RESEARCH ARTICLE

Prevalence of hepatitis B and C infections in hemodialysis patients [version 1; peer review: 1 approved, 1 approved with reservations, 2 not approved]

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Abstract

Introduction: Infections with hepatitis B and C viruses (HBV and HCV) are a major global health problem. Patients with chronic renal failure (CRF) on hemodialysis constitute a population at risk of HBV and HCV infections.

Objective: Determining prevalence of the surface antigen of hepatitis B virus (HBsAg) and antibodies to hepatitis C virus (anti-HCV) in patients who attended dialysis units in the city of Posadas (Argentina).

Materials and methods: The studied population comprised 172 patients with CRF in hemodialysis. HBsAg and anti-HCV antibodies were evaluated by enzyme-linked immunosorbent assay (ELISA).

Results: On a total of 172 hemodialysis patients included in the study, 98 were males (57%) and 74 were females (43%), aged between 12 and 85 years (mean 53.4). 8.7% (15/172) of the patients were positive for HBsAg and 9.9% (17/172) were positive for anti-HCV reagents. 72.1% of patients had a hemodialysis treatment time of less than 5 years. A history of having received previous transfusions was observed in both HBsAg positive cases (7/15) and the anti-HCV positive cases (5/17). Elevated transaminase levels were observed in patients with positive and negative serology.

Conclusion: The results of this study demonstrate a high prevalence of serological markers for HBV and HCV in patients with CRF on hemodialysis in city of Posadas (Argentina), as compared to cities in developed countries.

Keywords

hepatitis B, hepatitis C, chronic kidney failure, hemodialysis, serological markers

Open Peer Review

Approval Status

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1. **Marina C Berenguer**, University of Valencia, Valencia, Spain
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Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Karina Salvatierra (kariales@gmail.com)

Competing interests: No competing interests were disclosed.

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Introduction

Infections with hepatitis B and C viruses (HBV and HCV, respectively) are a major global health problem affecting 240 million people who suffer from chronic HBV infection and about 150 million who suffer from HCV infection^{1,2}. In most cases, these viruses cause chronic infection whose natural course leads to liver cirrhosis, liver failure and/or hepatocarcinoma in affected patients³.

Patients with chronic renal failure (CRF) on hemodialysis are at high risk of contracting viral infections with HBV and HCV, the most common cause of liver disease in these patients^{4,5}. Therefore, strict procedures for the control of hepatitis must be introduced in all dialysis units⁶.

The geographical distribution of HBV infection is not uniform throughout the world. Depending on the prevalence, different areas are classified as high, intermediate or low endemicity. HBV infection is highly prevalent (8–15%) in Southeast Asia, China, the Philippines, Africa, the Amazon basin and the Middle East. In Eastern Europe, Central Asia, Japan, Israel and Russia the prevalence is intermediate (2.7%), while in North America, Western Europe, Australia and South America the prevalence is low (<2%)⁷. In Latin America it ranges from 2 to 7%⁸. In developed countries the prevalence of HBV in patients treated with hemodialysis is 1%⁹, while in developing countries the prevalence ranges from 2% to 20%^{4,10,11}.

The prevalence of HCV in hemodialysis patients ranges from 2.6 to 22.9% (mean 13.5%) in developed countries, but can reach up to 70% in developing countries^{12–15}. In Latin America, the prevalence of HCV is also highly variable in hemodialysis patients, even within the same country. In Mexico, the prevalence is 6.7%¹⁶, in Colombia it ranges from 2.9 to 42.2%^{17,18}, while in Brazil ranges from 6–72% (mean 52%)¹⁹.

In recent years there was a significant decrease in the prevalence of both HBV and HCV infections in industrialized countries²⁰. This decline is attributed, among other factors, to the decrease in transfusions, vaccination against HBV and introduction of general biosecurity measures to prevent transmission of infection in hemodialysis units.

The aim of this study was to evaluate the prevalence of HBV and HCV in hemodialysis population dialysis units of four hemodialysis centers in the city of Posadas (Argentina).

Methods

In this study, a total of 172 patients diagnosed with CRF under hemodialysis attending four hemodialysis centers of the city of Posadas (Argentina) were included. Ethical approval to conduct the study was obtained by the hemodialysis centres involved in Posada, Argentina: Instituto Privado de Nefrología srl Roque Saenz Peña I; Instituto Privado de Nefrología srl Roque Saenz Peña II, Instituto de Nefrología IOT (Instituto de Ortopedia, Traumatología y Medicina Laboral de alta complejidad); Instituto de Nefrología Boratti. Institutional Review Board approval from the University of Misiones was not required as the private centers

involved are not affiliated with the University and the study was considered a human health research without risks. The protection and control mechanisms for this type of research in Argentina includes inclusion of a written informed consent obtained from each participant”.

