



## Seropositivity of Hepatitis and Cancer Management-Review and Recommendations

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### Abstract

**Background:** Hepatitis virus reactivation is one of the troublesome and preventable causes of mortality and morbidity in oncology patients. It causes significant morbidity either directly as liver injury or indirectly by delaying chemotherapy or definitive treatment. We started the research to find the cause of hepatitis virus (hepatitis B & hepatitis C) positivity, on subsequent admissions in patients who were previously negative by the same serological test. We conducted the research to find out the possible mode of acquisition of hepatitis virus

### Objectives

1. To emphasize the importance of serological test during every admission particularly in a cancer ward and to standardize the protocol
2. Preventing hepatitis virus reactivation related morbidity and mortality.
3. To ensure safety of patients and medical personal.
4. To enhance safety during blood transfusion.

**Materials and Methods:** Patients admitted during the period of January 2017 to March 2019 in department of surgical oncology, government Royapettah hospital who were negative for hepatitis B virus (HBV) /hepatitis C virus (HCV) on first or initial admission and treated after that with blood transfusion, chemotherapy, interventional procedures were included. Patients who became positive on routine serology were reaffirmed by specific tests like ELISA, RNA/DNA tests. Along with that liver function test, radiological assessment of liver was done and morbidity and mortality recorded.

**Results:** Among the seroconverted patients, 60(68%) were found to be positive for HBV and 26(29.5%) were HCV positive. Two patients were (2.27%) positive for both HBV&HCV. We found seroconversion in 38 patients. Female to male ratio was 1:0.9. In our study we found that 79% patients were between the age of 30 to 60. We noted that 32 (84.2%) patients with seroconversion was post chemotherapy. There were 11 patients (28 %) who got blood transfusion. In patients with seroconversion Adriamycin, CDDP, 5-FU based chemotherapy was used in 9,19,9 patients respectively. Musculoskeletal sarcoma and GIT cancers were most frequent among the seroconverted patients. During our hospital admissions 3 patients died of acute fulminant hepatic failure (mortality rate of 39 per 1000/year), 1 patient required ICU

admission and recovered. Half (n=19) of patients having fibro scan above 12.5 kilopascals probably indicating that these patients were in a chronic hepatitis state.

**Conclusion:** In our study we frequently encountered patients who were seropositive after treatment. It was found to be related to chemotherapy induced immunosuppression causing hepatitis virus reactivation. We used rapid card test to detect HBV and HCV antibody, which has very low sensitivity and not recommended for routine screening. Sensitivity and specificity of third generation EIA is 99% and is recommended for routine screening (32).

As an oncologist it is important to be aware about this potential life threatening and treatable condition. Timely administration of antiviral prophylaxis will reduce the viral reactivation related fulminant hepatic failure and death.

1. The serological tests recommended to detect HBV, in descending order are HBV-DNA, HBs Ag and HB e Ag
2. For HCV it is ideal to do HCV antibody as a screening test, followed by EIA and HCV RNA as a confirmative test.

**Keywords:** Hepatitis, HBV and HCV reactivation, chemotherapy induced hepatitis virus reactivation.

## Introduction

Hepatitis virus reactivation is one of the troublesome and preventable causes of mortality and morbidity in oncology patients. It causes significant morbidity either directly as liver injury or indirectly by delaying chemotherapy or definitive treatment. We started the research to find the cause of hepatitis virus (hepatitis B & hepatitis C) positivity, on subsequent admissions in patients, who were previously negative by the same serological test. We conducted the research to find out the possible mode of acquisition of hepatitis virus. We tried to detect the possibility of association with blood transfusion, chemotherapy related reactivation or getting infected during admission from others. It is imperative to know the hepatitis viral status for the safety of patients and medical personals. Acquiring viral transmission or reactivation during hospital admission despite all precautions cannot be underestimated.

The objectives of the study were

1. To emphasize the importance of serological test during every admission particularly in a cancer ward and to standardize the protocol
2. Preventing hepatitis virus reactivation related morbidity and mortality.
3. To ensure safety of patients and medical personal.

