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Original article

Chronic hepatitis C in hemodialysis patients: Prevalence and liver fibrosis impact in the National Center for Renal Health in Peru

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ABSTRACT

Background: Hepatitis C (HCV) remains a serious public health problem in high-risk persons such as patients on chronic hemodialysis. We aimed to estimate the serological prevalence of HCV, the HCV viral load and genotype, and liver fibrosis stage among patients on chronic hemodialysis at the National Renal Health Center in Lima, Peru.
Methods: From June 2019 to March 2021, all patients who received chronic hemodialysis were invited to participate. Subjects who provided written informed consent were enrolled. Patients with HCV-positive serology underwent determination of HCV viral load. Samples from subjects with detectable viral load, underwent determination of HCV genotype. Then, HCV infected subjects underwent determination of liver fibrosis using transitional elastography (Fibroscan 402): Metavir score: F0–F1: 2.5–7.5 kPa, F2: 7.6–9.5 Kpa, F3: 9.6–12 Kpa, F4 (Cirrhosis): 12.1–75 Kpa.
Results: Of the 303 subjects invited to participate, 174 (57.4%) subjects gave their written consent. Mean age was 52 years (range 22–91) and 116 (66.6%) were male. HCV serology was positive in 35.1% of patients (61/174); however, the prevalence of positive serology with detectable viral load was 20.11% (35/174). Genotype 1a was the most prevalent (85%). The majority (83.6%) of subjects with detectable viral load had values lower than 800.000 IU/mL. Twenty-nine of those 35 subjects underwent elastography evaluation, and 13 (44.8%) of them were found to have stage F2–F4 fibrosis.
Conclusions: The prevalence of HCV at the largest reference center for hemodialysis in Lima remains high, with GT1a predominance, viral load usually below 800,000 IU/mL and significant liver fibrosis.

1. Introduction

Viral hepatitis C (HCV) is a serious public health problem with approximately 3% of the world's population being infected. Patients on chronic hemodialysis (CHD) are known to be a population at risk for HCV infection worldwide. By 2015, chronic HCV infection was estimated to affect approximately 71 million people globally [1–3].

HCV infection has surpassed the human immunodeficiency virus (HIV) as the leading cause of death from viral infection in multiple countries including the United States [4]. Complications of chronic HCV occur after several years and include cirrhosis, liver failure, need for liver transplantation, and hepatocellular carcinoma. Complications of cirrhosis include portal hypertension, spontaneous bacterial peritonitis, gastrointestinal bleeding, and hepatic encephalopathy, among others [5].

There are also multiple extrahepatic manifestations of the disease such as uveitis, cryoglobulinemia, autoimmune thrombocytopenic purpura, membranoproliferative glomerulonephritis, porphyria cutanea tarda, among others [6]. Thus, HCV infection, its complications, and the resources dedicated to its treatment represent a major cause of expenditures for the health care systems. In the U.S., these expenses exceed $10 trillion annually [7].

In Peru, a recent sero-epidemiological study of viral hepatitis (A, B, C, D, and E), carried out in the 25 regions of the country, a low prevalence of HCV was found, estimated at 0.1% in the general population [8].

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It is also known that people who receive multiple blood transfusions and health care workers are known risk groups for HCV infection, but the highest prevalence (59%) has been reported in people receiving CHD [9,10]. The most important risk factor for HCV transmission in chronic dialysis patients is currently considered to be nosocomial transmission related to inadequate biosafety practices.

HCV infection is common among patients on CHD, is higher than the general population, and is associated with increased morbidity and mortality. In a study to determine the prevalence, incidence and risk factors of HCV infection, a prevalence of 10% was found between 2012 and 2015, with ranges of 4%–20% [11].

The Social Security of Health (EsSalud) is the second largest public health system in the country and is the main provider of CHD in Peru. The National Center for Renal Health (NCRH) of the Social Security system in Peru is the largest provider of specialized health care, including CHD, to people with advanced kidney disease from all districts of Lima.

CHD is the most frequent renal replacement therapy with a rate of 363 persons per million population (pmp), followed by peritoneal dialysis with 51 pmp and kidney transplant with 4 pmp. At the NCRH, 88% of the population is in the CHD program and 12% in the peritoneal dialysis program [12,13].