: Patients who participated in the study went daily to a hemodialysis center and participation was voluntary. Inclusion criteria encompassed individuals with CRF who were just starting hemodialysis treatment 30 days before obtaining blood samples.

All patients signed an informed consent statement for joining the study after explaining the scope of the study. A unique and anonymous code was assigned to each patient and patient confidentiality was ensured.

Blood samples were collected through venipuncture or by finger/heel stick in dry tubes (9.5 ml) with vacuum. After clot retraction, samples were centrifuged at 1,500 rpm for 5 minutes and stored in 5mL aliquots at -20°C (<http://www.cdc.gov/measles/lab-tools/serology.html>).

Serological markers: surface antigen of hepatitis B virus (HBsAg) and antibodies to hepatitis C virus (antiHCV) were detected by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Wiener, Lab. S.A.I.C.).

The following information from medical records were obtained: age, gender, time on hemodialysis, alanine aminotransferase (ALT) index, history of transfusions and history of drug abuse. An online information system was developed to analyze the information (available at <http://bioinf.itiud.org/hemodialysis.php>). The system allows computational analysis and deployment of information through generation of reports and statistics charts, designed to provide a simple reading of the results of the study. A descriptive analysis was performed by calculating means, medians and frequencies. Chi-square test was used to analyze the significant relationships between categorical data and Mann–Whitney U test was used for the comparison of continuous data ($p < 0.005$). Data were managed and analyzed using *InfoStat* software.

Results

Our final sample consisted of 172 patients: 98 males (57%) and 74 females (43%). Their ages ranged from 12 to 85 years with a mean age of 53.4 years ([Dataset 1](#)).

All patients had no history of tattooing, piercing, or use illegal drugs, and no human immunodeficiency virus (HIV) coinfection was found in any of the cases.

The cause of CRF in patients on hemodialysis was unknown in 31.4% of the cases, followed by diabetic nephropathy (22.1%). The etiology of CRF for these patients is detailed in [Figure 1](#).

Serum samples from hemodialysis patients were tested for presence of HBsAg and antiHCV by ELISA. Fifteen (15/172) cases were positives for HBsAg, whereas 17 (17/172) cases were positives for antiHCV. [Figure 2](#) shows the distribution of HBsAg and antiHCV cases by age group.

Figure 1. Etiology of chronic renal failure (CRF) for the studied population.

Figure 2. Cases of HBSAg and antiHCV by age group.

The majority of HBSAg positive cases were females (9/15), but this was not statistically significant ($p = 0.16$), while of the majority of cases positive for HCV markers were males (14/17); this result was statistically significant ($p = 0.02$). **Figure 3** presents the distribution of HBSAg and antiHCV markers of by gender.

All patients participating in this study had 4-hour hemodialysis sessions three times a week and 72.1% of patients showed a mean time of hemodialysis less than 5 years (**Figure 4**). The duration of hemodialysis was not a significant risk factor for HBSAg ($p = 0.9$) and antiHCV ($p = 0.2$) presence.

Transfusion history was observed in 47% (7/15) of cases positives for HBSAg. Positivity for HBSAg significantly correlated with transfusion ($p = 0.003$), while 29.4% (5/17) of cases positives for antiHCV did not show correlation with transfusion ($p = 0.23$) (**Figure 5**).

In our patient population, 154 (89.5%) cases showed normal concentration of serum ALT level (< 40 U/L), and 18 (10.5%) showed elevation in serum ALT level (> 40 IU/L) (**Figure 6**).

A total of six HBSAg positive cases out of 15 (33.3%) showed elevation in serum ALT level, whereas one (5.5%) of the cases positive for HCV out of 17 showed increased serum ALT level. This correlation was statistically significant ($p = 0.001$ and $p = 0.002$ respectively).

Dataset 1. Information from hemodialysis patients

<http://dx.doi.org/10.5256/f1000research.9068.d131385>

The raw analysis data for each patient are shown. A description of the data is provided in the text file.

Figure 3. Cases of HBsAg and antiHCV by gender. Chi-square Pearson test. HBsAg: $p = 0.16$; antiHCV: $p = 0.02$.

Figure 4. Cases of HBsAg and antiHCV by time of hemodialysis sessions. Chi-square Pearson test. HBsAg: $p = 0.9$; antiHCV: $p = 0.2$.

