking of HCV positive cases in India is exceptionally hard seeing as how there are limited number of community based studies. The data collected from blood donors and pregnant women was examined and put together and the seroprevalence rates of pooled anti-HCV were 0.44% and 0.88% respectively. The risk of HCV was higher among the people that were more exposed, such as IV drug users, people with STDs and hemodialysis patients (Goel et al., 2019).

A large number of genotypes of HCV are found in blood samples all around the world but currently there are six main groups of sequence variants that have been characterized namely from 1 to 6. In 80% of the cases, the HCV causes chronic hepatitis. The chronic hepatitis C patients have mild symptoms of liver disease. This is however a progressive disease and leads up to cirrhosis and hepatocellular carcinoma. Without a proper treatment, 1 out of every 3 patients develop cirrhosis within an average time of 20 years (Singh et al., 2004).

There is no argument about the notion that the hepatitis C virus causes hepatocellular carcinoma. The real question is that – is HCV a carcinogenic virus or does it simply create conditions such as inflammation and cirrhosis, which is a high risk factor for HCC too, that leads up to hepatocellular carcinoma (Lemon & Mcgivern, 2012).

Liver cancer is the sixth most common form of cancer in the world and the third most common cause of cancer related deaths due to its poor prognosis and fast spreading (Venook et al., 2010).

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It is very common in South – East Asian and African countries. Risk of HCC is higher in patients with cirrhosis due to viral infections (Xavier, 2007).

***Methods used in diagnosis of hepatitis C infection***

The diagnosis of Hepatitis C virus is done through various methods. Immunoassay, molecular based detection and biosensors are some of the methods used in diagnosis of viral hepatitis C infection.

1. All the immunoassay techniques rely on the serum having antibodies for a particular antigen (in this case, for hcv). Antibodies play a pivotal role in serological detection of diseases. The most common and regularly used serological methods for HCV detection are enzyme immunoassay (EIA), radio immunoassay (RIA), immuno chromatographic assay (ICA), and immuno chemiluminescence assay..
2. The serological detection sometimes falls short and may not provide definitive results. To deal with this, there are molecular assays which are very helpful in detecting the viral load in case of hepatitis B and C. PCR (Polymerase Chain Reaction) is the most actively used technique to quantify the viral load in the body of the recipient.
3. The techniques used in the above methods are time consuming and require a trained professional to handle the equipments. There are more precise and instant techniques that make use of biosensors. Theses biosensors are accurate and give results quickly (Heiat et al., 2014).

***Methods used in the diagnosis of hepatocellular carcinoma***

The diagnosis of hepatocellular carcinoma at an early stage plays a pivotal role is defining the prognosis of the patient. Since HCC is a relatively' fast progressing form of cancer, it is necessary to diagnose it as early as possible. Though unlike the diagnosis of HCV, which is more or less non – invasive, the diagnosis of HCC is done through both the techniques – invasive as well as non – invasive.

The non – invasive techniques include the likes of ultrasound, magnetic resonance imaging and their sub parts. The invasive technique is the one where the sampling of the liver tissue is done by physically accessing the liver with the help of a needle – fine needle biopsy.

Ultrasonography – colloquially known as ultrasound. This imaging technique uses high frequency sounds to penetrate the skin and gives an idea about the size and structure of the liver. This technique uses grayscale to view the structure and hence the application of this is limited to seeing the structure only. We cannot view the direction of blood flow in this.

Advances in the application of ultrasonography include the contrast enhanced ultrasonography. The advantage of CE-US over regular US is that in this we can see the blood flow inside the fine capillaries and this enhances the accuracy of diagnosis of HCC.

MDCT – multi detector computed tomography is the most common method that is currently being used to diagnose HCC. The current standard protocol of dynamic CT is a four – phase dynamic imaging consisting the acquisition of unenhanced images followed by enhanced images of portal venous, arterial and equilibrium phase images after the injection of contrast enhancement material. In this the enhancement patterns of the tumor differ according to the leakiness and vascularity of the vascular endothelial cells. Perfusion CT was introduced in early 1990s. In this the serial images are acquired earlier and then the analysis of temporal changes of tumor and vessel attenuation is done after the injection of contrast agent. Perfusion CT is limited due to certain factors such as radiation overdose, limited coverage of area in scanning and breathing motion artifacts.

Magnetic resonance imaging – MRI is currently one of the most powerful non – invasive techniques that uses magnetic waves to form an image of the organ. MRI provides better information on tissue components and soft tissue contrast. Perfusion MRI is a technique that evaluates tissue vasculature by tracking the pharmacokinetics of the injected contrast agent (Lee et al., 2012).

Fine Needle Aspiration is one of the more precise and accurate diagnosis technique that uses a needle to obtain sample directly from the patient's organ and then the histological testing of the sample is carried out in the lab. The procedure is performed percutaneously under real time guidance from an ultrasound (Sangalli et al., 1989).

***Standard Treatment of Hepatitis C***

In case of HCV, in a small proportion of patients, the virus is cleared naturally and there is no need for any treatment while in others, the virus may

lead to chronic hepatitis C. Chronic hepatitis C leads to a broad range of liver diseases and the most severe of them is liver cancer. Though it is still unknown how hepatitis C virus causes liver cancer but what researchers know for sure is that it causes cancer if left untreated for a long time. Treatment of hepatitis C infection includes antiviral drugs.

