Hepatitis C Virus Infection in Patients with End-Stage Renal Disease: A Study from a Tertiary Care Centre in India

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Background: Hepatitis C Virus (HCV) infection is common in patients with end stage renal disease (ESRD) and is an important cause of liver disease. We describe the demographic, clinical and biochemical profile of these patients from a tertiary care center of north India. **Methods:** Records of consecutive patients of HCV infection with ESRD on maintenance hemodialysis or with renal transplantation who presented to our unit from January 2009 to June 2013 were analyzed. The diagnosis of HCV was based on HCV-RNA positivity and/or positive anti-HCV serology. Those with positive anti-HCV serology and negative HCV-RNA on two occasions at 3-month interval, without treatment with interferon, were excluded. **Results:** 140 patients (median age 44 years [range 18–68], 69% males) were included. Six patients had co-infections (HBV 5, HIV 1). Most (99, 71%) patients were asymptomatic for liver disease and HCV was identified either on routine screening (39, 28%) or during investigation for raised liver enzymes (60, 43%). Remaining 41 (29%) were symptomatic for liver disease, either in the form of jaundice alone (14, 10%), or decompensated liver disease (27, 19%). Median time between initiation of hemodialysis and HCV detection was 33 (range 0–124) months. Thirty-four (27%) patients had received renal transplantation. In 11 patients HCV was detected after renal transplantation. In 23 (18%) patients anti-HCV was falsely negative but HCV-RNA was positive. Nearly 35% patients had concomitant diabetes. Median Bilirubin, AST, and ALT were 1.1 mg/dL, 42 IU/L and 44 IU/L, respectively. HCV-RNA was more than 5 log in 49/88(59%) patients. Median HCV-RNA was 6.5×10^5 IU/ml (Range 650 to >10 million IU/ml). Genotype-1 was the commonest genotype (30/56, 54%) followed by genotype-3 (17/56, 30%). **Conclusion:** HCV infection is usually asymptomatic in patients with ESRD, however, it may lead to jaundice and decompensated liver disease. False negative anti-HCV is quite common. We found that genotype-1 was commoner than genotype-3 in our cohort of ESRD patients. Most of the patients have high viral load. (J CLIN EXP HEPATOL 2016;6:21–25)

Prevalence of hepatitis C virus (HCV) infection is quite high (10–40%) in patients with end stage renal disease (ESRD); and HCV infection remains an important cause of liver disease in these patients.¹ Many Indian investigators have studied the prevalence of HCV infection in patients with ESRD, but the data on profile of these patients remains sketchy.^{2–12} HCV has a complex relation with kidney. On one hand, HCV infection leads to increased morbidity and mortality in patients with ESRD

due to cirrhosis and hepatocellular carcinoma;¹³ while on the other hand it can cause renal disease *per se* in form of glomerulonephritis and essential mixed cryoglobulinemia.¹⁴ Treatment of HCV and response rate with conventionally available therapy differs in patients with ESRD from normal population and poses big challenge.^{15,16} HCV leads to decreased graft and patient survival in patients who undergo kidney transplantation.¹⁷ Treatment with interferon for HCV infection is contraindicated after renal transplant due to risk of graft rejection.^{18,19} In this article we describe the demographic, clinical and biochemical profile of patients of HCV with ESRD from a tertiary care center of north India.

PATIENTS AND METHODS

Patients

Inclusion Criteria

In this retrospective study we included consecutive patients of ESRD who were on maintenance hemodialysis or who had history of renal transplantation, and were

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Abbreviations: ACLF: acute-on-chronic liver failure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESRD: end stage renal disease; GI: gastrointestinal; Hb: hemoglobin; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; INR: international normalized ratio; PT: prothrombin time; RNA: ribonucleic acid; RT: renal transplantation; USG: ultrasonography
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Table 1 Data of Patients Included and Excluded.

Anti-HCV	HCV-RNA	
Positive	Not available	Included n = 48
Positive	Positive	Included n = 67
Negative	Positive	Included n = 25
Positive	Negative ^a	Excluded
Negative	Negative	Excluded

^aHCV RNA negative on two occasions at three month interval in absence of history of treatment with interferon.

referred to the first unit of our out-patient department or in-patient department of our hospital between January 2009 and June 2013 (i.e. over a period of four and half years) for HCV infection. The diagnosis of HCV was based on HCV-RNA positivity and/or positive anti-HCV serology.