Figure 5. Distribution of cases of HBsAg and antiHCV by blood transfusion. Chi-square Pearson test. HBsAg: $p = 0.003$; antiHCV: $p = 0.23$.

Figure 6. Distribution of cases based on information of alanine aminotransferase (ALT) (U/L) levels. Mann-Whitney *U* test. HBsAg: $p = 0.001$; antiHCV: $p = 0.002$.

Discussion

Patients with CRF on hemodialysis are a group at high risk for HBV and HCV infections.

In Argentina the prevalence of HBsAg varies between the provinces, from 0.17% to 1.79%, and prevalence of antiHCV varies between 1.70% and 21%²¹. In our study we found a relatively high prevalence of serological markers for HBV and HCV in hemodialysis patients in Posadas (Argentina). The HBsAg antibody (indicator of active HBV infection) was found in 8.7% of the studied cases and antiHCV in 9.9%.

These values are comparable to values reported in several studies on hemodialysis patients. In Peru, HBsAg prevalence ranges from 0.2% to 4.8%²², in Brazil varies between 4% and 28%^{23,24}, in Cuba is 4%²⁵, and in Colombia HBsAg is 22%²⁶.

Various studies in hemodialysis units show different prevalence rates for HCV: in Peru between 90% and 4.65%²², in Uruguay from 16% to 3%²⁷, in Brazil 33.4% to 16%^{23,28}, in Mexico 6.7%¹⁶, and in Cuba 90%²⁵. The antiHCV prevalence in dialysis units in Cali (2.9%) and Bogotá (2.7%) is very low^{17,29}, while in Medellín is high (42.2%)¹⁸.

By exploring the correlation between risk factors and seropositivity for HBV and HCV in hemodialysis patients, it seemed that timing of hemodialysis was not a risk factor. History of transfusion correlated with the risk of HBV infection, but not with risk of HCV infection. The elevation of ALT enzyme activity was not a good index for HBV and HCV infection in these patients, since normal values were observed in a high percentage of patients positive for HBsAg and antiHCV.

Conclusion

The results of this study demonstrate a high prevalence of serological markers for HBV and HCV infections in CRF patients on

hemodialysis in Argentina, compared with results obtained from patients in developed countries.

Therefore, an effective strategy to prevent nosocomial transmission of HBV and HCV in hemodialysis units and reduce the prevalence of infection should be implemented in strict compliance with biosafety standards, measures of education, hygiene and HBV vaccination plans to prevent the infection.

Consent

Written informed consent to participate in the study and publish clinical data was obtained by the patients.

Data availability

F1000Research: Dataset 1. Patient characteristics, [10.5256/f1000research.9068.d131385](https://doi.org/10.5256/f1000research.9068.d131385)³⁰

Author contributions

Karina Salvatierra: study design, sample processing, data analysis, discussion of results, and writing the manuscript. Hector Florez: design and analysis of data, drafting the manuscript. Both authors agreed to the final content of the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

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The authors would like to thank the hemodialysis patients, authorities, and the staff of the four dialysis centers that collaborated in the study, making this research possible. Both authors agreed to the final content of the article.

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[Data Source](#)

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 21 March 2017

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Rafaela Ferrari

Cavanilles Institute of Biodiversity and Evolutionary Biology (ICBiBE), University of Valencia, Valencia, Spain

Even though it is a descriptive research, I think it's important for local researchers. However, I suggest some changes:

- the title "Prevalence of hepatitis B and C infections in hemodialysis patients" should be completed to include the geographical region
- P-values <0.05 were considered significant, not <0.005, is possible there were a typing error
- How many of the patients presented the symptomatology of hepatitis?
- How many of the patients included in the study were being vaccinated against hepatitis B virus?

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Sep 2017

karina salvatierra, Universidad Nacional de Misiones, Posadas, Argentina

Dear Reviewer Rafaela Ferrari.

Thank you so much for your feedback. We want to inform you:

1. In the abstract and in the text we describe the geographic location.
2. We have changed the P-values as you suggested. Mann-Whitney U test was used for the comparison of continuous non-normal data. P-values <0.05 were considered significant.

3. Hepatitis C is usually asymptomatic it rarely causes symptoms. Hepatitis C may not produce symptoms. The spectrum of the symptomatology of hepatitis B disease varies from subclinical hepatitis to icteric hepatitis to fulminant, acute, and subacute hepatitis during the acute phase, and from an asymptomatic chronic infection state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) during the chronic phase. In this case, patients was not presented symptomatology of hepatitis.

4. In respect of hepatitis B vaccination, 125/172 (73%) of the patients completed the vaccination scheme, while none of the HBsAg (+) cases have had HBV vaccination.

