Most Patients of Hepatitis C Virus Infection in India Present Late for Interferon-Based Antiviral Treatment: An Epidemiological Study of 777 Patients from a North Indian Tertiary Care Center

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Background: Interferon-based antiviral therapy is offered only to those HCV patients who have either chronic hepatitis or early cirrhosis. Advanced cirrhotics do not tolerate interferon-based therapy. Since HCV is asymptomatic in early stages and usually presents late, the eligibility for interferon-based therapy is thus limited. There are scarce studies from India, which looked specifically the eligibility of interferon-based therapy in HCV patients. **Aim:** To study the spectrum of presentation of HCV infection, determine their eligibility for interferon-based therapy, and follow for SVR. **Methods:** The records of all consecutive patients of HCV, >14 years age, who presented to our department between 2008 and 2014, were analyzed for categorization into chronic hepatitis, cirrhosis and hepatocellular carcinoma. Patients with detectable HCV RNA who have chronic hepatitis or Child A cirrhosis were considered eligible for Peg-interferon and ribavirin. Patients who received treatment were followed for SVR. **Results:** 777 patients (median age 49 [range 15–95] years, males 69%) were included. Cirrhosis was the most common presentation (56%, 439/777) followed by chronic hepatitis (37%, 287/777) and HCC (7%, 51/777). Of patients who had cirrhosis (including those with HCC), 36% (174/490) were Child A; 51% (250/490) were Child B and 14% (66/490) were Child C. Only 347/777 (45%) were eligible for Peg-interferon-alpha and Ribavirin. Among the remaining 430 patients, in 326 (76%) the disease was far too advanced. Of eligible patients only 54% actually received Peg-interferon-alpha and Ribavirin and 81% patients could complete the course. Of them only 70% could achieve SVR. **Conclusions:** Most HCV patients in India present late and only about 45% are eligible for Interferon-based antiviral treatment. At presentation 56% patients already have cirrhosis and 7% have HCC. Since HCV is usually asymptomatic in early stages, awareness about screening should be increased so that more patients are diagnosed early before they develop cirrhosis or HCC. (J CLIN EXP HEPATOL 2015;5:134–141)

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Abbreviations: AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; BCLC: Barcelona Clinic Liver Cancer; DAA: Directly acting agents; FNAC: Fine needle aspiration cytology; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; PCR: Polymerase chain reaction; PEG-IFN: Pegylated Interferon; RBV: Ribavirin; RNA: Ribonucleic acid; SMA: Smooth Muscle Antibody; SVR: Sustained virological response; WHO: World health organization

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INTRODUCTION

Hepatitis C virus (HCV) is a ribonucleic acid (RNA)-enveloped flavivirus, mainly transmitted by a parenteral route. It is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) the world over. HCV infection is a major public health matter of concern globally and especially for countries like India where health awareness is poor in general public.¹ It is estimated that 180 million people are infected worldwide,² and more than half of them are not even aware of their infection.³ There are several factors influencing interactions between the host and the HCV; therefore, the clinical picture and natural history are variable for both acute and chronic hepatitis. After acute infection, 75%–85% of patients develop chronic disease.⁴ Chronic HCV infection

often follows a progressive downhill course, and may ultimately result in cirrhosis, HCC, and the need for liver transplantation.⁵

There is paucity of large-scale prevalence studies on hepatitis C in the general population of India. The reported prevalence rates vary widely (range 0.09%–2.02%) as reported by the available four large population based studies.⁶ The burden of HCV infection in India is expected to be high with a population over 1.2 billion; as a result, its treatment modalities, as well as success rates, demand urgent attention.⁷ However, the eligibility and the success of treatment are highly dependent on the stage of presentation of HCV. Interferon-based treatment with Peg-interferon-alpha (Peg-IFN α) and Ribavirin (RBV) can only be offered to patients who have chronic hepatitis or early (Child A) cirrhosis. Patients who have advanced liver disease in form of Child B or C cirrhosis or liver failure are not eligible for interferon-based therapy and are generally offered liver transplantation and/or supportive care for cirrhosis, and recently direct acting antivirals (DAAs).

