

Factors Associated with Seroconversion of Hepatitis C Virus in End Stage Renal Disease Patients

Muhammad Anees, Nosheen Sarwar, Sajad Ahmad, Irfan Elahii and Fazal e Mateen

Department of Nephrology, King Edward Medical University, Lahore, Pakistan

ABSTRACT

Objective: To determine patient and dialysis services-related factors associated with seroconversion of hepatitis C virus (HCV) in hemodialysis (HD) patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Nephrology, Mayo Hospital, King Edward Medical University (KEMU), Lahore, from January to December, 2018.

Methodology: All patients on regular HD for more than three months were enrolled. All patients who seroconverted from HCV-negative to positive status three months after starting HD, were included. Patient-related factors (age, gender, blood transfusion, duration and frequency of dialysis, history of dental treatment and surgical intervention) and dialysis services-related parameters (dedicated staff, isolated room, hemodialysis machine, reverse osmosis plant, compliance of universal infection control measure) were noted.

Results: Out of 990 patients, 492 (49.7%) were reported as seroconverted for HCV during HD. Factors determined statistically significant for seroconversion were surgical intervention ($p < 0.001$), history of dental procedure ($p < 0.001$), blood transfusions ($p < 0.001$), multiple sexual partner ($p < 0.001$), age ($p = 0.035$) and duration of hemodialysis ($p < 0.001$). Factors not affecting seroconversion included frequency of dialysis ($p = 0.062$), history of renal transplant ($p = 0.097$) and family history of hepatitis ($p = 0.941$). A significant negative correlation was observed between the rate of seroconversion of HCV and the score of universal infection control measures ($r = -0.665$, $p = 0.018$).

Conclusion: There was a high rate of seroconversion of HCV in HD patients. Factors responsible for seroconversion were history of surgical intervention, dental treatment, blood transfusion, multiple sexual partners, age and duration of dialysis. The dialysis centres non-compliant with universal infection control measures were having high rate of seroconversion.

Key Words: Hemodialysis, Seroconversion, HCV, Blood transfusion, Dental treatment, Surgical intervention, Infection, Isolation.

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INTRODUCTION

Worldwide, chronic kidney disease (CKD) is the leading cause of morbidity and mortality. South Asian countries like Pakistan, have high prevalence of CKD (21.2-25%).¹ Dialysis and renal transplant are the main treatment modalities for these patients. HD is a double-edge sword, on one side it maintains the life of CKD patients and on other hand it increases the risk for the transmission of various diseases like hepatitis B, HCV and Human Immunodeficiency Virus (HIV) in these patients.

Seroconversion is defined as transition from anti-HCV negative to positive status after any medical (like HD) and surgical procedure. Numerous studies have reported the seroconversion of HCV in dialysis patients as 1.1% in United Kingdom in comparison with 48.9% in Pakistan.^{2,3} Risk factors for HCV infection in HD patients include number of blood transfusions⁴, duration of HD,⁵ mode of dialysis,⁶ prevalence of HCV infection in the dialysis unit, previous organ transplantation,⁷ younger age,⁸ and nosocomial transmission of HCV in HD units.⁹ It is of great concern because of high rate of death, hospitalisation and worse quality of life score among HD patients.¹⁰ Many studies have been conducted in Pakistan to determine the factors responsible for seroconversion of HCV in dialysis patients; but almost all of these are single-centre, small studies, and focused only on patient's related factors while ignoring the dialysis services-related factors, which play a significant role in seroconversion. So, there was a need to conduct multi-centric and large study to determine the factors responsible for the seroconversion of HCV in HD patients.

Correspondence to: Prof. Dr. Muhammad Anees, Department of Nephrology, King Edward Medical University, Lahore, Pakistan

E-mail: dranees109@hotmail.com

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METHODOLOGY

This cross-sectional study was conducted at the Department of Nephrology, Mayo Hospital, KEMU, Lahore after approval from Institution Review Board (IRB); and data was collected from 12 HD centres of Lahore and nearby district hospitals (Sheikhupura and Kasur).