The antiviral drugs have a defined course of medication and they are administered in steps. Initial treatments in the 1990s included the use of interferon and ribavirin (RBV). This resulted in the clearance of virus for 10% of the total patients. Moreover this regimen had contraindications in several patients. Due to neuropsychiatric effects of the interferon, this could not be administered to the patients with psychosis and unresolved depression issues. In patients with cirrhosis, the interferon increased the necro-inflammation and thus interferon therapy was not deemed fruitful for patients with liver cirrhosis.

The poor results in patients with chronic hepatitis C prompted for newer and less invasive treatment options. In light of this, the first generation of licensed drugs produced were protease inhibitors such as telaprevir (TVR) and boceprevir (BOC). Since the first generation of drugs was successful, there have been many directly acting antivirals (DAAs) in the market.

The disease that was once considered incurable is now curable to almost 100%. The only complication with DAAs is the drug-drug interaction that causes the efficacy of the drugs to alter and therefore each DAA needs to be tested for drug-drug interaction before including in the treatment regimen (Burstow et al., 2017).

### *Side effects of Interferon Therapy*

The standard IFN treatment causes side effects in the patients. IFN administration affects the bone marrow of the patient resulting in the reduced production of thrombocytes and granulocytes hence resulting in decreased amounts of granulocytes and thrombocytes during the therapy. Due to this the dosage of the medication needs to be changed according to each patient's blood profile. The interferon therapy is also limited in use where the patients with a compromised liver are concerned. Patients with liver cirrhosis have low platelets and are more vulnerable to infections. Neutropenia is one of the reasons to modify the dosage of IFN. In early weeks of treatment there are flu-like symptoms in the patients but later they are gone as the treatment progresses in its course. Other side effects of the IFN include fever, arthralgia, myalgia. To deal with these symptoms antipyretics such as paracetamol are given. Side effects also include the psychiatric symptoms such as acute depression and apathy. In 20% of patients autoimmune thyrodidtis has also been reported.

### *Ribavirin Side effects*

The most frequent side effect of ribavirin is hemolytic anemia. This often results in discontinuation of the drug. Erythropoietin is used to effectively counteract and reverse the ribavirin induced anemia. This allows full adherence to the ribavirin therapy. However this problem emphasizes on the need for new and less toxic drugs with higher efficacy. This has been largely interrupted as the mechanism by which the ribavirin enhances the IFN treatment efficacy and prevents relapse remains unknown. Viramidine is another drug used in therapy. This is an amidine version of ribavirin that is converted into ribavirin in hepatocytes by an enzyme called adenosine deaminase. Due to this breakdown happening in the hepatocytes, there is considerably less uptake of ribavirin into the blood and hence this reduces the cases of hemolytic anemia.

### *New Proposed Treatment for Hepatitis C*

Standard therapy for hepatitis C includes ribavirin and pegylated interferon alpha. But this therapy has its limitations such as limited efficacy in patients affected with HCV genotype 1. The new drug used for the treatment of hepatitis C, in addition to the standard therapy, is amantadine. This is mainly used to target the HCV genotype 1. Amantadine was reported to improve both virological and biochemical markers in hepatitis C patients, especially the ones that did not respond to the previously administered IFN treatment (Manns et al., 2006).

### *Standard Treatment for HCC*

In HCC, the only known definitive treatment is to transplant the liver. This is, to this date, only known cure for aggressive HCC. This offers a survival rate of up to 5 years and a recurrence rate of 15%. Another promising treatment for HCC is surgical resection. This is a treatment method for only a small number of patients because t to be able to perform this treatment, the tumor size needs to be small. Also this procedure cannot be carried out on patients with extensive liver cirrhosis as the procedure

poses an increased risk of decompensation in the patients with liver cirrhosis.

In the last decade, new methods such as radiofrequency ablation (RFA) and Transarterial chemoembolization (TACE) have been able to provide results at par with surgical resection. RFA is considered as the first treatment for small sized tumors. It uses an expandable electrode tip that extends into the tumor. A single electrode insertion is capable of producing a 3cm diameter necrotized area and thus allows a complete ablation of 2cm section leaving a 0.5 cm margin on each side, thus achieving surgical resection like results. TACE is used as standard treatment for intermediate stage of HCC (Raza & Sood, 2014).

### *Carcinogenicity of HCV*

In current scenario, no one knows for sure if hepatitis C virus is carcinogenic or not. There are clear evidences that people with chronic hepatitis C go on to develop hepatocellular carcinoma. But there is no confirmation as to whether the virus is directly carcinogenic upon tactile contact with the cells or does it create an environment in the cells that later leads to cancer. The latter seems to be more likely than the former. HCV is known to cause conditions such as inflammation, necrosis and fibrosis. These conditions then promote the formation of tumors. Though there is no proof that HCV is directly carcinogenic upon tactile contact. The presence of direct acting antiviral drugs is changing the prognosis of HCV patients for the better and we could hope for reduced incidences of hepatitis C associated hepatocellular carcinoma in the future. However, more studies need to be conducted to know the direct association of hepatitis C virus with hepatocellular carcinoma (Lemon & Mcgivern, 2012).

## Conclusion

Hepatitis C virus infects liver and causes inflammation in its acute stage but if left untreated it can turn into a chronic disease that is able to promote liver to final stage of cirrhosis and also to multiple incidences to hepatocellular carcinoma. The development of direct acting antiviral drugs have improved the chances of complete recovery from hepatitis C infection. However the evidences point to the fact that prolonged HCV infection leads to hepatocellular carcinoma which is a fast progressing form of cancer and has a poor prognosis. Though there is no certain evidence that hepatitis C virus is directly carcinogenic. Some researchers believe that it creates optimal environment for HCC occurrence whereas others believe that it is directly carcinogenic. There are strong arguments on both the side but more studies are needed to know for certain.

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