There are scarce studies from India, which have looked specifically the eligibility of interferon-based therapy in HCV patients. Hence, we aimed to study the spectrum of clinical presentation of HCV infection at our center, determined their eligibility for interferon-based antiviral treatment, and followed those treated for treatment response and outcomes.

PATIENTS AND METHODS

Patients

This retrospective study was conducted in the Department of Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India. The records of all consecutive patients with HCV disease, above age of 14 years, who presented to our department, between 2008 and 2014, were analyzed. HCV disease was diagnosed when detectable anti-HCV antibodies, HCV RNA or both were present in serum. These records were in specific pro-forma for each HCV patient that contained relevant information on clinical presentation, risk factors for HCV acquisition, hematological, biochemical, serological, radiological, and histological investigations. If patient had received antiviral therapy, relevant information to determine treatment outcome had also been recorded in the pro-forma. Those patient-records were excluded from the study that had incomplete data to derive any meaningful conclusion. For missing data on individual parameter, imputation method was employed.⁸

Clinical Evaluation

These data in pro-forma were analyzed to obtain information on history, physical examination, complete blood count, liver function test, renal function test, prothrombin

time, INR, ultrasound abdomen, hepatitis B surface antigen, HIV, ANA, SMA, baseline HCV RNA by quantitative real-time polymerase chain reaction (PCR) assay (Cobas Taqmen 48), HCV genotype by real-time PCR assay and upper gastrointestinal endoscopy, as indicated. Every patient was reviewed for risk factors of HCV acquisition, *viz.* blood transfusion, surgery, needle stick injury, dental procedure, tattooing, acupuncture, unprotected intercourse with multiple sexual partners and intravenous drug abuse. Patients with significant alcohol intake were defined as those who were consuming regularly >20 g of alcohol per day for at least ten years, prior to presentation.

Clinical Presentation Groups

After complete evaluation the HCV patients were categorized into one of the three presentation groups: Chronic hepatitis, cirrhosis or hepatocellular carcinoma. Diagnosis of cirrhosis was made on the basis of clinical, biochemical, radiologic, endoscopic or histologic findings. Severity of cirrhosis was graded based on the Child-Pugh classification. The diagnostic criteria for HCC were any of the following: hypervascular liver mass on triple-phase contrast-enhanced CT abdomen (with or without raised AFP) or fine needle aspiration cytology (FNAC).⁹ Patients with no evidence of cirrhosis or HCC were categorized as chronic hepatitis C. Spontaneously cleared HCV was defined when HCV RNA was not detectable in patients but with positive serology for hepatitis C (Anti HCV).

Eligibility for Antiviral Treatment

All patients who were in the stage of chronic hepatitis with detectable HCV RNA were eligible for antiviral therapy with PEG-IFN and RBV. Patients with compensated cirrhosis (Child-Pugh class A) were also eligible for antiviral therapy with PEG-IFN and RBV. Patients who had advanced liver disease in form of Child's B or C cirrhosis or liver failure were not considered eligible for therapy with PEG-IFN and RBV. Patients on treatment for HCC of BCLC stage A or B were also eligible for antiviral therapy with PEG-IFN and RBV if they had detectable HCV RNA.

All eligible patients were started on a combination therapy of PEG-IFN (α 2a or α 2b) subcutaneously plus oral ribavirin (RBV) at dosages recommended in the treatment guidelines. Peg-IFN α 2a was given at a dose of 180 mcg subcutaneously per week and Peg-IFN α 2b was given at a dose of 1.5 mcg/kg subcutaneously per week. Ribavirin was given at a dose of 800 mg/day for genotype 3 patients and at a dose of 1000 mg for those <75 kg in weight and 1200 mg for those >75 kg in genotype 1 patients. Information on sustained virological response (SVR), defined as undetectable HCV RNA at 24 weeks after treatment completion, was obtained. Patients whose SVR results were not available due to lost to follow up were considered as failed to have achieved SVR (intention-to-treat analysis).