Thank you so much

Best Regards

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 December 2016

<https://doi.org/10.5256/f1000research.9759.r15421>

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Rocio Hassan

Center for Bone Marrow Transplantation (CEMO), Instituto Nacional de Câncer (INCA), Rio de Janeiro, Brazil

This is a descriptive work that has as primary aim to evaluate the prevalence of HBV and HCV in a hemodialysis population of the city of Posadas (Argentina).

The research have been conducted with ethical and methodological correctness and results, although of limited reach, contribute with useful information on HBV and HCV prevalence in an at-risk group (hemodialysis patients) from a geographical region with paucity of such studies. Moreover, sero-prevalence of HBV in Misiones Province appear to be high, which may indicate a distinct epidemiological situation closer to that reported for neighbor Brazil than that described for Central and Southern Argentina.

Therefore, I consider that the manuscript is suitable for indexing, provided some restructuring is done in the text. Moreover, the article has, at present, 147 views and 50 download. This means it has raised interest in the scientific community and for that, I think it deserves to be corrected to include the suggestions of the reviewers.

I would like, then, to make some suggestions that I think may help improving the text.

1. In first place, and if it is possible, the present title "Prevalence of hepatitis B and C infections in hemodialysis patients" may be completed to include a characterization of the geographical region from where the results come from. The reader would then have an insight of the specific geographic and epidemiological context from the beginning.
2. In the introduction, it will be very important to geographically and epidemiologically situate Misiones Province, and specifically Posadas City, describing available results on HBV/HCV prevalence in this specific population.
3. Methods: It is desirable to check the English syntax and grammar of the first to third paragraphs. The phrase "The protection and control mechanisms for this type of research in Argentina includes inclusion of a written informed consent obtained from each participant" is unnecessary, since in the third paragraph it is stated that "All patients signed an informed consent statement".
4. Please, explain better the inclusion criteria. The statement "individuals with CRF who were just starting hemodialysis treatment 30 days before obtaining blood samples" is misleading, since it gives the impression that all individuals started hemodialysis 30 days before obtaining blood samples for the present study.
5. In the statistics description, replace "Mann-Whitney U test was used for the comparison of continuous data ($p < 0.005$)" by Mann-Whitney U test was used for the comparison of continuous non-normal data. P-values < 0.05 were considered significant.
6. Results: Please clarify the issue of HIV infection (vs. co-infection). Have all patients been tested for HIV infection, or only the HCV/HBV positive ones? If it is the first case, please correct the statement "human immunodeficiency virus (HIV) coinfection was found in any of the cases." by "human immunodeficiency virus (HIV) infection was not found in any of the cases."
7. Figure 1, please express decimal notation with periods instead of commas.
8. Gender association in HCV+ and HBV+ patients would be better presented as a stacked column graphic with percentage of male or female individuals for each category. Wouldn't Fisher's exact test be a better statistical to apply here?. The authors should provide in the Discussion a possible explanation for the gender association found in the study.
9. What was the specific statistical approach used for testing association between time of dialysis and HCV/HBV serostatus? Was it, as described in Fig. 4, a 2x6 Pearson Chsq test or, alternatively time was categorized in >5 vs ≤ 5 years? Risk is not well modelled by Chsq tests, and so, with the present statistical approach it only can be described as association. To model the risk, a logistic regression with HCV/HBV serostatus as dependent variable may be used instead. Again, the bar graphic with number of pts as scale is not very informative.
10. Respect of data on serum ALT levels, in figure 6, results of a Mann-Whitney test are provided, but the representation of data is as categories (till 40U/L - >40 U/L). The authors should either present categorical test results (i.e. Chisq or Fisher's) or a Box-and-whisker plot with data around the median value. This last would be a better graphical depiction for

the data.

11. Discussion needs to be rewritten to put the results in a stronger theoretical context. The authors should focus at least part of the discussion on the comparison of Misiones data with Brazilian available data and data from the rest of Argentina. In fact, most of the significant references from Brazil are listed in the article reference list, but they have not been used to highlight the similarity of Misiones' data. Important references from Misiones (and the rest of Argentina) are lacking, as it was pointed out in a previous review.

Additionally, I would like to ask the authors to include in the revised version of the ms some points addressed by a previous reviewer, which in my opinion are minor revisions.

