Title: CHRONIC HEPATITIS C PATIENTS LOST IN THE SYSTEM: PREDICTIVE FACTORS OF NON-REFERRAL OR LOSS OF FOLLOW UP TO HEPATOLOGY UNITS

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CHRONIC HEPATITIS C PATIENTS LOST IN THE SYSTEM: PREDICTIVE FACTORS OF NON-REFERRAL OR LOSS OF FOLLOW UP TO HEPATOLOGY UNITS

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ABSTRACT

Introduction

Several barriers remain in the hepatitis C care cascade, which need to be removed in order to eliminate Chronic Hepatitis C. These barriers include deficiencies in screening and confirmatory diagnosis as well as difficulties in accessing treatment.

Aims

To identify factors associated with the non-referral of patients with positive HCV-antibody and to identify factors associated with loss of follow-up or non-attendance of these patients to specialist consultation after their referral.

Methods

Observational and retrospective single-centre-study, including all positive HCV serologies performed between January 2013 and May 2018 in the Virgen Macarena health area before implementing the one-step diagnosis. Non-referred patients and patients who were lost to follow-up after being referred were identified.

Results
A total of 54 (77.4%) patients diagnosed in PC and 54 (22.2%) from hospital specialists were not referred (p < 0.001). Predictors for non-referral were: stay in prison/institutionalized (p = 0.04), suffering COPD (p = 0.07), a normal AST value (p = 0.034) or test requested by PCP (p = 0.004). Patients referred from PC were more likely to be lost to follow-up than those referred from hospital specialists (p < 0.001). Predictors for loss of follow-up included: opioid replacement therapy (p = 0.034), absence of high blood pressure (p = 0.039) and test requested by PCP (p = 0.049).

Conclusions
A high percentage of patients with positive HCV serology were not referred or lost follow-up, mainly those belonging to high risk social groups or those with associated comorbidities. Patients with average values of transaminases or those diagnosed in primary care were also less referred.

Keywords

List of abbreviations
Hepatitis C virus (HCV), hepatocellular carcinoma (HCC), direct-acting antivirals (DAA), sustained virological response (SVR), Chronic Hepatitis C (CHC), Primary care (PC), Primary Care Physician (PCP), High Blood Pressure (HBP), Chronic Kidney Disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), People who inject drugs (PWID).

INTRODUCTION
Hepatitis C virus (HCV) infection constitutes a major public health problem, with approximately 80 million of viremic infected worldwide. It is currently, an important cause of cirrhosis and hepatocellular carcinoma (HCC), representing about 20% of liver transplants in Spain.
The introduction of direct-acting oral antivirals (DAAs) have revolutionized HCV infection treatment, especially in developed countries, improving the safety and efficacy of the therapy, with virological response rates exceeding 95%. Furthermore, the rapid virological response observed with combinations of these drugs has enabled the shortening of treatment duration, with equivalent rates of sustained viral response (SVR). Given their effectiveness, excellent tolerability, and safety profile, they currently represent the first therapeutic option for patients with Chronic Hepatitis C (CHC), when treatment is recommended.

In 2016, WHO adopted a global strategy to eliminate viral hepatitis as a public health threat by 2030, which required a 90% reduction in incident cases of hepatitis B and C and a 65% reduction in mortality, therefore requiring the treatment of 80% of patients with chronic viral hepatitis.

However, although these advances in treatment have been revolutionary, multiple barriers must be removed in order to advance towards eliminating the disease, especially in regard to deficiencies in screening and confirmatory diagnosis in risk and vulnerable groups, as well as the poor adherence of this population to the health system.

Even though risk factors for HCV infection are well known (parenteral drug use, hemodialysis, tattoos, exposure to HCV-infected blood and homosexual relations), chronic infection is frequently underdiagnosed, as it is an asymptomatic disease especially in initial stages. In addition, access to treatment may be affected by the difficulties in completing the diagnostic process despite previous positive HCV antibodies, or problems in the referral circuit to specialist care. Moreover, due to the absence of symptoms, neither the patients nor the PCP may consider it relevant enough to be referred to specialist care.

This study aims to identify factors associated with the non-referral of patients with positive HCV-antibody and to identify factors associated with the loss of follow-up or non-attendance of these patients to specialist consultation after their referral.

METHODS
Study design
This was an observational and retrospective single-centre study, including all positive HCV serologies (Anti-HCV +) performed between January 2013 and May 2018 in the Virgen Macarena health area before implementing the one-step diagnosis of HCV infection. Virgen Macarena health area covers the North and Northwest areas of Seville, with a reference population of 481,296 inhabitants.

