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Seroprevalence of hepatitis B, hepatitis C and HIV infection among patients undergoing haemodialysis in Buenos Aires, Argentina

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Abstract

Introduction. Blood-borne infections are a major cause of harm in individuals on haemodialysis (HD). In particular, knowledge about hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) status in HD patients is a major concern, since these infections may cause comorbidities in this setting. There is a paucity of data regarding this issue in Argentina.

Hypothesis/Gap Statement. The epidemiological surveillance of HBV, HCV, and HIV is a fundamental tool for planning and implementing health strategies in order to prevent and control viral transmission of these viral agents.

Aim. To determine the seroprevalence of HBV, HCV and HIV infections in HD patients in Buenos Aires, Argentina.

Methodology. Seven hundred and forty-eight HD patients were included in a retrospective cross-sectional study. Serological assays were performed to determine HBV, HCV and HIV status. HBV HBsAg and anti-HBc IgG were analysed using AxSYM (samples before 2010) or the Architect Abbott system (samples since 2010), anti-HCV IgG testing was performed using the anti-HCV enzyme immunoassay AxSYM HCV V3.0 and ARCHITECT anti-HCV, while HIV was tested for using AxSYM HIV 1/2 gO and ARCHITECT HIV Ag/Ab Combination. HCV genotyping was carried out by phylogenetic analysis of the NS5B partial gene.

Results. Infection with one of the viruses was detected in 31.1% of patients [HBV in 82 (11.0%), HCV in 179 (23.9%) and HIV in 6 (0.8%)]. Thirty-two (4.3%) patients had 2 virus markers [27 (3.6%) with HCV/HBV, 4 (0.5%) with HCV/HIV and 1 (0.13%) with HBV/HIV]. Finally, a single patient (0.13%) presented all three markers. Time on dialysis was correlated with HCV but not with HBV infection. The HCV subtype distribution in HD patients was inverted with respect to that observed in the general population (HCV-1a 73.2% and HCV-1b 26.8% in HD vs HCV-1a 26.5% and HCV-1b 73.5% in the general population, P <0.001).

Conclusion. Despite the implementation of universal precautionary biosafety standards for dialysis, infection with HBV and HCV continues to occur at very high rates in HD patients. The results emphasize the need to carry out proactive tasks for early diagnosis and treatment of infected individuals and to vaccinate those with non-protective antiHBs antibodies in order to reduce morbidity and mortality in HD patients.

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Keywords: HIV; hepatitis B virus; hepatitis C virus; haemodialysis; prevalence.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERSD, end-stage renal disease; ESS, effective sample size; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, Haemodialysis; HIV, human immunodeficiency virus; ML, maximum-likelihood.

Nucleotide sequences for the HCV have been deposited in GenBank under accession numbers MK187268/272/278/287/292-294/298/299/301/330/338 and MN982201-MN982231.

INTRODUCTION

The prevalence rate for dialyzed patients in Argentina is 637 patients per million individuals (approximately 29700 patients), with haemodialysis (HD) being the most widely applied treatment for patients with end-stage renal disease [1]. Blood-borne viruses, such as hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV), have a consistently higher prevalence among HD patients than in the general population [2]. This finding may be due to several factors, including repeated and prolonged access to the bloodstream, the simultaneous treatment of multiple patients in the same facility, and the lack of effective biosafety measures [2]. This issue is a major healthcare concern, since these viruses are a significant cause of increased morbidity and mortality [3]. The prevalence rate varies among countries and even among health centres within the same area [2, 4–6]. Coinfection is a common finding among HD patients and it may be associated with the worst clinical outcomes [7–9].

No large-scale dialyzed patient prevalence studies for HBV, HCV and HIV have been conducted in Argentina. Flichman *et al*. reported a low infection prevalence in blood donors tested nationwide [10]. The authors analysed the prevalence of HBsAg (0.19%), anti-HCV (0.46%) and anti-HIV (0.20%) titres in more than two million samples.

With regard to the Argentine population undergoing dialysis, data are unfortunately fragmented and dissimilar. The Argentine Chronic Dialysis Registry reports a prevalence of 1.02, 2.40, and 0.91% for HBsAg, anti-HCV and anti-HIV, respectively [1]. Other studies conducted on different dialysis populations from Argentina showed a significantly higher prevalence for HCV, ranging from 10.6–38.0% [11–14]. Disparities in reported HCV prevalence rates as well as a paucity of data for HBV and HIV warrant the present research work. Therefore, the main goal of this study was to estimate the prevalence of HBV, HCV and HIV among HD patients from the Ciudad Autónoma de Buenos Aires, Argentina.