All patients, who seroconverted from anti-HCV negative to positive status three months after starting HD, till the time of study initiation, were included. The patients who were anti-HCV positive before starting of dialysis or became positive within three months of dialysis initiation, were excluded from the study. Patient-related factors (age, gender, duration and frequency of dialysis, duration of seroconversion of HCV, history of blood transfusion and any surgery, dental procedures, multiple sexual partners and family history of HCV) were noted. Blood samples of patients were sent for hematological and biochemical parameters for evaluation. Dialysis services-related factors were obtained regarding total number of the patients, number of seroconverted patients, dialysis unit settings (separate room, reverse osmosis plant, dedicated staff and separate HD machines for HCV positive and negative patients). Working of the dialysis staff was also observed; whether the staff is following universal infection control measures in the form of wearing of gloves, hand-washing and disinfection of the machine external surface with disinfectant between dialysis shifts, according to international guidelines. Scoring of the hospitals was done on the basis of the compliance for universal infection control measures as shown in Table I. Higher score meant that universal infection control measures were implemented and assumed that seroconversion rate would be minimum.

Data was entered using SPSS version 23.0. Continuous variables were expressed as mean \pm Standard Deviation (SD). Categorical variables were presented as frequencies and percentages. Relative risk (RR) was used to determine effect of clinical and biochemical parameter on seroconversion.

Pearson correlation coefficient was employed to establish the relationship between seroconversion numbers and scores, based on universal infection control measures. Student t-test was used to determine any difference between variables. A *p*-value of less than 0.05 was considered as statistically significant.

RESULTS

Total patients included in the study were 990 from 12 dialysis centres. Mean age of the patients was 45.93 ± 14.47 years; and most of the patients were males 658 (66.5%) and getting twice weekly dialysis 845 (85.4%). Among all, half of the patients 492 (49.7%) were experiencing seroconversion of HCV during dialysis. HCV by PCR was positive in 402 patients. Anemia (Hb < 11 g/dl) was present in 576 (58.2%) patients with mean Hb of 10.11 ± 2.95 gm/dl and dose of the Erythropoietin (EPO) was 7264 IU per week. Factors determined statistically significant

for seroconversion of hepatitis C in dialysis patients were surgical intervention ($p < 0.001$), history of dental procedure ($p < 0.001$), history of blood transfusions ($p < 0.001$), multiple sexual partner ($p < 0.001$) as shown in Table II. Younger age (44.96 ± 13.94 vs. 46.90 ± 14.92 years, $p = 0.035$) and longer duration of dialysis (37.62 ± 32.43 vs. 25.61 ± 25.21 months, $p < 0.001$) were found statistically significant in seroconversion of HCV in dialysis patients. Factors not affecting seroconversion were frequency of hemodialysis ($p = 0.062$), history of renal transplant ($p = 0.097$), and family history of hepatitis ($p = 0.941$). A significant negative correlation was observed between the seroconversion rate of HCV in HD patients and the score of universal infection control measures ($r = -0.665$, $p = 0.018$) of the dialysis services.

DISCUSSION

In Pakistan, the prevalence of HCV in general population is 11.55% and it is 24.97% in patients with different chronic diseases.¹¹ Similarly, much higher pattern of HCV prevalence (27.2%) was observed in CKD patients by Shafi *et al.*¹² In this present study, high seroconversion rate of HCV was observed in dialysis patients, which is very alarming for healthcare professionals and nephrologists. Same pattern was observed in other local¹³ and international studies from Egypt and East Asian countries like Indonesia,⁴⁻¹⁴ which is much higher than developed countries like UK (0.05% per year).¹⁵ The observed high prevalence of HCV in HD patients shows that there are additional factors responsible for seroconversion in dialysis patients. In this study, dialysis setups with non-dedicated staff, shared room, reverse osmosis plant for HCV positive and negative patients, and on dialyser reuse programme were having high rate of seroconversion. According to Belgian perspective multi-centre study,¹⁶ seroconversion rate is 0% just by following universal infection measures even without isolation. In the literature, there is a lot of discussion on the isolation of HCV positive patients; and most of the guidelines from UK Renal Association and Center for Disease Control (CDC) guidelines do not recommend isolation.¹⁷ But, studies from India and Saudi Arabia are showing definite benefits of isolation of HCV positive from HCV negative patients.^{18,19} In this context, there is a need to develop local recommendations for isolation of HCV positive patients in countries with very high prevalence of HCV in general population and where there is high rate of seroconversion during dialysis.