4. To enhance safety during blood transfusion.

## Materials and Methods

Patients admitted during the period of January 2017 to March 2019 in department of surgical oncology, government Royapettah hospital who were negative for hepatitis B virus (HBV) /hepatitis C virus (HCV) on first or initial admission and treated after that with blood transfusion, chemotherapy, interventional procedures were included. Patients who became positive on routine serology were reaffirmed by specific tests like ELISA, RNA/DNA tests. Along with that liver function test, radiological assessment of liver was done and morbidity and mortality recorded. All patients with hepatitis were treated in medical gastroenterology (MGE) / hepatology department and the response to treatment was recorded. All the parameters were analyzed by standard statistical methods.

## Results

Among 4770 admissions during the study period (January 2017 to March 2019) total 88(incidence =1.84%) patients were found to be either HBV or HCV positive. Among these patients 60(68%) were found to be positive for HBV and 26(29.5%) were HCV positive and 2 patients were (2.27%) positive for both HBV&HCV.

We found seroconversion (positive on subsequent admissions by same serology) in 38 patients. Female to male ratio was 1:0.9

Table-1 depicting the frequency of hepatitis virus positivity among seroconversion.

**Table-1.** Abstract of positivity.

HBV	19
HCV	17
HBV&HCV	2

**Table-2**

	HBV	HCV	HBV&HCV	Total
Seroconversion	19	17	2	38
Age				
12-30yrs	3	1	0	4
30-60yrs	16	13	1	30
>60yrs	0	3	1	4
Gender				
Male	7	10	1	18
Female	12	7	1	20
Chemotherapy				
Yes	17	13	2	32
No	2	4	0	6
Blood transfusion				
Yes	6	4	1	11
No	13	13	1	27

**Table-4** Type of cancer associated with seroconversion and reactivation

Primary number	STS &bone	gynac	breast	GIT	Skin	GUT	multiple	H&N	parathyroid
	9	6	4	9	1	3	1	5	1

In patients with seroconversion Adriamycin, CDDP, 5-FU based chemotherapy was used in 9,19,9 patients respectively. Musculoskeletal sarcoma and GIT cancers were most frequent among the seroconverted patients followed by gynecological and head & neck cancers. 90% reactivation occurs within 3 to 6 months after chemotherapy. Three patients died of acute fulminant hepatic failure (mortality rate of 39 per 1000/year), 1 patient required ICU admission and recovered.

Liver stiffness, as measured by transient elastography during USG abdomen, is a surrogate marker for cirrhosis in hepatitis virus positive patients. A liver stiffness value below 7.1 kilopascals (kPa) rules out significant liver fibrosis, where as a liver stiffness value above 12.5 kPa is predictive of cirrhosis. Between these thresholds, the liver stiffness value is

In our study we found that 79% patients were present between ages of 30 to 60. HBV was positive in 10.5% in patients with <30 years of age. HCV positivity was noted in 10.5% patients with age >60 years. There was no significant gender difference in seroconversion incidence and there was more incidence of HBV among females and HCV among males. We found that 32 patients with seroconversion (84.2%) were post chemotherapy. There were 11 patients (28 %) who got blood transfusion.

**Table-3** Mode of treatment proceeding seroconversion

	HBV	HCV	HBV & HCV
Chemo therapy only	4	4	0
Chemo radiation	6	5	1
Blood transfusion+ surgery	0	1	0
Blood +chemo radiation	4	0	0
Radiation +surgery	0	1	0
Surgery only	2	2	0
Blood transfusion + chemotherapy	2	3	1
Chemo radiation + surgery	1	1	0

inconclusive. In our study we found that 12(31%) patients were below 7.1 KPa and 4 patients were 7.1 to 12.5 KPa, and 50 % (n=19) of patients having fibro scan above 12.5 kilopascals probably indicating that these patients were in chronic hepatitis state.

In our study 2 patients who underwent surgery without blood transfusion or chemotherapy or chemo radiation were among the seroconverted.

**Discussion**

There are four phases of HBV infection – interaction between the virus and the host immune system

1. Immune tolerance
2. immune clearance
3. Immune control
4. Immune escape

### Mechanism of liver injury in HBV reactivation

Liver injury due to HBV reactivation associated with immunosuppression due to chemotherapy occurs by 2 mechanisms.

