ORIGINAL ARTICLE

Clinicoepidemiology and Diagnosis of Hepatitis C: Evaluating HCV Core Antigen Assay as a Diagnostic Tool in a Tertiary Care Teaching Hospital of North India

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Abstract

Introduction: One of the main causes of primary hepatocellular carcinoma and chronic hepatitis is the hepatitis C virus (HCV), with significant variability in its genotypes affecting pathogenicity and treatment outcomes. In India, prevalence ranges from 0.5 to 1.5%, with certain regions showing higher rates. Diagnostic methods include serological and molecular assays, with the HCV core antigen (HCV cAg) assay emerging as a cost-effective substitute for HCV RT-PCR testing.

Materials and methods: This study enrolled 292 suspected hepatitis cases from May 2019 to May 2020 in a North Indian tertiary care institute. Demographic, biochemical, and clinical data were collected. Seroprevalence was determined using Qualisa™ HCV ELISA. Sixty seronegative and 30 seropositive samples underwent HCVc-Ag testing and HCV RT-PCR. Genotyping was carried out using AmpliSens® HCV-genotype PCR kit. The HCV core antigen assay was evaluated by taking HCV RT-PCR as the gold standard test.

Results: Of the 292 patients, 98 (30%) were seropositive for HCV, predominantly in the 40–59 age-group. Surgery and blood transfusion were significant risk factors. Co-infections included human immunodeficiency virus (HIV) (3.06%) and hepatitis B virus (HBV) (6.12%). Genotype 3a was the most prevalent. HCV core antigen assay showed 93.75% sensitivity, 93.10% specificity, 88.24% positive predictive value, 96.43% negative predictive value, and 93.33% accuracy.

Conclusion: Hepatitis C virus core antigen is a dependable and economical substitute to HCV RT-PCR for diagnosing HCV infection. Regular screening in high-risk groups is essential for early detection and prevention.

Keywords: Diagnostic assay, HCV core antigen, HCV RT-PCR, Hepatitis C virus, North India, Seroprevalence.

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Highlights

- The study revealed the recent prevalence and clinical picture of hepatitis C among patients attending the tertiary referral center in North India.
- The study demonstrated that the HCV core antigen (HCV-Ag) assay had an excellent diagnostic accuracy and can be used as a reliable and cost-effective alternative to expensive molecular tests for diagnosing hepatitis C virus (HCV) infection.

Introduction

One of the main causes of primary hepatocellular malignancy and chronic hepatitis is the HCV. The pathogenicity of different HCV genotypes can differ and can affect how well a treatment works. Fifty to eighty-five percent of those infected have a persistent acute infection that results in long-term viremia.[1] The high likelihood of chronicity and the unavailability of a vaccination render HCV infection a significant public health issue.

As of 2022, the World Health Organization (WHO) estimated that around 58 million people globally are living with chronic HCV infection making it a significant public health concern worldwide.[2] With a prevalence of more than 3.5%, East Asia, North Africa, and the Middle East have the greatest HCV prevalence.[3] Hepatitis C virus infection is believed to impact between 0.5 and 1.5% of the population in India.[4] Certain regions like northeast India, tribal communities, and parts of Punjab have higher prevalence rates.[5] About 15–20% of all chronic liver disorders and 5–10% of cases of hepatocellular carcinoma are caused by HCV infection.[6]

The genetic variability within the HCV genome is quite diverge. It is categorized into seven primary genotypes and over 100 distinct subtypes and these genotypes exhibit more than a 30% variation in their genomic sequences, whereas in Quasi-species, the differences in genomic sequences are around 20%.[7]

Hepatitis C virus consists of multiple genotypes. Genotype-1 is particularly prevalent in Western nations, such as Europe and

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North America, with HCV-1 (subtype A1B1) accounting for 60–70% of cases.[8] In contrast, HCV-2 is more commonly found in parts of Middle and West Africa, while HCV-3 is primarily seen in India. Genotypes 4, 5, and 6 are more common in selected endemic regions: HCV-4 is especially widespread in Egypt and sub-Saharan Africa, HCV-5 in South Africa, and HCV-6 in China and Southeast Asia.