In this study, the dialysis services not ensuring the implementation of universal infection control measures and inappropriate patient-to-nurse ratio were having high rate of seroconversion as compared to centers that followed them. Dialysis staff thinks that HCV is transmitted only by blood and they never realised that they themselves are responsible for this due to limited knowledge and understanding. They know that by wearing gloves they will protect themselves but if they are not going to change the gloves while switching between the patients, they will transfer the virus from positive to negative patient.

Table I: Scoring of the hospitals on the basis of universal infection control measures.

Serial No.	HD services related factor with coding.
1	Segregated room for HCV positive and negative patients: Yes=1 All other setups=0
2	RO plant: separate=1 same=0
3	Dialyzers reuse program: No=1 Yes=0
4	Dedicated staff for hepatitis positive and negative patients: Yes=1 No=0
5	Category of staff: Technologist=1 Nurses, Technician=0
6	Screening of staff for hepatitis B and C status: Yes=1 No=0
7	Inj. Heparin separate vial for each patient: Yes=1 No=0
8	Inj. EPO administration: Prefilled syringe =1 Vial=0
9	Wear clean gloves: Yes=1 No=0
10	Disinfection of the external surface of HD machine and let it air dry: Yes=1 No=0
11	Remove gloves and perform hand hygiene before wearing new gloves: Yes=1 No=0
12	Apply antiseptic solution on the AV fistula site and allow to dry: Yes=1 No=0

Table II: Factors affecting seroconversion.

Serial No.	Parameters	Seroconversion frequency		RR	95% CI	p value
1	Surgical intervention	Yes	No	1.47	1.303-1.663	<0.001*
	Yes	154(15.6%)	80(8.1%)			
	No	338(34.1%)	418(42.2%)			
2	History of dental procedure	Yes	No	1.87	1.654-2.107	<0.001*
	Yes	104(10.5%)	29(2.9%)			
	No	338(34.1%)	469(47.4%)			
3	History of blood transfusion	Yes	No	1.55	1.317-1.832	<0.001*
	Yes	384(38.8%)	305(30.8%)			
	No	108(10.9%)	193(19.5%)			
4	Frequency of dialysis	Yes	No	1.21	0.991-1.484	0.062
	Twice/week	431(43.5%)	414(41.8%)			
	Thrice/week	61(6.2%)	84(8.5%)			
5	Multiple sexual partner	Yes	No	1.80	1.418-2.289	<0.001*
	Yes	8(0.8%)	1(0.1%)			
	No	484(48.9%)	497(50.2%)			
6	Family history of hepatitis	Yes	No	1.01	0.836-1.213	0.941
	Yes	64(6.5%)	64(6.5%)			
	No	428(43.2%)	434(43.8%)			
7	History of renal transplant	Yes	No	0.73	0.502-1.059	0.097
	Yes	18(1.8%)	31(3.1%)			
	No	474(47.9%)	467(47.2%)			

*Statistically significant value. RR: Relative risk, CI: Confidence interval.

According to this study, practice of not disinfecting the dialysis machine external surfaces with antiseptic solution between two shifts and not letting it air dry, were having high rate of seroconversion. It is important to remember that HCV stability on inanimate surfaces is still detectable for up to five days.²⁰ Dialysis units supervised by dialysis technologists and nephrologists were having less rate of seroconversion than the centres run by others. The consultant nephrologists, who are actively involved in training of their staff and observing the staff whether they are following the infection control measures were having less rate of seroconversion. It means that trained staff make a significant difference in preventing seroconversion of hepatitis C in dialysis units. Few years back, recommended treatment for HCV patient was interferon and ribavirin with certain limitations due to adverse effects of the drugs. It has been observed locally as well, that most of nephrologists do not prescribe any treatment for these patients. In this study, although about 80% of the patients were having active disease in the form HCV positive by PCR, but only few patients were getting any treatment. With the advent of new treatment strategies, direct antiviral agents (DAA) for infected patients, it will be easy to manage and eradicate HCV in HD patients as well.