Exclusion Criteria

We excluded those patients whose HCV RNA level (if available) was negative on two occasions at 3-month interval, provided HCV RNA negativity was not the result of interferon therapy (Table 1).

Evaluation

The aims and objectives of the study were to describe the demographic, clinical and biochemical profile of patients of HCV with ESRD from a tertiary care center of north India. The diagnosis of HCV was made on the basis of positive HCV RNA and/or positive HCV antibodies (ELISA). Patients who were Anti HCV negative but HCV RNA positive were included in the study.

During the initial visit, detailed clinical history was noted along with physical examination findings. Baseline parameters complete blood count, kidney function tests, liver function tests, prothrombin time, HBsAg, Anti-HCV & HIV were recorded. HCV RNA and genotype were obtained whenever possible. Ultrasonography (USG) abdomen and upper gastrointestinal (GI) endoscopy reports were also noted.

RESULTS

Demographic Characteristics

A total of 140 patients were included in this study. Their median age was 44 (range 18–68) years. Majority of the patients [91 (65%)] were within 41–60 years range (Table 2). Out of total 140 patients 69% (n = 97) were males. Six patients (5%) had co-infection; five with HBV and one with HIV. Forty nine (35%) patients had concomitant diabetes.

Table 2 Age Groups of Patients.

Age groups	No of patients (n = 140)	%
11–20	3	2%
21–30	8	6%
31–40	24	17%
41–50	49	35%
51–60	42	30%
61–70	14	10%

Clinical Characteristics

Asymptomatic Patients

Most [99/140 (71%)] patients were asymptomatic for liver disease and HCV was identified either on routine screening [39/140 (28%)] or during investigation for raised liver enzymes [60/140 (43%)] as per conventional upper limit of AST (42 IU/dL) and ALT (48 IU/dL). Seventy-nine of 140 (56%) patients had high AST and ALT (without evidence of jaundice or ascites) if we take the upper limit of ALT 30 and 19 IU/dL for males and females, respectively as per new criteria.¹²

Symptomatic Patients

Remaining 41/140 (29%) were symptomatic for liver disease either in the form of jaundice alone [14/140 (10%)] or decompensated liver disease [27/140 (19%)]. The decompensation was in the form of ascites alone in 7/140 (5%) and jaundice plus ascites in 20/140 (14%). The etiology of decompensation in these 27 patients was due to end stage liver disease in 24 patients and acute-on-chronic liver failure (ACLF) in 3 patients. The acute event in ACLF was hepatitis E virus infection in two, and anti-tubercular therapy in one.

Investigations

Table 3 shows median values for common biochemical parameters like Hb, platelets, PT/INR, creatinine, bilirubin, albumin and liver enzymes (AST and ALT).

Table 3 Biochemical Parameters of Patients.

Parameters	Median	Range	Unit
Hb	9.3	6.4–12.8	Gm/dl
Platelets	1.12	0.26–5.36	Lac/cu-mm
INR	1.3	0.8–3.2	–
Creatinine	5.6	1.3–13.6	Mg/dl
Bilirubin	1.1	0.2–24	Mg/dl
Albumin	2.4	1.4–3.8	gm/dl
AST	42	11–1219	IU/L
ALT	46	13–1342	IU/L

Ultrasound was available in all 140 patients. 62 (44%) patients had normal liver, 46 (33%) had hepatomegaly and 32 (23%) had coarse and shrunken (cirrhotic) liver on ultrasound. Fatty liver was present in 32 of these 46 patients (70%) with hepatomegaly. The rest 14 had hepatomegaly due to chronic hepatitis C itself. Thirty-five of 140 (25%) patients had ascites on ultrasound. Of these 24/35 (69%) patients had cirrhotic liver on ultrasound [8 of 32 patients (25%) of cirrhosis had no ascites]. Eleven patients of 35 with ascites (31%) had no evidence of cirrhosis on ultrasound. Portal vein was dilated (>13 mm) in 22 (16%) patients. Splenomegaly was found in 36 (26%) patients. Hepatocellular carcinoma was detected in two patients only.