Treatments are interferon-free oral regimens, combining 2 or more drugs called direct-acting agents (DAAs) including sofosbuvir-ledipasvir, sofosbuvir-velpatasvir, grazoprevir-elbasvir, glecaprevir/pibrentasvir. DAAs are highly effective and well tolerated, with cure rates greater than 90%, even in patients who have traditionally been difficult to treat. In patients with chronic kidney disease including stages IV or V and patients in hemodialysis, no dose adjustments of DAAS are recommended, and patients should be treated according to general recommendations [13].

The metabolism of DAAs varies between different classes, with only a few being indicated for use in people receiving hemodialysis. In Peru, there are currently several registered schemes of interferon-free HCV treatments, which are effective and safe in patients with hemodialysis; therefore, there is the potential of implementing therapeutic interventions that reduce or even eradicate HCV infection from the hemodialysis programs, especially in the public sector [14,15].

The study aimed to estimate the serological prevalence of HCV infection, to determine the HCV viral load and genotype, as well as to determine the stage of liver fibrosis in patients on CHD at the NCHR, the main reference center for hemodialysis in the Peruvian Social Security system in Lima, Peru.

2. Materials and methods

This is an observational case series study of adults on CHD cared for at the NCRH. The study protocol and informed consent were approved by the Ethics Committee of the Guillermo Almenara National Hospital (EsSalud). All patients who received CHD at the study center were invited to participate. Subjects who provided written consent were enrolled. Patients with HCV-positive serology determined with the Cobas® analyzer y and the immunoassay 601 from Roche Diagnostics, underwent determination of HCV viral load by means of RT-PCR (Abbott Realtime m2000 system/Xpert® HCV Viral Load). In subjects with detectable viral load, the HCV genotype was determined by means of Abbott HCV Real Time Genotype II/Roche Applied Science. Then, subjects with detectable HCV viral load underwent determination of liver fibrosis using transitional elastography (Fibroscan 402 with M and XL probes). The Metavir score was as follows: F0–F1: 2.5–7.5 kPa, F2: 7.6–9.5 Kpa, F3: 9.6–12 Kpa, F4 (Cirrhosis): 12.1–75 Kpa.

A case report form (CRF) was prepared to collect information including: date of birth, sex, time since the first hemodialysis, date of the first positive local serology, frequency of dialysis, time since the first hemodialysis at the NCRH-EsSalud, number of centers where the volunteer received hemodialysis, history of surgery (yes/no, and type of surgery) before HCV diagnosis, history of blood transfusions or derived products (yes/no, and number) before HCV diagnosis, type of venous access for hemodialysis (AV fistula/catheter), use of dedicated hemodialysis machines (yes/no), use of individual filters (yes/no), comorbidities (such as diabetes mellitus, HIV infection, and other immunosuppression conditions), history of transplantation, number and type of sexual partners, and history of intravenous drug use.

2.1. Data collection and management

The information was collected from the NCRH medical charts by study staff and recorded in the CRF. The source documents for laboratory results were the official reports issued by Laboratorio Roe (HCV serology, viral load HCV and genotype HCV) and elastography of the liver for determination of liver fibrosis (Fibroscan®) by the imaging center of the Delgado Clinic.

2.2. Human subject protection

The protocol and informed consent were reviewed and approved by the Ethics Committee of the Guillermo Almenara National Hospital. All study procedures were carried out after the volunteer provided written consent. All reasonable precautions were taken to protect the privacy of the volunteer's information including the use of codes for identification.

3. Results

Of the 303 patients receiving CHD at the NCRH, 174 (57.4%) provided written informed consent and were enrolled in the study. Mean age was 52 years (range 22–91) and 116 (66,6%) were male. HCV serology was positive in 35.1% (61/174) of study volunteers; however, the prevalence of active HCV (positive serology and detectable viral load) was 20.11% (35/174). Genotype 1a was the most prevalent (85%). The majority (83.6%) of subjects with detectable viral load had values below 800,000 IU/mL. Twenty-nine of the 35 subjects with active HCV underwent Fibroscan evaluation, and 13 (44.8%) subjects were found to have liver fibrosis in stage F2–F4. None of them had previous diagnosis of hepatic cirrhosis or manifestations of portal hypertension. No cases were found with hepatocellular carcinoma. See Table 1 for more details.