There are two primary types of tests utilized for diagnosing HCV: serological assays and molecular assays. The serological assay recommended by WHO is the anti-HCV antibody test.[9,10] Although serological assays are relatively simple and cost-effective, they cannot reliably identify cases in the acute phase of illness due to the prolonged time required for seroconversion, also, there are high chances of false-negative results with the anti-HCV antibody test, especially in immunocompromised individuals.[11]

To differentiate between spontaneously cured cases, chronic or active HCV infections, use of a confirmatory test becomes necessary. The most commonly used confirmatory test is the HCV RT-PCR (reverse transcription polymerase chain reaction); however, it is expensive, requires technical expertise to prevent false-positives, and has a longer turnaround time.[8,12] Consequently, a considerable number of cases seropositive for anti-HCV antibodies do not proceed with confirmatory HCV tests, leading to loss to follow-up, particularly in low and middle-income countries (LMIC) like India.

HCV core antigen is a newly developed test, which has proven to be a reliable cost-effective alternative to HCV RT-PCR detecting active infection.[13] Particularly nowadays, when non-interferon, pan-genotypic oral therapies are used for the treatment of HCV infection, HCV-Ag alone is adequate for diagnosing acute cases of HCV, despite its slightly lower diagnostic sensitivity compared with HCV RT-PCR.[12] However, as there is limited data about the performance of this test therefore assessing the diagnostic utility of this assay is crucial for optimizing patient care and enhancing disease surveillance efforts.

The epidemiological landscape of hepatitis C is a complex interplay of various factors such as high-risk population, socioeconomic status, access to healthcare infrastructure, access to preventive measures and treatment modalities. Understanding the epidemiology of hepatitis C is very useful in designing effective public health interventions and clinical management strategies. With this background, in this study, we analyzed changing demographic pattern, clinical parameters and evaluated HCVc-Ag assay as an substitute to HCV RT-PCR in diagnosing HCV infection.

Materials and Methods

In this study, 292 patients with signs and symptoms suggestive of hepatitis were enrolled over a 1-year period (from May 2019 to May 2020) at a tertiary care facility in North India. Patients attending. Demographic data, biochemical profiles, and clinical features were documented for each patient. The blood samples collected from these patients were subjected to anti-HCV antibody testing using Qualisa™ HCV ELISA (Tulip Diagnostics Inc., Bambolim Goa, India) for determining the HCV seroprevalence.

Of these 292 samples, 60 seronegative samples and 30 seropositive samples were subjected to HCVc-Ag and HCV RT-PCR using QuickTiter™ HCV cAg Kit (Cell Biolabs Inc., San Diego CA, USA) and COBAS® TaqMan® HCV RT-PCR test kit (Roche Diagnostics Inc., Basel, Switzerland) respectively (Fig. 1). Out of the 292 samples, 60 seronegative and 30 seropositive samples were also subjected to genotyping of HCV. This was done using the AmpliSens® HCV-genotype PCR kit (Central Research Institute for Epidemiology, Moscow, Russia) to determine the prevalent genotypes among the study population (Fig. 1).

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 26. Odds ratios (OR) and 95% confidence intervals (CI) were computed. *p*-values were determined using the Chi-square test, Fisher's exact test, and proportion comparisons, with a *p*-value of <0.05 deemed statistically significant. For diagnostic evaluation of HCV core antigen, HCV RT-PCR testing was used as the gold standard.

Results

The study was conducted among the 292 patients, of these 98 (30%) patients were seropositive for HCV. In this study, we found that the seroprevalence of HCV among the patients attending the hospital was around 30%. The maximum number of anti-HCV antibody positive patients (47.9%) were from the age-group 40–59 years. As indicated in Table 1, seroprevalence of HCV in the age-group 20–39 years was significantly lower compared with those above the age