METHODS

Study population

In this retrospective cross-sectional study, patients on HD were tested for anti-HCV, HBsAg and anti-HIV as part of a screening programme conducted at Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno (CEMIC), a university hospital located in Buenos Aires, Argentina. Samples were collected between January 2001 and December 2018.

Laboratory assays

HBV HBsAg and anti-HBc IgG were analysed using AxSYM (Abbott Diagnostics, USA; samples before 2010) and the Architect Abbott system (Abbott Diagnostics, Wiesbaden, Germany; samples since 2010). Anti-HCV IgG testing was performed using the anti-HCV enzyme immunoassay AxSYM HCV V3.0 (Abbott, Wiesbaden, Germany) and ARCHITECT anti-HCV (Abbott Wiesbaden, Germany). HIV was tested for using AxSYM HIV 1/2 gO (Abbott, Wiesbaden, Germany) and ARCHITECT HIV Ag/Ab Combination (Abbott Wiesbaden, Germany). All tests were performed following the manufacturers' recommendations.

HCV genotyping, RT-PCR and sequencing

Serum RNAs were extracted with Magna Pure (Roche) following the manufacturer's instructions. Reverse transcription was carried out with MMLV-RT (Promega) with random hexamer primers using the manufacturer's protocol. The amplification of the HCV NS5B partial region was performed as described previously [15]. Subsequently, the amplified DNAs were purified and then sequenced in both senses (Instituto Nacional de Tecnología Agropecuaria, Castelar, Argentina).

Phylogenetic analysis and HCV genotype

A broad sequence search was performed using keywords on the National Center for Biotechnology Information (NCBI) central nucleotide search website (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome) to retrieve sequences of HCV containing NS5B regions. One hundred and fifty-nine sequences were randomly selected so that all HCV genotypes and each of the geographical regions of interest were represented. NS5B sequences were aligned with CLUSTALX v2.0 software. A maximum-likelihood (ML) phylogenetic tree was estimated using IQ-TREE v1.6.12 software, setting the model parameters according to those suggested by the Bayesian information criterion [16]. A non-parametric ultrafast bootstrap analysis of 10000 replicates was carried out for branch support. In order to verify the obtained results, a Bayesian phylogenetic analysis was simultaneously carried out with MrBayes v3.2.7a [17]. Analyses were run for five million generations, and sampled every 5000 generations. Convergence of parameters [effective sample size (ESS) ≥200, with a 10% burn-in] was verified with Tracer v1.7.1. Phylogenetic trees were visualized with FigTree v1.4.4.

Statistical analysis

Continuous variables were expressed as a median (Q1–Q3) and categorical variables as a number (percentage). Student's *t*-test and the Mann–Whitney U test were used for comparing continuous variables. The statistical analysis was carried out using the SPSS statistical software package release 19.0 (IBM SPSS, Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study population

A cohort of 748 patients was analysed; the median (Q1–Q3) age was 59 (44–70) years old and 410 (54.8%) were male. Sixty-three out of 748 (8.4%) were kidney transplant patients and 182 (24.3%) had received blood transfusion. Median (Q1–Q3) time on dialysis treatment was 25 (7–76) months.

Table 1. Characteristics of the study population by infection

Parameter	Total, *n* (%)	Uninfected, *n* (%)	Infected patients, *n* (%)*	*P*
Patients	748 (100)	515 (68.85)	233 (31.15)	–
Age	59 (44–70)	61 (48–73)	53 (40–65)	<0.001
Gender				
Male (%)	410 (54.8)	292 (56.7)	118 (52.9)	0.123
Female (%)	338 (45.2)	223 (43.3)	115 (47.1)	
Months on dialysis (Q1–Q3)†	25 (8–77)	20 (6–47)	98 (26–149)	<0.001
Transfusion‡	48 (24.4)	42 (28.9)	6 (11.5)	0.012
ALT, IU/L (Q1–Q3)	15 (11–24)	14 (11–20)	20 (13–37)	<0.001
AST, IU/L (Q1–Q3)	15 (11–21)	14 (11–19)	19 (13–28)	<0.001

*Infected patients, patients infected by HBV, HCV or HIV.
†Available for 184 patients.
‡Available for 197 patients.

Prevalence of HBV, HCV and HIV infection

Infection with one of the three viruses was detected in 233 (31.1%) subjects from the cohort. Thus, 515 (68.9) patients were not infected by any of the studied viruses. The median age (Q1–Q3) of the uninfected patients was 61 (48–73) and 292 (56.7) were male. Table 1 summarizes the characteristics of the study population according to infection by any of the three considered viruses. Thirty-two (4.27%) patients had markers of infection with two virus types [27 (3.6%) with HCV/HBV, 4 (0.5%) with HCV/HIV and 1 (0.13%) with HBV/HIV]. Finally, only one patient (0.13%) presented all three virus type markers.