Table 1
Study volunteers and characterization of HCV burden (serostatus, viral load, genotype, and liver fibrosis) among adults on chronic hemodialysis at the NCRH. EsSalud.

Characteristic	Subjects (%), [range]
Subjects enrolled	174
Mean age in years	52 [22–91]
Male	116 (66.6)
Cause of end stage renal disease	174 (100)
Unknown	127 (72.9)
Glomerulonephritis	29 (16.7)
Chronic arterial hypertension	6 (3.4)
Type 2 diabetes mellitus	5 (2.9)
Obstructive uropathy	3 (1.7)
Eclampsia	2 (1.2)
Lupus nephritis	1 (0.5)
Alport's syndrome	1 (0.5)
Subjects with positive serology	61 (35.1)
Subjects with positive serology and detectable viral load	35 (20.11)
HCV viral load	35 (100)
<100,000 IU/mL	29 (83.6)
≥100,000 IU/mL	6 (16.4)
HCV genotype	35 (100)
1a	30 (85.7)
3	1 (2.9)
Unable to determine	4 (11.4)
Liver fibrosis on Elastography	29 (100)
F0–F1	16 (55.2)
F2–F3	7 (24.4)
F4	6 (20.4)

Medical charts disclosed that primary glomerulonephritis (n = 29) was the most frequent (16.7%) cause of chronic kidney disease. Other causes were chronic arterial hypertension (n = 6), type 2 diabetes mellitus (n = 5), obstructive uropathy (n = 3), eclampsia (n = 2), lupus nephritis (n = 1), polycystic kidney disease (n = 1), and Alport syndrome (n = 1). Importantly, the cause was unknown in 86 subjects (49%). See Table 1 for more details.

None of the volunteers had tattoos, piercing, contact with relatives with HCV, or sexual partners with HCV. There was also no history of illicit drug use. Volunteers with positive HCV serology had an average of 3 hemodialysis sessions per week and were on hemodialysis for at least 5 years. Most volunteers (85) were dialyzed only at the NCRH. Sixteen volunteers were dialyzed in two other centers in the past, 35 in one and 3 in three.

Most subjects (94.2%) had alanine amino transferase (ALT) levels within normal range, and the others (5.8%) had levels between 1 and 3 times the upper normal limit.

Twenty-five volunteers had history of kidney transplant, 5 had nephrectomy, 4 had cholecystectomies, and 18 had history of other types of surgeries.

Five volunteers had history of receiving 5 or more blood transfusions, 3 received 3 to 5transfusions, and 9 receive 2 or less transfusions.

Access for hemodialysis was arterial-venous fistula in 153 volunteers and long-term hemodialysis catheter in 21 volunteers.

Comorbidities were chronic arterial hypertension (n = 26), type 2 diabetes mellitus (n = 3), systemic lupus erythematosus (n = 2), tuberculosis (n = 2), and type 1 diabetes mellitus (n = 1). Two volunteers were found to have coinfection with hepatitis B virus (HBV) surface antigen and 28 volunteers had isolated HBV anticore. There were no cases of coinfection with the human immunodeficiency virus.

Fourteen of 26 volunteers (53.8%) with HCV antibody positive and HCV RNA negative had received combined therapy with Peginterferon plus ribavirin more than 10 years ago.

4. Discussion

The prevalence of HCV infection was found to remain high among adults receiving CHD at the NCRH, the largest center providing specialized kidney health care services in Lima Peru. The risk of HCV infection in this population has been associated with the time under hemodialysis and the number of blood transfusions received [16]. It is also recognized that HCV can be prevented by strictly following the biosafety recommendations for hemodialysis centers [17].

In a previous study at a dialysis center in Peru, the prevalence of HCV infection in hemodialyzed patients was found to be 59%, with 4.5% having HBV coinfection [18]. Our study provides more current data from a cohort of patients on CHD at the NCHR, showing HCV seroprevalence of 35.1% and coinfection with HBV of 1.13%. The prevalence of HCV-positive antibodies and HCV RNA viral was 20.11%. As can be seen, there is a high prevalence of HCV antibodies in hemodialysis centers in Peru, they are related to poor biosecurity measures and the lack of standardized protocols that were progressively implemented in all hemodialysis centers, whose prevalence has been reduced over the years; however, they remain high due to the accumulated prevalence of previous decades and the limitations of treatment with antiviral agents against HCV.