1. Uncontrolled viral replication during immunosuppression causes direct cytolytic destruction of hepatocytes. After chemotherapy or immunosuppression has been ceased, immune reconstitution may cause severe immune mediated injury to infected hepatocytes
2. An elevated/enhanced immune response against hepatocytes expressing viral proteins- causing necrosis of liver cells.

The delayed reactivation associated with immune reconstitution may occur up to six months after cessation of immunosuppression<sup>(1,2)</sup>. HBV reactivation due to chemotherapy induced immunosuppression can result in asymptomatic biochemical hepatitis, acute symptomatic hepatitis may lead to fulminant liver failure and death<sup>(3)</sup>.

### HBsAg negative, anti-HBc positive patients

Clearance of HBsAg occurs at a rate of 0.5% per year in patients with previously diagnosed chronic hepatitis B (CHB)<sup>(4)</sup>. Individuals may have serological evidence of past HBV exposure, both scenarios leads to an HBsAg negative/hepatitis B core antibody (anti-HBc) positive state. These patients remain at risk of HBV reactivation due to immunosuppression due to the persistence of the HBV in the form of cccDNA in hepatocytes and other tissues<sup>(5,6)</sup>.

Anti-HBs may not be detectable during a window period of several weeks to months after the disappearance of HBsAg. During this period, the diagnosis of acute HBV infection is made by the detection of IgM anti-HBc in serum. IgM anti-HBc may become detectable during exacerbations of chronic hepatitis B and is often used as a surrogate for active viral replication. Anti-HBc of the IgG class is found in persons who recover from acute hepatitis B and also is the form found in those who progress to chronic infection.

### Tests for HBV

**Table-5** serologic tests and inference

Marker /tests	Inference
Anti-HBs	Prior infection or vaccination
IgM anti HBc	Window period
Anti HBc	Acute & chronic infection
IgG anti-HBc	Recovery phase or progress to chronic infection

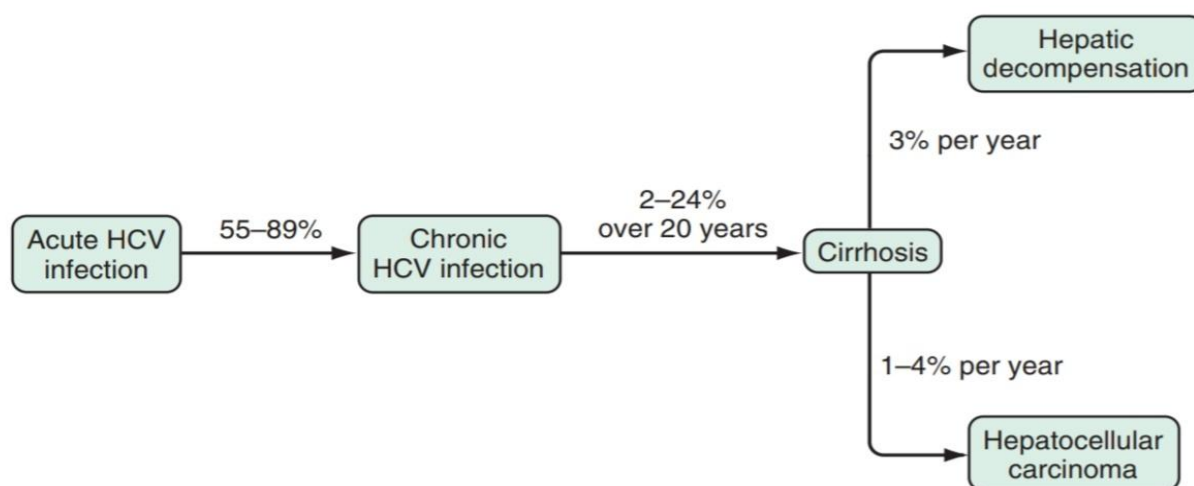
As per American Gastroenterology Association guidelines on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy, the risk estimate is more than 10% when Adriamycin based chemo therapy<sup>(7,8)</sup>. In our study, besides Adriamycin, CDDP and Paclitaxel also been associated with reactivation.