- Add information on demographics and the prevalence of HCV and HBV separately for each of the four participating hemodialysis centers in the city of Posadas. The data can be included as a supplementary table, if so allowed by the Journal.
- Please, describe the HBV vaccine history of patients.
- If possible, include the information of HBV and HCV serological status of CRF patients prior to hemodialysis.
- In the Methods section, please state the period of time of sample collection.
- In respect to the association between transfusion history and HBsAg, it would be important to indicate the period of transfusion, in order to rule out (if it was a recent event) or strongly suggest (if it occurred before the 1960s) that transfusion was the source of HBV infection.
- There is potential for more in-depth analysis and comparison. The authors should include more discussion and compare with their findings. For example, it is known that Misiones is a high HBV prevalence area in Argentina (please read the papers by Delfino *et al.*, *J Clin Virol* 2012 and *Arch Virol* 2014).

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 05 December 2016

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Patients with chronic renal failure (CRF) receiving hemodialysis are at higher risk for acquiring Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections than the general population. The susceptibility to acquire viral hepatitis during hemodialysis has several potential underlying reasons related to both the patient and the hemodialysis procedure. Strict infection control measures are essential to prevent nosocomial transmission.

So the aim of this article was to investigate the prevalence of HBV and HCV infection in the hemodialysis population of a region of Argentina as well as risk factors for infection.

Serum testing for the presence of hepatitis B surface antigen (HBsAg) and anti-HCV antibodies (antiHCV) by ELISA and subsequent correlation of sero-positivity to HBV and HCV with timing of hemodialysis, history of transfusion, alanine aminotransferase (ALT) index, allowed the authors the opportunity to describe HBV and HCV prevalence in the present cohort of hemodialysis patients.

The study is adequately described; however, it could have been more detailed. Some suggestions are as follow:

- Please compare the difference in sero-positivity results between the four hemodialysis centers in the city of Posadas, which can eventually reflect difference in the biosecurity procedures of each center.
- Describe whether the patients included in the study were being vaccinated against hepatitis B virus.
- It would be necessary to clarify the HBV and HCV serological status of patients with CRF before starting hemodialysis treatment.
- In the Methods section, please state the period of time of sample collection.
- The authors correlated transfusion history with HBsAg or anti-HCV serological status and reported a significant association with positivity for HBsAg. It would be important to

indicate the year of transfusion, in order to rule out (if it was a recent event) or strongly suggest (if it occurred before the 1960s) that transfusion was the source of HBV infection.

- It would have been interesting to determine anti-HBc total antibodies as well.
- There is potential for more in-depth analysis and comparison. The authors should include more discussion and compare with their findings. For example, it is known that Misiones is a high HBV prevalence area in Argentina (please read the papers by Delfino *et al.*, J Clin Virol 2012 and Arch Virol 2014).

This is a well written but very simple study describing prevalence of HBV and HCV seromarkers in a particular region of Argentina. It could be updated with more detailed information and we do not consider it to be of an acceptable scientific standard. Therefore, this article is not suitable unless the content is extensively edited.

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 22 August 2016

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Marina C Berenguer

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The aim of this study was to evaluate the prevalence of HBV and HCV in hemodialysis population dialysis units of four hemodialysis centers in the city of Posadas (Argentina).

Serum samples from hemodialysis patients were tested for presence of HBsAg and antiHCV by ELISA. Fifteen (15/172) cases were positives for HBsAg, whereas 17 (17/172) cases were positives for antiHCV.

This is a descriptive study on local seroprevalence of HBV and HCV infection in a region of Argentina. The title is appropriate. The abstract provides adequate summary of the content. The methods are adequately described. The conclusions are adequate.

There is though missing information which is relevant: no information on viremia, underlying disease severity, sequential data overtime.

The following questions should be asked to the authors:

- How many of the patients were viremic?

- Was there any information on underlying disease severity
- How many were HBV and HCV coinfecting?
- Do the authors have sequential data to try to clarify whether there is an increase, stability or decrease of positive cases?
- Were there HBV patients coinfecting with HDV?
- Were there differences in positivity results by center?

In essence, this is a simple study describing prevalence of HBV and HCV seromarkers in a particular region of Argentina. There have been many studies published to date on seroprevalence of these viruses around the world.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 29 Aug 2016

karina salvatierra, Universidad Nacional de Misiones, Posadas, Argentina

Dear Reviewer Marina C Berenguer

Thank you so much for your feedback. We want to inform you:

- Unfortunately, we do not have information regarding viremic, disease severity, and sequential data.
 - There were not patients coinfecting with HBV and HCV.
 - This is a simple study describing prevalence of HBV and HCV seromarkers in a particular region of Argentina. So far, there is no studies regarding this topic in this region
- Given the limitations on what is counted in the region to do research, this is the first step to go ahead and propose further research.

Thank you so much
Best Regards

Competing Interests: No competing interests were disclosed.

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