HBsAg and anti-HBc IgG were detected in 82 patients (11.0%), 43 female and 39 male. Thus there was a similar distribution of positive cases between genders (12.7% female vs 9.5% male, *P*=0.162). Neither patient age nor time on dialysis were statistically associated with HBV infection. In this sense, patients infected with HBV were 60 (44–69) years old and the uninfected ones were 58 (44–71) years old, *P*=0.984. When considering time on dialysis, patients infected with HBV had been on dialysis for 19 (4–156) months, while those uninfected had attended dialysis for 26 (8–74) months, *P*=0.927. No association was found between transfusion history and the risk of acquiring HBV [2 transfused individuals (4.2%) and 10 non-transfused ones (6.7%), *P*=0.521]. There was no association between HBV detection and plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Thus, subjects infected with HBV showed ALT 15 IU l^{-1} (11–26) and AST 17 IU l^{-1} (11–23), whereas the corresponding figures among non-HBV infected patients were 15 IU l^{-1} (11–24) for ALT, and 15 IU l^{-1} (11–21) for AST (*P*=0.911 and *P*=0.572 for ALT and AST, respectively).

Regarding HCV, anti-HCV was detected in 179 (23.9%) patients. Plasma HCV RNA, indicative of active HCV infection, was detected in 125 (69.8%) patients. There was no significant gender-related variation for positive cases [80 females (23.7%) and 99 males (24.1%), *P*=0.879]. Unlike the findings for HBV, HCV infection in dialyzed patients was statistically associated with age [62 (48–72) years old for the uninfected subjects and 49 (39–61) years old for the infected ones, *P* <0.001], and with the time on dialysis [19 (6–46) months for uninfected patients and 101 (31–154) months for the infected ones, *P* <0.001]. In addition, subjects without transfusion history showed the highest number of HCV cases [40 non-transfused individuals (26.8%) versus 5 transfused (10.4%), *P*=0.018]. Finally, ALT and AST were higher in patients infected with HCV. Thus, patients with HCV showed ALT 24 IU^{-1} (15–41) and AST 21 IU l^{-1} (14–32), whereas the levels for non-HCV infected patients were 14 IU l^{-1} (11–20) for ALT and 14 IUl^{-1} (11–19) for AST (*P* <0.001 for both ALT and AST).

HIV showed the lowest prevalence. Only 6 (0.8%) patients were positive for anti-HIV. Statistical analysis for age, years of attending dialysis, gender, or transfusion history was not possible due to the small number of positive cases.

HCV genotype distribution and phylogenetic analysis

As result of the particularly high prevalence of HCV infection found in this work, a phylogenetic analysis of HCV sequences was carried out in order to determine and compare the genotype of HCV infecting dialyzed patients to those infecting individuals from the general population.

Nucleotide sequences from the NS5B region of 43 out of 179 HCV-positive cases were analysed. The genotype distribution obtained by phylogenetic analysis was 30 (73.2%) HCV-1a, 11 (26.8) HCV-1b, 1 (2.3%) HCV-2c and 1 (2.3%) HCV-3a.