UGI endoscopy was done in 52/140 (37%) patients. This included all 32 patients with diagnosis of cirrhosis based on ultrasound findings. Findings included: no varices in 25 (48%), small varices (grade I and II) in 14 (27%), and large varices (grade III and IV) in 13 (25%) patients. Portal hypertensive gastropathy was present in 20 (39%) patients while gastric antral vascular ectasia (GAVE) was seen in 14 (26%) patients. Nine (17%) patients had both gastropathy and GAVE. Ectopic and/or fundal varices were seen in 5 (9%) patients.

Renal Status

Most common etiology of renal failure was diabetes [45/140 (32%)] followed by glomerulonephritis [30/140 (21%)], hypertension [20/140 (14%)] and interstitial nephritis [12/140 (9%)]. Etiology was not specified or unknown in rest 33/140 (24%) patients. Median time between initiation of hemodialysis and HCV detection was 33 months (range 0–124 months). Thirty eight (27%) patients had received renal

transplantation and of them 10 (26%) had more than one renal transplantation (retransplantation). In 12 patients (32%) HCV was detected after renal transplantation. Total 110 (79%) patients were on hemodialysis. Eight patients were on hemodialysis after renal transplantation due to graft failure.

Hepatitis C Virus Status

In 25 patients (18%) HCV RNA was positive while Anti HCV was falsely negative. HCV RNA was available in 92/140 (66%) patients. Less than 3 log, 3–6 log and >6 log HCV RNA was seen in 15 (16%), 23(25%) and 54(59%) patients. Median HCV RNA was 6.5×10^5 IU/ml (range 650–> 10 million IU/ml).

Genotyping was available for 62/140 (44%) patients. Genotype 1 was the most common genotype 33 (54%) followed by genotype 3 [19 (30%)]. Genotype 2 was seen in only 2 patients and genotype 4 was seen in 3 patients. Two patients had mixed genotype while genotype could not be determined in 3 patients.

DISCUSSION

There are several studies from India and abroad citing high prevalence (10–40%) of HCV infection in ESRD patients on hemodialysis (Table 4).^{2–12} Our study was not aimed to know the prevalence. The aim of our paper was to study the clinical spectrum of HCV in ESRD patient in Indian setting. Male predominance was seen in our study as in other studies which can be attributed to higher incidence of ESRD *per se* in males owing to higher incidence of hypertension and diabetes. Most common age group was 41–60 years in our study, again correlating with higher incidence

Table 4 Prevalence of HCV Infection in End Stage Renal Disease Patients in Various Indian Studies.

Author	Place	Year	Total no. of patients	Patients with HCV infection (%)	Method
Salunkhe ²	Lucknow	1992	31	45%	anti-C100-3 antibody assay
Chadha ³	Pune	1993		12.1%	
Sumathy ⁴	South India	1993		37.5%	
Arankalle ⁵ VA	Pune	1995	57	24.5%	3rd Gen RIBA
Jaiswal SP ⁶	Indore	1996	105	41.9%	Ant HCV ELISA
Gosavi ⁷	Mumbai	1997	72	27.8%	Anti HCV 2nd Gen ELISA
Agrawal SK ⁸	Delhi	1999	69	42%	
Chandra M ⁹	Hyderabad	2004	256	46%	Anti HCV ELISA and HCV RNA
Reddy ¹⁰	Hyderabad	2005	151	13.23%	Anti HCV & HCVcAg by ELISA
Medhi ¹¹	Delhi	2008	250	17.2%	Anti HCV & HCVcAg by ELISA
Jasuja ¹²	Delhi	2009	119	27.7%	HCV PCR

of ESRD in this age group. In our study, co-infection was not a common finding while it was quite high (up to 50%) in certain studies.^{9,19} However, it has been reported 3.7% in another study consistent with our findings.²⁰

Most of the HCV patients are asymptomatic at the time of presentation and as many as 30% patients even had normal values of liver enzyme according to conventional limits of AST and ALT. Therefore routine screening at regular intervals (AST, ALT every month and HCV RNA every 6 month) is recommended in ESRD patients where prevalence of HCV is quite high. ALT levels tend to be depressed in ESRD patients probably due to suppression of ALT synthesis in hepatocytes, defective release of ALT into blood stream or accelerated clearance.²¹ Recently defined upper limit of ALT (30 and 19 IU/dL for males and females respectively)²² might help in picking up more patients with HCV infection but may lead to unnecessary testing as most of them may not have HCV. On the other end of spectrum 23% patients have underlying cirrhosis based on ultrasound findings. This finding is important because these patients might need simultaneous liver-kidney transplantation and will not be suitable for kidney transplantation alone. Other studies also noted that up to 25% patients with HCV and ESRD had bridging fibrosis or cirrhosis on liver biopsy (METAVIR >3) precluding renal transplantation.^{23,24}