In Pakistan, surgical and dental procedures, multiple uses of injections and needle stick injury are imperative risk factors for transmission of HCV in general population. According to this study, history of surgical intervention, dental procedure and renal transplant are substantial factor for seroconversion of HCV in HD patients. In the last couple of years there is emphasis of health authorities on creating awareness on the spread of HCV among general population, dental and general surgeons. According to Averbukh *et al.*,²¹ the improper use of sterile technique and lack of medical education likely increase the risk of HCV transmission during dental care in under-developed countries. Pakistan has been reported as one of the countries with the highest frequency of injections use in the world with an average of more than 9 injections per person annually.²² Pakistan National Hepatitis Strategic Framework (NHSF) introduced a policy that syringes used in health sector are auto-disabled, preventing the reuse of syringes and eliminating a major risk factor for HCV in the country. There is a need to look into the matter whether these clinics and hospitals are following universal infection control measures or not. While considering the infection control platform, nephrologists hope that through dropping HCV rate in general population, we can control HCV in dialysis patients, as well.

In this study, blood transfusion was an important risk factor for seroconversion of HCV in HD patients, as observed by another local,³ and international study.²³ In this study, majority of the patients were anemic. For maintaining Hb, the patients were getting underdosage of EPO, (8000 units per week), which is much less as compared to developed countries (12000 units per week).²⁴ Other reason of

underdosage of EPO in these patients was use of vials for multiple patients instead of using pre-filled syringes for individual patients. Apart from underdosing, these vials are source of seroconversion of HCV in dialysis patients,²⁵ as well. There is a dire need to discourage this practice among dialysis centres to reduce seroconversion.

For maintaining Hb, these patients need multiple blood transfusions. Before blood transfusion, screening is employed in Pakistan; but it has been observed that most of the blood transfusion centres are screening blood for hepatitis through devices/ immunochromatography (ICT) kit, which is very crude laboratory technique. Blood transfusion authorities in Pakistan recommend this method of screening in centres which are arranging blood transfusion for less than 100 units per month; and ELISA is recommended for bigger centres. But due to improper check and balance of these hospitals, bigger hospitals are still using ICT kit method. There is a need to implement the recommendations of the regulatory authority to stop dissemination of HCV at gross-level by implementing ELISA method for screening before blood donation in primary, secondary and tertiary care hospitals.

In this study, patients who were having longer duration of dialysis were having high rate of seroconversion. Similar observation was made by Somi *et al.*⁷ According to him, mean duration of dialysis was significantly longer (OR=1.01, 1.00-1.02) with median of 102 months as compared to 25 months in patients with no seroconversion. It means that as far as patients are getting dialysis and remained hooked with dialysis machines, they are at high risk for getting seroconversion. In this study, seroconversion of HCV was more common in younger age group than patients with older age group. Similar observation has been made by another study, in which similar pattern of age involving HCV was observed.³ Seroconversion is more in younger age patients; but it may be due to the fact that mean age of the dialysis patients is younger in contrast to developed countries.

CONCLUSION

There is a significant rate of seroconversion of HCV in HD patients. Factors responsible for seroconversion were history of surgical intervention, dental treatment, blood transfusion, multiple sexual partners, age and duration of dialysis. The dialysis centres non-compliant with universal infection control measures were having high rate of seroconversion.

RECOMMENDATIONS:

Universal infection control measures must stringently be followed by dialysis staff.

Continuous professional development of dialysis staff must be provided on regular basis.

Blood transfusions must be avoided, and if it is necessary, then ELISA method should be used for screening.

There is a need for creating local guidelines for isolation of HCV positive and negative patients to stop the seroconversion. These guidelines should be implemented in likewise countries, where there is high prevalence (> 10%) of HCV in general population.