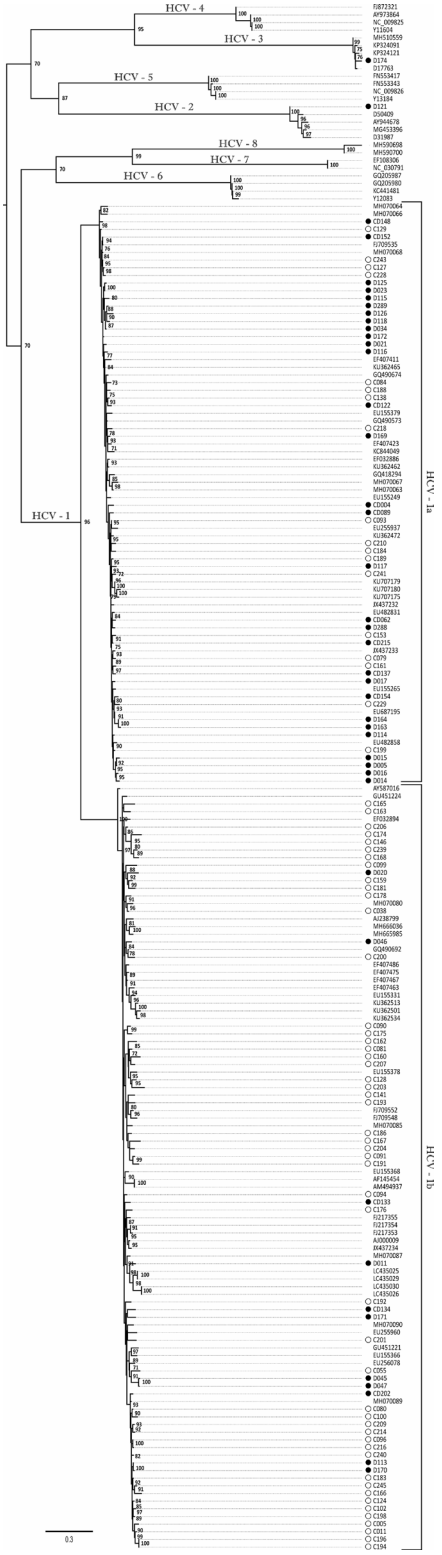

Fig. 1. HCV ML phylogenetic tree (TIM2+F+I+G4 model for nucleotide substitutions) for the NS5B partial region (314nt). Branch lengths are proportional to the evolutionary distance between the samples. Numbers on each node represent the ultrafast bootstrap support (branch support >70% is shown). Samples are identified as follows: sequences obtained in this work have symbols before their names representing the source – solid circle, dialysis; empty circle, no dialysis – while sequences without symbols are those chosen randomly from GenBank.

NS5B sequences from dialyzed patients infected with HCV-1 were compared to those from 68 HCV-1-infected patients who attended the same hospital but did not undergo HD during the same period. In this cohort, the distribution of subtypes was significantly different: 50 (73.5%) HCV-1b and 18 (26.5%) HCV-1a, P <0.001.

Patient age was statistically associated with HCV-1 subtypes distribution [51 (47–58) years old for HCV-1a and 59 (50–66) years old for those infected with HCV-1b, P=0.008]. On the other hand, there was no significant differences in subjects' ages for HD patients and subjects attending the same hospital [51 (45–64) years old and 57 (49–62) years old, respectively, P=0.293].

Phylogenetic analysis showed the formation of one supported cluster belonging to HCV-1a. This cluster comprising sequences D005, D014, D015 and D016 from patients undergoing dialysis was the only one confirmed by both phylogenetic approaches, ultrafast bootstrap and Bayesian analysis (Fig. 1).

DISCUSSION

The determination of the prevalence of blood-borne infections in the haemodialysis (HD) setting is useful to establish the status of the population undergoing dialysis and to monitor the effectiveness of the implemented sanitary and strategies and to identify their achievements and limitations. To our knowledge, this is the first large-scale survey that analyses HBV, HCV and HIV viral markers in a population undergoing HD in Argentina.

It is well known that the dialysis procedure plays a preponderant role in the transmission of HBV and that prevalence mostly depends on the baseline population rates [2, 18]. In developed countries, HBV prevalence in dialysis centres varies between 0 and 6.6%, while in developing countries it ranges more widely between 1.3 and 14.6% [18]. In the present study, the prevalence of HBsAg was consistent with that found in low-income countries. This high prevalence could be a consequence of the low coverage rate of HBV vaccination (less than 40%) in populations not reached by mandatory vaccine schedules [1, 19]. Other reason may be an upward trend of new HBV cases, observed in the last 10 years, in people 20 to 59 years old who represent a large proportion (49%) of HBV-infected individuals in the present study [20]. In this scenario, it is crucial to increase the HBV vaccination coverage and to improve the standard precautions and/or dialysis-specific procedures in order to prevent disease dissemination in our country.

Interestingly, no association was found between HBV infection and time on dialysis. A possible explanation may be the fact that, as is known in our country, most patients who start dialysis are not vaccinated against HBV. However, once they start treatment, they are immediately vaccinated. In this way, it has been observed that protection levels against HBV are approximately 30% in the first 5 months of dialysis and that they reach up to 80% at 15 years under treatment [1].

With regard to HCV, almost a quarter of analysed patients were positive. This prevalence is within the previously reported range in our country for patients undergoing dialysis and it is significantly higher than that described in the general population [13, 14, 21, 22]. This situation is repeated all over the world, with people who attend HD centres being a high-risk group for HCV infection [2, 6]. In addition, prevalence was associated with time on dialysis. In this sense, the majority of HCV-infected patients were younger but had a longer treatment history. These data coincide with previously published data also reporting that dialyzed patients do not have the same age-based epidemiological distribution for HCV infections. A similar situation has previously been described in Argentina [1, 14] and other parts of the world [2].