Table 1 Baseline Characteristics of Included Patients.

Parameter	Value
Age, years	49 (15–95)
Gender, % (n/n)	
Males	69% (538/777)
Females	31% (239/777)
BMI, kg/m ²	24.5 (15.0–42.2)
Known to be HCV + for, months	2 (1–180)
Co-morbidities, % (n/n)	
Diabetes	21% (165/777)
Alcoholics	19% (149/777)
ESRD	9% (71/777)
Co-infections, % (n/n)	
HIV	0.9% (7/777)
HBV	1.7% (13/777)
(Two patients had all the three infections: HCV, HBV, HIV)	
Risk factors for HCV acquisition, % (n/n)	
Blood transfusion	32% (248/777)
Dental extraction	7% (55/777)
Surgery	35% (274/777)
Needle stick injury	1.5% (12/777)
Tattoo	1% (8/777)
Acupuncture	0.1% (1/777)
Dialysis	7% (56/777)
IV drug abuse	1% (6/777)
Past history of jaundice, % (n/n)	25% (194/777)
HCV RNA, % (n/n)	
High ($>4 \times 10^5$ IU/mL)	45% (261/581)
Low ($615\text{--}4 \times 10^5$ IU/mL)	46% (269/581)
Undetectable or very low (<615 IU/mL)	9% (51/581)
HCV genotype, % (n/n)	
Genotype 3	68% (319/470)
Genotype 1	26% (121/470)
Genotype 4	4% (18/470)
Genotype 2	1% (6/470)
Genotype 3 + 4	1% (4/470)
Genotype 1 + 3	0.5% (2/470)
IL28b, % (n/n)	
C/C	53% (61/115)
C/T	42% (48/115)
T/T	5% (6/115)

Statistical Analysis

Continuous data was represented as median (range) and categorical data was expressed as number and percentage. Statistical analysis was done using SPSS 17.0 (Chicago, Illinois). To deal with problem of missing data, simple imputation method was employed, in which a single value was filled in for each missing value by means of methods such as the last observation carried forward or the baseline observation carried forward.

RESULTS

Patients

A total of 799 patients of HCV who were admitted during the study period were enrolled. Twenty-two patients were excluded from the study due to incomplete records; hence remaining 777 patients were included in the study and their data was analyzed.

Baseline Characteristics

The baseline characteristics of study patients are shown in Table 1. The median age at presentation was 49 (range 15–95) years and majority of patients were males (69%, 538/777). The patients were known to be HCV positive for a median of 2 months (range 1–180 months). Diabetes mellitus was present in 21% (165/777) and 9% (71/777) had end-stage renal disease (ESRD). The median BMI of the patients was 24.5 kg/m² (range 15.0–42.2 kg/m²); while 9% (72/777) patients were obese with a BMI ≥ 30 kg/m². Nineteen percent (149/777) patients gave history of alcohol abuse in cirrhotic doses. Co-infection with HIV was present in 0.9% (7/777) patients and with HBV in 1.7% (13/777) patients. Two patients had all the three infections (HCV, HBV and HIV). Past history of surgery was the most common risk factor for HCV acquisition which was present in 35% (274/777) patients; followed by a history of blood transfusion, present in 32% (248/777) patients. History of hemodialysis was present in 7% (56/777) and history of dental extraction was present in another 7% (55/777). Other risk factors included needle stick injury in 1.5% (12/777), tattooing in 1% (8/777), IV drug abuse in 1% (6/777), and acupuncture in 0.1% (1/777). Past history of Jaundice was present in 25% (194/777).