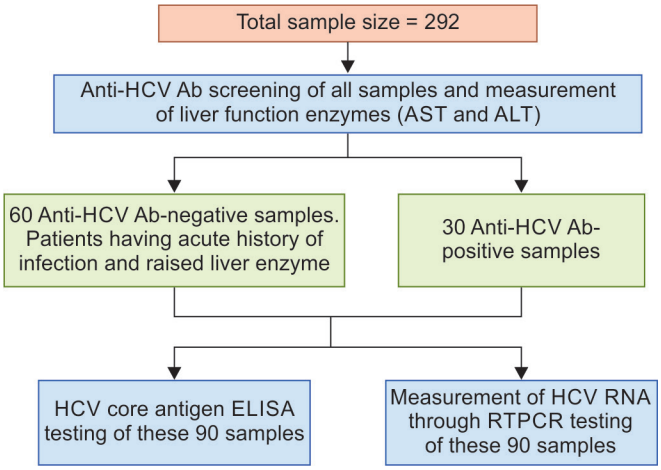

Fig. 1: Showing the flowchart of HCV core antigen test evaluation

Table 1: Age distribution and seropositivity of hepatitis C virus infection

S. No.	Age-group	Total cases N = 292 (%)	HCV seropositive cases N = 98 (%)	Sero-prevalence (%)	Chi-square	Odd's ratio	p-value
1	<20 years	10 (3.4%)	1 (1.1%)	1%	1.4	0.2	0.143
2	20–39 years	105 (35.9%)	25 (25.5%)	23.8%	2.6	0.4	0.008
3	40–59 years	121 (41.4%)	47 (47.9%)	38.8%	1.6	1.4	0.108
4	>60 years	56 (19.2%)	25 (25.5%)	44.6%	1.9	1.8	0.052

HCV, hepatitis C virus

Table 2: Distribution of risk factors in seropositive cases of hepatitis C

S. No.	Risk factors	Total cases N = 292 (%)	HCV seropositive cases N = 98 (%)	p-value	Chi-square	Odd's ratio
1	Blood transfusion	25 (8.56%)	15 (15.30%)	0.007	7.323	3.323
2	Hemodialysis	9 (3.08%)	3 (3.06%)	0.731	0.118	0.989
3	Unsafe injection	32 (10.95%)	8 (8.16%)	0.374	0.79	0.63
4	IV drug abuse	15 (5.13%)	5 (5.12%)	0.794	0.068	0.989
5	H/o tattooing/body piercing	23 (7.87%)	8 (8.16%)	0.92	0.01	1.016
6	H/o surgery	64 (21.92%)	23 (23.47%)	0.76	0.093	1.144
7	Dental procedure	12 (4.14%)	5 (5.12%)	0.768	0.087	1.436
8	Unknown	112 (38.35%)	31 (31.63%)	0.121	2.408	0.645

HCV, hepatitis C virus

Table 3: Biochemical profile in HCV seropositive patients

Biochemical markers	HCV seropositive samples N = 98 (%)	p-value	Chi-square	Odd's ratio
S. Bilirubin <1 mg/dL	52 (53.06%)	0.0002	13.696	2.691
S. Bilirubin >1 mg/dL	46 (46.94%)			
ALT <30 U/mL	40 (40.81%)	<0.0001	25.752	3.7593
ALT ≥30 U/mL	58 (59.19%)			
AST <30 U/mL	44 (44.89%)	<0.0001	41.898	5.775
AST ≥30 U/mL	54 (55.11%)			
Urea ≤35 mg/dL	59 (60.21%)	0.1845	1.438	1.4073
Urea >35 mg/dL	39 (39.79%)			
Creatinine ≤1.2 mg/dL	64 (65.31%)	0.377	0.782	1.309
Creatinine >1.2 mg/dL	34 (34.69%)			

HCV, hepatitis C virus

Table 4: Showing clinical feature of HCV seropositive cases

Clinical feature	Total cases N = 292 (%)	HCV seropositive cases N = 98 (%)	p-value	Chi-square	Odd's ratio
Fever	112 (38.35%)	50 (51.02%)	0.001	10.4	2.318
Nausea and vomiting	84 (28.76%)	38 (38.77%)	0.011	6.494	2.038
Pain abdomen	65 (22.26%)	21 (21.43%)	0.925	0.009	0.93
Dark urine	86 (29.45%)	42 (42.86%)	0.001	11.804	2.557
Stool discoloration	45 (15.41%)	39 (39.79%)	0.0001	64.497	20.712
Joint pain	87 (29.79%)	29 (29.59%)	0.935	0.007	0.986

HCV, hepatitis C virus

of 39 ($p < 0.05$). However, the seroprevalence rates did not differ between males and females.

The history of surgical interventions was the most prevalent risk factor for HCV acquisition in our study as given in Table 2, and it was present in 23.47% (23/98) of seropositive individuals. However, only blood transfusion has a statistically significant association ($p = 0.007$) with HCV seropositive cases. We also found that 3.06% (3/98) of seropositive individuals were co-infected with human immunodeficiency virus (HIV). In addition, 6.12% (6/98) of the patients also had hepatitis B virus (HBV) infection in addition to HCV. Only one patient (1.02%) who tested positive for HCV also had co-infections with HIV and HBV.