HCV genotype distribution in HD patients is a valuable tool to understand the transmission routes. Some studies have found a matching distribution of genotypes among patients undergoing dialysis and the general population, while others observed a frequency bias [23]. In Argentina, HCV-1b has been reported as the most prevalent subtype, both in the general population and in dialyzed patients [12, 24]. This subtype has been associated with older individuals and patients who received transfusions [25]. Unexpectedly, in the cohort included in this study, a high prevalence of HCV-1a, which has mostly been found in younger individuals and intravenous drug users, was observed [25, 26]. However, in the present study, even when HD patients were younger, no significant differences were found between both populations (HD and ambulatory patients). Therefore, this finding could be a consequence of an epidemiological change in HCV in Argentina, where it has been stated that although HCV-1b entered earlier in the country it is currently on a demographic plateau, while HCV-1a was introduced later but is still in a growing phase [27]. Moreover, the greater prevalence of the HCV-1a genotype determined in the present study was similar to that described in other risk groups such as HCV/HIV individuals, trans-sex workers and intravenous drug users [21, 28–30]. Additionally, a lower prevalence of HCV-2 and HCV-3 has been detected in dialyzed patients, compared to that previously reported in the general population [14, 31].

As stated for HBV, the prevalence of HIV in patients undergoing dialysis largely depends on the local prevalence in the general population [4]. In this study, the observed prevalence has been higher than that described in the general population but close to that reported by the Argentine Chronic Dialysis Registry [1, 32].

Unfortunately, there are no large-scale studies of nosocomial infections in dialyzed patients from Argentina. The only information about outbreaks of HCV or HBV in dialysis facilities in Argentina is restricted to congress publications. In this context, Besonne *et al.*, reported an outbreak of HBV and HCV in HD patients in the city of Rosario, Argentina [33, 34]. However, several studies worldwide have indicated that the prevalence of HBV, HCV and HIV tends to be higher in patients in dialyzing settings than in the general population [2, 6]. This finding suggests a close association between undergoing dialysis and being infected. The availability of better facilities and more trained staff has been associated with significantly decreased HCV and HBV prevalence [2], so prevention measures seem not to be sufficiently effective. On the other hand, in Argentina, nosocomial outbreaks of HIV have not been reported since 1993 [11]. As a result, the positive cases found in this study may be a consequence of the progression to end-stage renal disease (ERSD) due to HIV infection rather than a consequence of the dialysis procedure itself. It is well known that the risk of progression to ERSD is significantly higher in HIV-seropositive patients [4, 35]. Progression to ERSD has increased in recent years due to the greater longevity of HIV-infected patients, thanks to antiretroviral therapy efficacy [36].

The present work has some limitations. One of these is the lack of information about of HBV, HCV and HIV patient status prior to dialysis. However, when considering data from the general population, we can attribute the identified high prevalence to the risk associated with HD. Second, the serological tests were not confirmed by nucleic acid detection. Third, the time undergoing treatment is unknown for some patients. However, we had sufficient data to perform the statistical analysis. Lastly, the samples included in this study came from a single centre in Buenos Aires and prevalence can vary significantly between dialysis units [2, 4–6]. Therefore, despite the size of the cohort, caution should be exercised in extrapolating the results to the whole country. Nevertheless, more than one-third of the Argentinean population lives in the area of Buenos Aires, so the study can be regarded as an acceptable approximation of the current situation.

Overall, almost one-third of the studied patients presented one of the three analysed viruses. Unfortunately, the implementation of universal precautionary biosafety standards in dialysis units would appear to be insufficient to contain blood-borne infections. Further efforts, such as HBV vaccination and HCV treatment with new drugs, highly trained staff and better facilities will be required to prevent HD patients from continuing to be a vulnerable population at high risk of acquiring blood-borne infections. In addition, HCV subtype distribution was uneven compared to the general population. Finally, these study findings could contribute to the planning and implementation of health strategies in order to reduce the transmission of infections in the dialysis setting, as well as monitoring and evaluation of their effectiveness.

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Author contributions
M. J. P., analysis and interpretation of data, drafting of the article. Final approval of the version to be published. A. P. M., analysis and interpretation of data, providing intellectual content of critical importance to the work described. Revision of the article. Final approval of the version

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical statement

Written informed consent to participate in the study was obtained from patients. The study protocol was approved by the Ethics Committee at Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires (record number 02032015-2/2015) in accordance with the 1975 Helsinki Declaration.

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