Clinical Presentation Groups

After complete evaluation the HCV patients were categorized into one of the three presentation groups: Chronic hepatitis, cirrhosis or hepatocellular carcinoma. Cirrhosis was the most common presentation with 56% (439/777) patients in this group. Chronic hepatitis represented 37% (287/777) patients, while HCC was present in 7% (51/777) patients (Figure 1). All patients of HCC also had underlying cirrhosis, hence a total of 490 (63%) patients had cirrhosis.

Figure 1 Patient distribution in various disease categories.

Patients with cirrhosis (including those with HCC) were further categorized into Child-Pugh A, B and C depending on severity of liver disease. Thirty-six percent (174/490) patients were Child A; 51% (250/490) were Child B and 14% (66/490) had Child C cirrhosis. Ascites was present in 53% (259/490) patients and 76% (371/490) patients had esophageal or gastric varices. Fifteen percent (72/490) cirrhotics had history of variceal bleeding.

Eligibility for Antiviral Treatment with Peg-Interferon-Alpha and Ribavirin

Patients with detectable HCV RNA who have chronic hepatitis or Child A cirrhosis are generally eligible for antiviral treatment with Peg-IFN and RBV. Of patients with chronic hepatitis in 78% (223/287) had detectable HCV RNA (thus eligible for antiviral treatment), in 8% (22/287) the HCV RNA was negative, and in 15% (42/287) HCV RNA levels were not available. Among cirrhotic patients, of 174 patients with Child A cirrhosis, detectable HCV RNA was present in 71% (124/174) and were eligible for antiviral treatment. Thus, out of all 777 HCV patients only 347 (45%) were eligible for antiviral treatment (Figure 1). Among the remaining 430 patients in 326 (76%) the disease was far too advanced to offer any antiviral treatment.

Of patients eligible for antiviral treatment with Peg-IFN and RBV only 54% (189/347) actually received antiviral treatment. The rest could not receive treatment mainly because it was unaffordable for them. Moreover, eighty-one percent (153/189) patients could complete the anti-

viral treatment and of them 70% (107/153) could achieve the sustained virological response (Figure 2).

DISCUSSION

This is the largest study from India, which clearly documents that majority of patients of HCV in India, at their clinical presentation have advanced disease, and they have already lost their chance of complete cure of their HCV related liver disease. The only hope for these patients with advanced HCV-related liver disease is usually liver transplantation. Our study showed that of 777 consecutive patients of HCV who presented to our department from 2008 through 2014, only 45% were eligible for antiviral treatment with Peg-IFN α and RBV. Cirrhosis was already present in 63% patients, and it was advanced (Child B or C) in 65%. HCC was present in 7%.

HCV has a huge disease burden in India.¹ The data on prevalence of HCV infection in India is scanty and the only sources are a few screening studies done on blood donors and pregnant women, and few community-based studies. In India, mandatory screening for HCV started in 2000.⁶ The seroprevalence of anti-HCV in blood donors in various places in India, since the year 2000, has ranged from 0.13 to 1.09%.¹⁰⁻¹⁵ Seropositivity of HCV in antenatal women in India ranges from 0.19% to 1.6%.^{16,17} These data, however, cannot be extrapolated to the community as blood donors and pregnant women represent a selected and healthy population sample. In a community-based epidemiologic study, which was carried

Figure 2 HCV disease pyramid with respect to treatment eligibility and treatment success rate.

out in a district in West Bengal, of 3579 individuals screened, 0.87% were HCV antibody positive.¹⁸ As compared to West Bengal, in states of Punjab and Haryana the prevalence of HCV seems to be much higher. In a study done by Sood et al,¹⁹ prevalence rate of HCV infection in Mullanpur (district Ludhiana of Punjab) was found to be 5.2% of 5258 subjects screened door-to-door. This prevalence rate is possibly the highest in South Asia. Data from rest of the country are very limited. Data from western India revealed a seroprevalence of 0.78%.²⁰ Thus an estimated average prevalence of 0.8% (0.4%–1.0%) is reasonably suggested by a recent meta-analysis²¹ while another systematic review suggests a prevalence of 1.0–1.9%.²² Although the prevalence of HCV infection in Indian population is lower than that reported from industrialized countries of the west, the total reservoir of infection is significant. The WHO estimates that approximately 12 million Indians are suffering from HCV (while the prevalence in the US is just 2–4 million and in Europe is 5–10 million).²³ This calls for urgent public health measures, including health education to limit the magnitude of the problem.¹⁸