### HCV associated seroconversion

Worldwide estimates of the prevalence of HCV antibodies, range from 1.6% to 2.8%(10,24).The highest prevalence is reported in low-income countries, including Egypt (15%), Pakistan (4.7%), and Taiwan (4.4%),<sup>21</sup> and is lower in North America (range, 1.1%-1.3%), Australia (1.7%), and Eastern and Western Europe (range, 0.5%-4.5%)<sup>(9)</sup>. The latest epidemiologic reports suggest that there are currently 80 million HCV-RNA-positive individuals around the globe.<sup>(24, 27)</sup>

Chronic hepatitis virus which affects millions of patients<sup>(11)</sup>. Negative findings on screening for HCV antibodies with detectable HCV RNA will leads to serum False-negative results.

Among patients with cancer receiving chemotherapy, liver dysfunction caused by hepatitis B virus (HBV) reactivation is a significant problem,<sup>(13,14)</sup> occurring in 14% to 72% of patients who did not receive prophylactic antiviral therapy, leading to liver failure in 13% of cases and death in 6% of cases<sup>(13,14,20,21)</sup>. We also found that 3 patients died of HBV without anti viral prophylaxis and no mortality reported among HCV infected individual.



**Tests for HCV**

Assays	Test type	Value	Inference
Serological -indirect	EIA(enzyme immune assay)	Ratio >9	Prior infection
Serological -indirect	3 <sup>rd</sup> generation- EIA	Detect antibodies-against NS3,4,5 and HCV core antibody	7-8 weeks after infection – sensitivity and specificity 99%(32)
Virological –direct	HCV RNA	10-15 IU/ml	Quantitative
Virological –direct	HCV core Antigen	Cheaper alternative to HCV RNA	Confirm HCV viremia

Direct assays like HCV RNA tests represent the state of art for determining HCV viremia in anti HCV positive patients<sup>(33)</sup>. Serological assays are used initially for diagnosis; virological assays are required for confirming infection, monitoring response to treatment, and evaluating immunocompromised patients. A cheaper and faster alternative to nucleic acid testing for HCV RNA to confirm HCV viremia is the HCV core antigens assay.

In contrast, the incidence and consequences of HCV reactivation (HCVr) during cancer treatment remain poorly defined. HCVr appears to be less common and to have less severe consequences than HBV reactivation,<sup>(12,14,15,17,18)</sup> with only a few fatal cases of fulminant hepatitis attributed to HCV having been reported<sup>(18,19)</sup>.

The management of chronic HCV infection has been neglected in many cancer centers, likely due to treating patients concomitantly with chemotherapy and older HCV therapy, such as interferon<sup>(28)</sup>. In current scenario direct-acting antiviral (DAAs) have changed the treatment

paradigm for chronic HCV infection and improved virologic outcomes, even in HCV-infected patients with cancer<sup>(29, 30)</sup>. In some regions of Europe and Asia, HCV antibodies have been reported in up to 2.8% of patients with solid tumors<sup>(31)</sup>. For screening HCV antibodies and to confirm HCV RNA is widely used and approved by US-FDA.

**Conclusion**

In our study we frequently encountered patients who were seropositive after institution of treatment. It was found to be related to chemotherapy induced immunosuppression causing hepatitis virus reactivation.

We used rapid card test to detect HBV and HCV antibody, which has very low sensitivity and not recommended for routine screening. The sensitivity and specificity of third generation EIA is 99% and is recommended for routine screening<sup>(32)</sup>.

As an oncologist it is important to be aware about this potential life threatening and treatable



condition. Timely administration of antiviral prophylaxis will reduce the viral reactivation related fulminant hepatic failure and death.

The serological tests recommended to detect HBV, in descending order are HBV-DNA, HBs Ag and HB e Ag

For HCV it is ideal to do HCV antibody as a screening test by EIA and HCV RNA as a confirmative test

Along with above mentioned tests the following may be recommended

1. All patients are to be screened by third generation EIA and card test is not to be used as standard method of screening.
2. Proper sterilization
3. Prior vaccination for high risk patients and all medical and paramedical staffs against HBV.
4. All cancer patients to be evaluated with liver function tests.
5. All hepatitis seropositive patients who are planned for chemotherapy should be given under cover of antiviral treatment especially for HBV.

### Limitations of the study

It is retrospective study with a small sample size, card test was used to find HBV/HCV which does not reflect the true incidence and prevalence in our study.

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