Patients who are seroconverted for HCV must get treatment with DAA drugs.

ETHICAL APPROVAL:

The study was approved by the IRB of King Edward Medical University, Lahore. (No-253(RC) KEMU, Dated 19TH April 2018.

PATIENTS' and DIALYSIS UNITS' CONSENTS:

Informed consents were obtained from patients and all dialysis centres of the concerned hospitals.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MA: Main idea, conceptual framework and final writeup, grafting the work and revising it critically for important intellectual content.

NS: Data collection.

SA: Literature review and refreshing.

IE: Supervision of the data collection from all centres and data entry in the SPSS.

FM: Data analysis and final approval of the version to be published.

REFERENCES

- Khan YH, Mallhi TH, Sarriff A, Khan AH, Tanveer N. Prevalence of chronic kidney disease in Asia: A systematic review of population-based studies. *J Coll Physicians Surg Pak* 2018; **28(12)**:960-6. doi: 10.29271/jcpsp.2018.12.960.
- Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: The DOPPS. *Kidney Int* 2004; **65(6)**:2335-42. doi.org/10.1111/j.1523-1755.2004.00649.x.
- Ismail T, Batool K, Abbasi ZA, Khurshid T. Seroconversion of patients undergoing haemodialysis from HCV negative to HCV positive status. *J Rawalpindi Med Coll Stud Supp* 2016; **20(S-1)**:34-7.
- Rinonce HT, Yano Y, Utsumi T, Heriyanto DS, Anggorowati N, Widasari DI, et al. Hepatitis B and C virus infection among hemodialysis patients in Yogyakarta, Indonesia: Prevalence and molecular evidence for nosocomial transmission. *J Med Virol* 2013; **85(8)**:1348-61. doi.org/10.1002/jmv.23581.
- Zahrán A. Hepatitis C virus seroconversion in hemodialysis units with a high prevalence of hepatitis C: Do we need isolation? *Menoufia Med J* 2014; **27(3)**: 551-5. doi: 10.4103/1110- 2098. 145511.
- Johnson DW, Dent H, Yao Q, Tranaeus A, Huang CC, Han DS, et al. Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: Analysis of registry data. *Nephrol Dial Transplant* 2009; **24(5)**:1598-603. doi: 10.1093/ndt/gfn684.
- Somi MH, Etemadi J, Ghojzadeh M, Farhang S, Faramarzi M, Foroutan S, et al. Risk factors of HCV seroconversion in hemodialysis patients in Tabriz, Iran. *Hepat Mon* 2014; **14(6)**:1-6. doi: 10.5812/hepatmon.17417.
- Fabrizi F, Messa P, Martin P. Transmission of hepatitis C virus infection in hemodialysis: Current concepts. *Int J Artif Organs* 2008; **31(12)**:1004-16. doi: 10.1177/039139880803101204.
- Nguyen DB, Gutowski J, Ghiselli M, Cheng T, Bel Hamdounia S, Suryaprasad A, et al. A large outbreak of hepatitis C virus infections in a hemodialysis clinic. *Infect Control Hosp Epidemiol* 2016; **37(2)**:125-33. doi:10.1017/jice.2015.24710.
- Bruchfeld A, Roth D, Martin P, Nelson DR, Pol S, Londoño MC, et al. Elbasvir plus grazoprevir in patients with hepatitis C virus infection and stage 4-5 chronic kidney disease: Clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2017; **2(8)**:585-94. doi.org/10.1016/S2468-1253 (17)30116-4.
- Arshad A, Ashfaq UA. Epidemiology of hepatitis C infection in Pakistan: Current estimate and major risk factors. *Crit Rev Eukaryot Gene Expr* 2017; **27(1)**:63-77. doi: 10.1615/CritRevEukaryotGeneExpr.2017018953.
- Shafi ST, Hassan MZ, Saleem M, Anjum R, Abdullah W, Shafi T. Frequency of hepatitis C in hospitalized patients with chronic kidney disease. *Pak J Med Sci* 2017; **33(1)**:18-21. doi: https://doi.org/10.12669/pjms.331.11553.
- Hussain Y, Shahzad A, Azam S, Munawar N. Hepatitis-C and it's seroconversion in end stage kidney disease patients on maintenance hemodialysis and factors affecting it. *Pakistan J Med Sci* 2019; **35(1)**:66-70. doi.org/10.12669/pjms.35.1.366
- Amin Elzorkany KM, Zahran A. Hepatitis C virus status in hemodialysis patients in Menoufia Government, Egypt, five years apart: Do we have any improvement? *Saudi J Kidney Dis Transpl* 2017; **28(5)**:1126-32. doi: 10.4103/1319- 2442. 215151.
- Sauné K, Kamar N, Miédougé M, Weclawiak H, Dubois M, Izopet J, et al. Decreased prevalence and incidence of HCV markers in haemodialysis units: A multicentric French survey. *Nephrol Dial Transplant* 2011; **26(7)**:2309-16. doi: 10.1093/ndt/gfq696.
- Jadoul M, Cornu C, Van Ypersele De Strihou C, Bernis P, Christophe JL, Carlier B, et al. Universal precautions prevent hepatitis C virus transmission: A 54 month follow-up of the Belgian multicenter study. *Kidney Int* 1998; **53(4)**:1022-5. doi.org/10.1111/j.1523-1755.1998.00823.x
- Bravo Zuñiga JI, Loza Munárriz C, López-Alcalde J. Isolation as a strategy for controlling the transmission of hepatitis C virus (HCV) infection in haemodialysis units. *Cochrane Database Syst Rev* 2016; **8**:CD006420. doi: 10.1002/1465