In our study we showed that by the time patients of HCV present to hospital, 63% already have cirrhosis. The reason for this late presentation is that most HCV patients in the early stage (chronic hepatitis stage) either have no symptoms or have only very mild non-specific symptoms. In a community study from Haryana on 1630 cases of HCV,²⁴ only fatigue was the most common symptom present in 69% of patients, followed by abdominal pain in 47%. Symptoms like malaise and body ache were found among 14% of patients in this study.²⁴ In community, till very late stage of disease, these non-specific symptoms are treated symptomatically, and blood tests are usually not carried out. Even if biochemical investigations are done, they are usually normal. In the community study from West Bengal, serum alanine aminotransferase (ALT) levels were

elevated in only 31% (8 of 26) of anti-HCV-positive subjects.¹⁸ In spite of mild or no symptoms and normal or near normal biochemistry, these patients are infective, even though they do not know they are infected, and have a potential to spread the disease to others. These asymptomatic individuals comprise of a large reservoir of HCV carriers, who can act as a pool for its continuous transmission.²⁵ HCV RNA is detectable in more than 80% of these cases suggesting actively replicative virus with potential of transmission.¹⁸ In a previous study by Amarapurkar²⁶ it was found that the majority of patients who develop chronic HCV infection are asymptomatic; but 60–80% develop chronic hepatitis as indicated by elevated ALT; around 30% maintain normal ALT. One-third of chronically infected patients develop progressive liver injury, fibrosis and cirrhosis over a period of 20–30 years, and 15% develop hepatocellular carcinoma.²⁶ As no protective vaccine is available and as the treatment is costly, lengthy, with a poor success rate, screening of healthy population remains the only means of primary prevention of HCV transmission.¹⁰ Routine blood screening for Hepatitis C infection should be mandatorily carried out in all hospitals.

The only method to control the HCV pandemic is prevention of HCV transmission and early treatment of those infected. Over the last few years, numerous HCV vaccine approaches have been assessed in mice and primates, but only a few vaccines have progressed to human trials.²⁷ Since, there is no hepatitis C vaccine available as yet, the only other preventive method is safe healthcare practices. Unsafe therapeutic injections and transfusion of unsafe blood are the predominant mode of transmission of HCV in India.¹ Unsafe therapeutic injections include contaminated multi dose vials and saline bags from reinsertions of used needles and syringes, use of single needle or syringe to administer intravenous medication to multiple patients, and also due to the use of spring loaded finger

stick devices without changing the platform to monitor blood sugar levels in multiples patients.^{28,29} Hence, to reduce the burden of HCV infection and to decrease the incidence of HCV infection, healthcare workers should play an important role.³⁰ The safe injection practices should be followed meticulously. These include the use of aseptic technique for injection equipment, not to administer medication from same syringe to multiple patients, use of fluid infusion and administration sets for one patient only, use of single dose vials, not to administer medication from single dose vial to multiple patients or combine leftover contents.²⁸

The natural history of HCV shows that the majority of patients may become chronically infected and will not spontaneously resolve the infection. About 30% of chronically infected patients will evolve to cirrhosis within 20–30 years,²⁶ with an increased risk of hepatic decompensation and HCC. The goal of HCV treatment is to eradicate the virus and prevent the complications of chronic liver disease. The standard-of-care for HCV, till recently, has been combination therapy with Peg-IFN α and RBV.³¹ Selecting patients for interferon-based antiviral therapy is mainly based on patient factors including fibrosis stage, probability of adverse events of therapy, and comorbidities, such as chronic kidney disease or psychiatric disease, that may preclude or modify therapy options. Decompensated chronic liver disease is usually a contraindication for therapy by Peg-IFN α /RBV. Thus only a proportion of HCV patients are eligible for interferon-based antiviral therapy, and our study has showed that in India, most patients are already ineligible by the time they present.