The biochemical profile of the HCV seropositive cases is shown in Table 3. The association of increased levels of liver enzymes (ALT, AST) and bilirubin in HCV seropositive patients was significant ($p < 0.05$). However, no significant association between levels of blood urea and creatinine levels in HCV seropositive patients was observed ($p > 0.05$).

In this study, we studied the correlation of clinical features in anti-HCV seropositive patients as given in Tables 4 and 5; there was a strong association of fever, nausea and vomiting, dark colored urine, and light-colored stool with anti-HCV seropositive patients ($p < 0.05$). It is worth noting that seropositive patients have 20-fold association of having light-colored stool (OR = 20.712) in this subset.

In this study, HCV RT-PCR and HCV cAg were done in 90 samples (30 HCV seropositive and 60 HCV seronegative with acute history of raised liver enzyme). Out of these 90 samples, 32 samples were positive for HCV RT-PCR. Genotype 3a was found in maximum number (65.62%) of patients followed by genotype1a and 3b. Genotypes 2, 5, and 6 were not isolated in any sample. The genotype distribution of HCV is shown in Figure 2. HCV core antigen assay was evaluated taking HCV RT-PCR as the gold standard test, HCV

Table 5: Showing correlation between HCV core antigen and HCV RT-PCR testing

HCV RT-PCR		
HCV core Ag	*HCV RT-PCR positive*	*HCV RT-PCR negative*
HCV core antigen positive	30 (true positive)	4 (false-positive)
HCV core antigen negative	2 (false-negative)	54 (true negative)
Total	32	58

Core Ag, core antigen; HCV, hepatitis C virus; RT-PCR, reverse transcription polymerase chain reaction

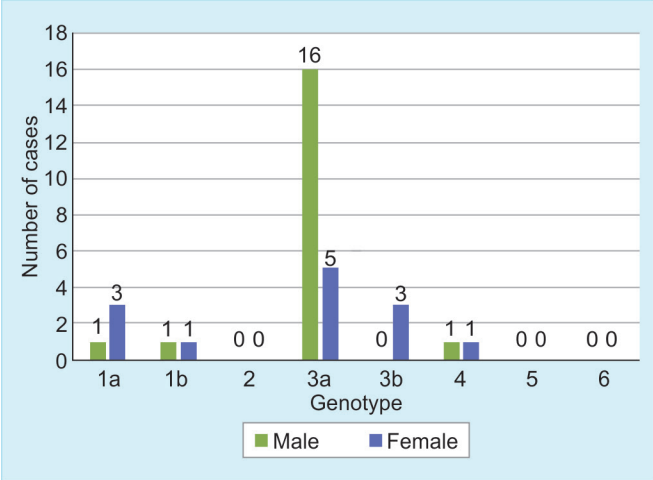

Fig. 2: Gender wise distribution of HCV genotypes

core antigen assay demonstrated a sensitivity of 93.75%, specificity of 93.10%, positive predictive value of 88.24%, negative predictive value of 96.43%, and an accuracy of 93.33%.

Discussion

Hepatitis C virus infection poses a significant challenge to the healthcare system, potentially leading to a range of clinical outcomes from acute infection to chronic hepatitis and hepatocellular carcinoma. The intricate and unpredictable nature of HCV infection, along with its chronic nature, highlights the challenges associated with its prevention and management.[14] Understanding the prevalence of HCV among patients and the distribution of each genotype is crucial for developing effective treatment strategies.

In this study, we found that the seroprevalence of HCV was around 30%. Similar seroprevalence has been reported by Kumar et al. in their study.[15] The high HCV prevalence of 30% in this study can also be attributed to the fact that it included only symptomatic patients and those with a suspicion of hepatitis, rather than a general population sample. This selective inclusion likely resulted in a higher observed prevalence, as these patients had more likelihood of having risk factors or clinical indications associated with HCV infection. However, it has been observed that the prevalence of HCV in India's general population ranges from 0.4 to 1.0%.[16] In this study, seroprevalence of anti-HCV in the 20–39 year age-group was significantly lower compared with those above the age of 39, similar observation was also documented by Sood et al. in their study, where they observed the highest prevalence of HCV in the 41–60 age-group.[17] Before the 1990s, an effective HCV testing was not available, and blood transfusions or organ transplants were not routinely screened for HCV.[18] Many old patients may have been exposed to the virus unknowingly through these routes. Over time, accumulation of the risk factors and behavior associated with HCV infection may have led to a higher prevalence in older age-groups.