- 1858.CD006420.pub2.
18. Agarwal SK. Hemodialysis of patients with HCV infection: Isolation has a definite role. *Nephron Clin Pract* 2011; **117(4)**:328-32. doi: 10.1159/000319984.
 19. Saxena AK, Panhotra BR, Sundaram DS, Naguib M, Venkateshappa CK, Uzzaman W, et al. Impact of dedicated space, dialysis equipment, and nursing staff on the transmission of hepatitis C virus in a hemodialysis unit of the middle east. *Am J Infect Control* 2003; **31(1)**:26-33. doi: 10.1067/mic. 2003.55.
 20. Doerrbecker J, Friesland M, Ciesek S, Erichsen TJ, Mateu-Gelabert P, Steinmann J, et al. Inactivation and survival of hepatitis C virus on inanimate surfaces. *J Infect Dis* 2011; **204(12)**:1830-8. doi: 10.1093/infdis/jir535.
 21. Averbukh LD, Wu GY. Highlights for dental care as a hepatitis C risk factor: A review of literature. *J Clin Transl Hepatol* 2019; **7(4)**:346. doi: 10.14218/JCTH.2019.00023.
 22. Jafri W, Jafri N, Yakoob J, Islam M, Ali Tirmizi SF, Jafar T, et al. Hepatitis B and C: Prevalence and risk factors associated with seropositivity among children in Karachi, Pakistan. *BMC Infect Dis* 2006; **6**:101. doi.org/10.1186/1471-2334-6-101.
 23. Nasser MET, Younes KM, Sany DH, Youssef SS, Mahmoud M, El-Sayed BS. HCV seroconversion in two egyptian hemodialysis units: Role of detection method and patients isolation. *Open Access Maced J Med Sci* 2014; **2(1)**:124-7. doi.org/ 10.3889/oamjms.2014.022.
 24. Streja E, Park J, Chan T, Lee J, Soohoo M, Rhee CM, et al. Erythropoietin dose and mortality in hemodialysis patients : Marginal structural model to examine causality. *Int J Nephrol* 2016; Article ID 6087134, 8 pages. doi.org/10. 1155/2016/6087134.
 25. Siddiqi S, Hamid S, Rafique G, Chaudhry SA, Ali N, Shahab S, et al. Prescription practices of public and private health care providers in Attock District of Pakistan. *Int J Health Plann Manage* 2002; **17(1)**:23-40. doi: 10.1002/hpm.650.

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