Attaining SVR (sustained viral response) has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, HCC, and liver-related complications. In our study, of those patients who could complete the treatment with Peg-IFN α /RBV, 70% were able to achieve SVR. Based on the genotype profile of HCV in India (genotype 3 prevalence 68% and genotype 1 prevalence 26%) an SVR of 70% is reasonable and compares well with data from West. However, the alarming fact is that even if the patient was a good candidate for antiviral therapy, it could be started in 54% patients and only 81% could complete the therapy. Thus out 347 patients who were eligible for antiviral therapy only 44% (153/347) could actually receive and complete the therapy. The main reason for this dismal data with treatment obtainment and compliance is poor economic condition of the patients. According to the data from the Reserve Bank of India in 2012, the population of India living below poverty line was 21.92%.³² Most Indian patients have no medical insurance to cover the cost of therapy.

Recent years have seen development of a large number of new molecules that are revolutionizing the treatment of hepatitis C. Some of the new DAAs like sofosbuvir have been called game-changers because they offer the

prospect of interferon-free regimens for the treatment of HCV infection.³¹ The latest guidelines from AASLD and EASL in 2014 and 2015 have now incorporated DAAs in the management of patients with HCV.^{33,34}

In the era of IFN-free oral combinations of DAAs, cirrhotic patients with more advanced liver disease may also become candidates for antiviral therapy. IFN containing therapies were frequently contraindicated in this group of patients, and previous antiviral regimens resulted in a very low efficacy and poor tolerance. The safety and efficacy profile of these new DAAs is particularly relevant in these difficult-to-treat HCV patients. However, till now data on the potential impact of significant portal hypertension in the achievement of SVR by these DAAs is still lacking.³⁵

One of the newly approved DAAs (sofosbuvir) has just reached the Indian market. Sofosbuvir is a highly potent inhibitor of the NS5B polymerase in the HCV, and has shown high efficacy in combination with several other drugs, with and without PEG-IFN, against HCV.³⁶ It offers many advantages due to its high potency, low side effects, oral administration, and high barrier to resistance. The efficacy and safety were demonstrated in many large and well-designed phase 2 and phase 3 clinical trials like NEUTRINO,³⁷ PROTON,³⁸ ELECTRON,³⁹ ATOMIC,⁴⁰ COSMOS,⁴¹ FUSION,⁴² FISSION,³⁷ NUCLEAR,⁴³ POSITRON,⁴² and the like. It is generally well-tolerated. Adverse events that occurred include: Headache, insomnia, fatigue, nausea, dizziness, pruritus, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia; however, the exact safety profile can only be judged when this drug is actually used on a large scale.³⁶ The limitations posed by Peg-IFN α /RBV therapy, as adequately pointed out by the current paper, would be offset by the wide availability of sofosbuvir and other DAAs. Patients who have advanced liver disease or those who had contraindications to Peg-IFN α , are likely to benefit most by these new DAAs.

There were a few limitations in our study. First, this being a retrospective study, it has all the limitations of retrospective studies like missing data and incomplete records. However, we have utilized the accepted imputation method to make up for the missing data.⁸ Second limitation is that our center being a tertiary care hospital with liver transplant facility, there would have been a referral bias and more patients with advanced liver disease are likely to have been included. We accept this limitation, hence the title of our study reflects that this data is from a tertiary care centre.