The parenteral route is the predominant way by which HCV spreads and other routes include unsafe medical procedures, drug abuse, needle stick injuries, hairdressing, and tattoos.[10] Surgery was the most common risk factor for HCV transmission in this study, accounting for 23.47% (23/98) of seropositive individuals. A significant association was also with history of blood transfusion history. Similarly, history of surgical interventions was the most prevalent risk factor for HCV was also reported by Karaca et al. in their study.[19] Significant association of HCV infection with blood transfusion was also highlighted by Raina et al. and Engle et al., in their research.[20,21] This may be explained by the fact that receiving blood transfusions exposes the vulnerable patient to a significant amount of infectious viruses.

In this study, we found that 3.06% (3/98) seropositive patients were co-infected with HIV also. Moreover, 6.12% (6/98) patients were infected with HBV also along with hepatitis C. In the study of Saha et al., they found HCV and HIV coinfection in about 2% of the patients which was less than our study.[22] In another study done by Sharma et al. in HCV and HIV, coinfection was estimated to be as high as 13%.[23] Our findings indicate that HIV seropositive individuals are at an increased risk of acquiring HCV co-infections Consequently, routine parallel screening for HIV, HBV and HCV in these individuals is recommended.

Higher ALT, AST, and bilirubin levels were significantly correlated with anti-HCV seropositive individuals, according to our observations. Additionally, Mushtaq et al. discovered a strong positive correlation between viral load and liver aminotransferases (AST and ALT).[24] A similar association between the HCV viral load and several aminotransferases (AST and ALT) was identified by Zechini et al. in their study.[25]

In our study, Genotype 3a was found in the maximum number of patients followed by Genotype1a and 3b. Genotypes 2, 5, and 6 were not isolated in any sample. The study done by Prakash et al. shows that HCV genotypes 3a and 1a were the most prevalent circulating genotypes in Uttar Pradesh, India.[26] Similar results were found in the investigation of Amarapurkar et al. and Hissar et al. also.[27,28]

Considering HCV RT-PCR to be the gold standard test, we found that the HCVc-Ag assay was a good predictive marker of HCV viremia. It had an excellent sensitivity and specificity of 93.75 and 93.10%, respectively. Buket et al., in their study, reported that the HCVc-Ag assay had a similar sensitivity and specificity of 86.5 and 100%, respectively.[29] However Reddy et al. reported a lower sensitivity and specificity of 60 and 83%, respectively in their study.[30] HCV core antigen assay had certain advantages over anti-HCV antibody testing like it can be detected within 2–3 weeks of infection, much before the anti-HCV antibody which is detected after at least 12 weeks of infection, thereby shortening the window period of HCV infection by 8–10 weeks.

Hepatitis C virus core antigen assay is easy to perform, has a short turnaround time and low cost compared with HCV RT-PCR. Hepatitis C virus core antigen exhibits comparable diagnostic sensitivity to molecular assays and can serve as an alternative to HCV RT-PCR. Furthermore, HCV core Ag has a strong correlation with RNA levels, suggesting its potential use as an RNA level predictor for response-guided therapy and response monitoring.[31,32]

Conclusion

Clinicoepidemiological analysis of HCV will help clinicians in understanding risk factors and clinical patterns of HCV infection. Therefore, regular screening particularly among high-risk groups such as recipients of blood transfusions, is crucial for early detection and prevention. Expanding the screening efforts in high-prevalence area helps achieve an early diagnosis leading to better clinical outcomes, and enabling prompt initiation of suitable therapy and management. We also observed that HCVc-Ag assay had an excellent sensitivity and specificity of >93%. Hence HCV core antigen testing may be used as quicker and more cost-effective substitute for HCV RT-PCR molecular test.

Ethics Committee Approval

Ethical clearance was duly obtained from the Institute Ethics Committee vide letter no. IEC/103/RMLIMS/2019 dated April 6, 2019, before starting the study.

Authors Contributions

Apurva Rautela and Nikhil Raj are equally contributed to the manuscript.

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