In our study 18% patients had false negative anti HCV antibodies, while HCV RNA was positive. Anti-HCV assays are of two types: enzyme immunoassay (EIA) and recombinant immunoblotting assay (RIBA). EIA is more commonly used due to its simplicity and reduced cost. The first-generation EIA (EIA-1) was flawed by high false-negative and false-positive rates. The following two successive generations of EIA (EIA-2 and EIA-3), further increase the sensitivity and specificity. Such commercial assays are now widely used in clinical practice. In ESRD patients receiving maintenance dialysis, previous studies showed that the false-negative rates of EIA-2 were 2.6% and 7%, respectively, to diagnose HCV infection, taking HCV-RNA as the reference standard.^{25,26} The EIA-3 provided excellent accuracy, with 0–0.23% false-negative rates.²⁷ The 18% false negativity of anti-HCV in our study may be due to use of EIA kits of previous generations. Therefore, HCV RNA should be obtained in ESRD patients if HCV is suspected. The antibody response in patients on chronic haemodialysis and after renal transplantation is poor and the ELISA test alone may miss and underestimate the prevalence of hepatitis C infection in these patients.^{28–30}

Genotype 3 is most common genotype in India but we found in ESRD patients genotype 1 is more common than 3. Our findings are similar to findings of other studies from India^{31,32} but in one study genotype 3 was reported to be more common than genotype 1.³³ Genotype 2 and other

genotypes are infrequent. Reasons for higher prevalence of genotype 1 in this population are not clear.

Mean HCV RNA level was 6.5×10^5 IU/ml and 59% patients had high (more than 6 log) RNA. High RNA can be one reason for rapid progression of liver disease in ESRD patients. Most other studies have shown that ESRD patients have low viral load which is in contrast to our finding. Ajay Duseja et al reported median HCV RNA 1.3×10^5 IU/ml in total 17 patients.³¹

Special consideration in ESRD patients is to be given for timing of collection of blood samples for HCV RNA. The sample should be collected prior to dialysis as heparin used during dialysis may interfere with the PCR technique. In addition to that, the adsorption of the HCV RNA onto the inner surface of dialysers with further destruction of viral particles by the hydraulic pressure employed by the blood for dialysis can result in lower HCV RNA levels.³⁴

HCV leads to decreased graft and patient survival in patients who undergo kidney transplantation.¹⁷ In a recent systematic review³⁵ of the published medical literature on the impact of HCV status on survival of patients who received renal transplantation (RT) it was found that presence of anti-HCV antibody was an independent and significant risk factor for death and graft failure after RT. As a cause of death, hepatocellular carcinoma (HCC) and liver cirrhosis were significantly more frequent among anti-HCV positive than anti-HCV negative RT patients.³⁵

There are several limitations in this study. This is a retrospective study, and like most retrospective studies it has limitation of missing data. Keeping this limitation in mind, we tried to use the available data as best as possible. HCV RNA and genotype were not available in many patients. Some of the patients with HCV would have been missed as HCV RNA was not done in every patient. In some patients anti-HCV testing was done by first or second generation ELISA. HCV RNA testing was done by different methods. The other limitation of the study was mixing hemodialysis patients and renal transplant patients which might have distorted the clinical spectrum. Moreover, some patients had more than one RT and some post-RT patients were now again on hemodialysis. Thus this comprises a heterogeneous population. Because of these limitations it is urged that reader should use cautious interpretation of the data presented.

In conclusion, this study shows that HCV infection is asymptomatic in 71% patients with ESRD, however, it may lead to jaundice and decompensated liver disease. False negative anti-HCV is quite common, hence screening by HCV RNA is recommended. Unlike in non-ESRD patients of India, where genotype 3 is more common, we found in the ESRD patients genotype 1 to be the most common genotype. Most of the patients have high viral load. Further prospective studies are needed to find out whether high viral load in these patients leads to rapid progression of liver disease.

CONFLICTS OF INTEREST

All authors have none to declare.

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