Thus to conclude, our study shows that most patients of HCV infection in India present late to hospitals and only about 45% are eligible for antiviral treatment with Peg-interferon and Ribavirin. At presentation 56% patients already have cirrhosis and 7% have HCC. Since HCV is usually asymptomatic at treatable stage, awareness about screening should be increased so that more patients are

diagnosed at treatable stage. We hope that with the availability of DAAs in Indian market at affordable price, most HCV patients in India who were considered ineligible will now benefit from these new drugs.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

- Puri P, Anand AC, Saraswat VA, et al. Consensus statement of HCV task force of the Indian national association for study of the liver (INASL). Part I: status report of HCV infection in India. *J Clin Exp Hepatol*. 2014;4:106–116.
- Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis*. 2005 Sep;5:558–567.
- Denniston MM, Kleven RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: national health and nutrition examination survey 2001–2008. *Hepatol Balt Md*. 2012 Jun;55:1652–1661.
- Afdhal NH. The natural history of hepatitis C. *Semin Liver Dis*. 2004;24(suppl 2):3–8.
- Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci*. 2006;3:47–52.
- Mukhopadhyaya A. Hepatitis C in India. *J Biosci*. 2008 Nov;33:465–473.
- Rao P, Koshy A, Philip J, et al. Pegylated interferon alfa-2b plus ribavirin for treatment of chronic hepatitis C. *World J Hepatol*. 2014 Jul 27;6:520–526.
- He Y. Missing data analysis using multiple imputation: getting to the heart of the matter. *Circ Cardiovasc Qual Outcomes*. 2010 Jan;3:98–105.
- Kumar A, Acharya SK, Singh SP, et al. The Indian National Association for study of the liver (INASL) consensus on prevention, diagnosis and management of hepatocellular carcinoma in India: the puri recommendations. *J Clin Exp Hepatol*. 2014;4(suppl 3):S3–S26.
- Pandit DP, Pagaro MP, Nabamita C. Prevalence of antibodies to hepatitis C virus in voluntary blood donors: are women better donors? *J Clin Diagn Res JCDR*. 2014 Apr;8:DC20–DC23.
- Gupta N, Kumar V, Kaur A. Seroprevalence of HIV, HBV, HCV and syphilis in voluntary blood donors. *Indian J Med Sci*. 2004 Jun;58:255–257.
- Pahuja S, Sharma M, Baitha B, Jain M. Prevalence and trends of markers of hepatitis C virus, hepatitis B virus and human immunodeficiency virus in Delhi blood donors: a hospital based study. *Jpn J Infect Dis*. 2007 Nov;60:389–391.
- Giri PA, Deshpande JD, Phalke DB, Karle LB. Seroprevalence of transfusion transmissible infections among voluntary blood donors at a tertiary care teaching hospital in rural area of India. *J Fam Med Prim Care*. 2012 Jan;1:48–51.
- Gowri V, Chandraleka C, Vanaja R. The current seroprevalence of hepatitis C virus in a tertiary care centre in vellore, Tamil Nadu. *Indian J Community Med Off Publ Indian Assoc Prev Soc Med*. 2012 Apr;37:137.
- Arankalle VA, Chadha MS, Jha J, Amrapurkar DN, Banerjee K. Prevalence of anti-HCV antibodies in western India. *Indian J Med Res*. 1995 Mar;101:91–93.
- Mehta KD, Antala S, Mistry M, Goswami Y. Seropositivity of hepatitis B, hepatitis C, syphilis, and HIV in antenatal women in India. *J Infect Dev Ctries*. 2013 Nov;7:832–837.
- Sood A, Midha V, Bansal M, Sood N, Puri S, Thara A. Perinatal transmission of hepatitis C virus in northern India. *Indian J Gastroenterol Off J Indian Soc Gastroenterol*. 2012 Jan;31:27–29.
- Chowdhury A, Santra A, Chaudhuri S, et al. Hepatitis C virus infection in the general population: a community-based study in West Bengal, India. *Hepatol Balt Md*. 2003 Apr;37:802–809.