High seroprevalences have also been reported in other countries in the region [19]. The prevalence of HCV among patients on hemodialysis was 71% in a hemodialysis center in Caracas-Venezuela, 90% in a study performed in Cuba, and 33.4% in the Santa Catarina state in Brazil. The prevalence of HCV varies within regions of a given country, as reported in Argentina (23.8% in the Northeast, 45.5% in the North, 46.7% in the Midwest and 35.3% in the Southeast), In Peru, HCV prevalence varied between 90% and 4,65%, and in Uruguay varied between 16 and 3%. Interestingly, in studies conducted in hemodialysis units in Cali and Bogotá-Colombia, the seroprevalence of HCV was very low (2.9 and 2.7%, respectively); however, it was high in Medellín (42.2%). Possibly, the low prevalence found in Cali and Bogotá reflect the impact of the strict biosecurity measures that have been implemented for more than a decade.

As for the HCV genotypes among adults on hemodialysis, our study found that genotype 1a was the most frequent (85%) followed by genotype 3, in contrast to what has been reported in other countries. The predominant genotypes are 1b and 3 in Colombia; 1b, 3a, and 1a in Brazil and Venezuela. In other areas of the world, predominate 1a and 1b in Indonesia and Jordan; and 1b, 2a y 2b in Japan. In contrast, genotype 4 predominates (84%) in Egypt, followed by genotype 1. Genotype 1b predominates in Germany and France and 1b, 3a and 2a-b in Italy.

On the other hand, while isolation is not recommended for hemodialyzed patients infected with HCV, the monthly determination of ALT and semi-annual HCV serology screening are important to detect transmissions within a center and to ensure that precautions are being applied correctly and continuously. In our study, the ALT levels remained normal in most study volunteers, like the findings of other studies in this type of patient population.

Limitations of the study include the fact that the results found apparently correspond to a single center, although the NHRC is the most important center that provides CHD and concentrates the care of patients from the 3 most important tertiary hospitals in Lima (Rebagliati: 50.2%, Almenara 37.7%, and Sabogal: 12.1%). On other hand, 129 of 303 registered patients refused to participate in the study due to limitations due to the restrictions established by the COVID-19 Pandemic, as well es the detected cases of morbidity, mortality, and isolation in this population. We did not collect information about the reasons for not accepting to participate, so there is a potential for bias from an unknown variable. It is important to mention that due to not having your consent, your data could not be included in the established CRF; however, in the 2015 and 2018 censuses corresponding to 293 and 300 patients under CHD at the NCHR, a prevalence of 42.3% and 38% of HCV-positive antibodies was found, without quantifying HCV RNA due to lack of reagents.

5. Conclusion

The prevalence of HCV at the largest reference center for hemodialysis in Lima remains high, with GT1a predominance, viral load usually below 800,000 IU/mL and significant associated liver fibrosis. In the era of interferon-free HCV treatment regimens, interventions are urgently needed to reduce disease progression among HCV infected patients on CHD.

Author contribution

P. Martin Padilla-Machaca and Ada Cabrera designed the study, Eduardo Luna-Victoria and Ada Cabrera collected the data, Rocio Galloso, Pedro Montes, analyzed the data, P. Martin Padilla-Machaca contributed to writing and proof of reading the manuscript. Administration technique and materials were supported by Juan-Carlos Gomez de la Torre. All authors contributed the manuscript for important intellectual content and approved the submission.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Martin Padilla, Eduardo Luna-Victoria, Ada Cabrera, Juan-Carlos Gomez-De la Torre, Rocio Galloso, and Pedro Montes reports financial support which was provided by Asociacion Peruana para el Estudio del Higado.

Data available statement

All original data are available upon reasonable request to the corresponding authors.

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Ethics statement

This study was approved by the Ethics Committee of the Guillermo Almenara National Hospital.

Informed consent

All participates provided written informed consent.

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