- Sood A, Sarin SK, Midha V, et al. Prevalence of hepatitis C virus in a selected geographical area of northern India: a population based survey. *Indian J Gastroenterol Off J Indian Soc Gastroenterol*. 2012 Sep;31:232–236.
- Arankalle A, Chobe P, Banerjee K. Hepatitis C virus in Pune, India. *J Assoc Phys India*. 1992 Aug;40:562–563.
- Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014 Nov;61(1 suppl):S45–S57.
- Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int Off J Int Assoc Study Liver*. 2011 Jul;31(suppl 2):61–80.
- WHO | Hepatitis C [Internet]. [cited 2014 Dec 1]. Available from: <http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html>.
- Verma R, Behera BK, Jain RB, Arora V, Chayal V, Gill PS. Hepatitis C, a silent threat to the community of Haryana, India: a community-based study. *Australas Med J*. 2014;7:11–16.
- Singh P, Kaur R, Kaur A. Frequency distribution of hepatitis C virus in different geographical regions of Punjab: retrospective study from a tertiary care centre in North India. *J Nat Sci Biol Med*. 2014 Jan;5:56–58.
- Amarapurkar D. Natural history of hepatitis C virus infection. *J Gastroenterol Hepatol*. 2000 May;15(suppl 1):E105–E110.
- Verma R, Khanna P, Chawla S. Hepatitis C vaccine. *Hum Vaccines Immunother*. 2014 Jul;10:1927–1929.
- Amarapurkar D. How can we reduce the burden of Hepatitis C? *Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc*. 2011 Aug;17:227–228.
- Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *J Hepatol*. 2006 Oct;45:607–616.
- Alter MJ. Healthcare should not be a vehicle for transmission of hepatitis C virus. *J Hepatol*. 2008 Jan;48:2–4.
- Puri P, Anand AC, Saraswat VA, et al. Consensus Statement of HCV Task Force of the Indian National Association for study of the liver (INASL). Part II: INASL recommendations for management of HCV in India. *J Clin Exp Hepatol*. 2014;4:117–140.
- Reserve Bank of India [Internet]. [cited 2014 Dec 1]. Available from: <http://www.rbi.org.in/scripts/PublicationsView.aspx?id=15283>.
- Fullreport [Internet]. [cited 2015 Apr 23]. Available from: <http://www.hcvguidelines.org/fullreport>.
- Summarypdf [Internet]. [cited 2015 Apr 23]. Available from: <http://www.easl.eu/medias/cpg/HEPC-2015/Summary.pdf>.
- Lens S, Mariño Z, Forns X. Efficacy of new direct acting antivirals in transplant recipients and patients with advanced disease. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. 2014 Dec 15;46(suppl 5):S197–S205.
- Bhatia HK, Singh H, Grewal N, Natt NK. Sofosbuvir: a novel treatment option for chronic hepatitis C infection. *J Pharmacol Pharmacother*. 2014;5:278–284.
- Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013 May 16;368:1878–1887.
- PROTON Study: PSI-7977 QD with PEG/RBV: 12-week Safety, RVR, cEVR, & SVR12 in Treatment-naïve Patients with HCV GT2 or GT3 [Internet]. [cited 2014 Nov 30]. Available from: http://www.natap.org/2011/EASL/EASL_22.htm.

39. HCV new drugs – Report 3 (ELECTRON study phase 2: GS7977+Rbv GT1) [Internet]. [cited 2014 Nov 30]. Available from: http://www.natap.org/2013/EASL/EASL_44.htm.
40. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2013 Jun 15;381:2100–2107.
41. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet*. 2014 Jul 26.
42. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013 May 16;368:1867–1877.
43. Lawitz EJ, Rodriguez-Torres M, Denning J, et al. All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in treatment-naïve genotype 1 hepatitis C (nuclear). *J Viral Hepat*. 2013 Oct;20:699–707.