Patients and methods
Positive HCV serologies provided by the Microbiology Unit were retrospectively analysed. A single anti-HCV serology result was included per patient, and identified with an anonymous code. We collected demographic variables (sex, age), route of infection, risk behaviours (active alcohol or active drugs use), medical history (comorbidities, active treatments), data related with the positive anti-HCV test (including the doctor who requested the serology and who referred the patient to the specialist) and liver function tests, using the electronic medical record (Diraya). AST and ALT transaminase values <40 were considered normal.

Two groups were identified: non-referred patients and patients who had been referred but did not attend or were lost to follow-up in hepatology consultations. For the analysis of factors related to loss of follow-up or non-attendance to medical consultations, two periods of time were considered, 2013-2015 and 2016-2018. HIV-HCV coinfected patients who had been referred to the Infectious Diseases Unit, Internal Medicine or Pediatric Gastroenterology Unit and those who died during the follow up period were excluded.

Ethical approval
This study was approved by the Research Ethics Committee of Virgen Macarena University Hospital, Seville, Spain. The collected data was handled confidentially in an anonymous database that was only accessed by the researchers involved in accordance with current Spanish laws.

Statistical analysis
Demographic and baseline characteristics were reported in percentages and frequencies, while the quantitative variables, depending on whether or not they followed a normal distribution, were summarized by mean and standard deviation and median and interquartile range (IQR), respectively. For the analysis of quantitative variables, the chi-square test was used to compare the groups, statistical significance was considered with p value <0.05. 

Data from this study was analysed by per-protocol and intention to treat. The analysis was performed using SPSS 25 (IBM Corporation).

RESULTs

A total of 1600 patients with positive HCV serology were identified. Finally, 1228 patients were analysed (Figure 1), of which 983 patients were referred to the specialist care during the analysed period of study. 71% (882) of the patients were men with a median age of 55 (50-62) years.

Non-referred patients

Compared to referred patients, non-referred were younger with a median age of 54 (48-61) vs 56 (50-62) years (p = 0.002); had a higher drug use (6.9% vs 3.8 p = 0.027); methadone therapy (19.6 vs 11.1% p <0.001), psychiatric disorder (17.6 vs 7.3% p <0.001), and COPD (2.4 vs 0.05% p <0.001). Elevated rates of change of address were also most frequent in non-referred patients (21.6 vs 5.5% p <0.001).

Non-referred patients had lower transaminase levels than referred patients (AST = 20 (17-40.75) IU / L vs 50 (34-79) IU / L p <0.001; ALT = 22 (15-50) IU / L vs 51 (30-89) IU / L p <0.001) (Table 1).

27.2% positive anti-HCV serologies requested from PC (691) were not referred compared to 10.5% requested from specialist care (514).

In the multivariate analysis, factors associated with a lower referral were: prisoners or institutionalized patients (OR 8.30 (1.10-62.85), p = 0.04), COPD (OR10.58 (1.92-58, 34)), p = 0.07), normal AST values (OR 2.24 (1.16-4.36), p = 0.034) or primary care serology request (OR 2.97 (1, 42-6.24), p = 0.004) (Table 2).

When we analysed referrals by periods of time (2013-2015 and 2015-2018), the
characteristics of non-referred patients were similar in both groups. Specifically, the predictors of non-referral prior to 2015 were: homeless population (OR 26.83 (2.28-316.17, p = 0.009) or having normal transaminase values (OR 5.81 (2.41-13 , 66) p <0.001), while the predictive factors for non-referral after 2015 were suffering from a psychiatric disorder (OR 3.61 (1.57-8.30), p = 0.003) and having normal transaminase values (OR 2.76 (1.10-6.91) p = 0.030).

**Patients who were lost to follow-up or did not attend consultations**

Patients who were lost to follow-up or did not attend specialist consultations had higher drug use (7.6 vs 2.6% p = 0.001); opioid replacement therapy (methadone) (16.6 vs 9.5% p <0.001) or were in prison / institutionalized (3.1 vs 0% p <0.01) than those who attended consultations. In addition, those who were lost to follow-up had a higher rate of change of address (9.4 vs 4.3% p = 0.004).

When we analysed comorbidities, patients who attended specialist consultation had higher percentages of hypertension (19.9 vs 7.6% p <0.001), diabetes (9.3 vs 4.9% p = 0.021) and CKD (2.5 vs 0 % p = 0.007) than those who did not attend. On the contrary, patients who were lost to follow-up had higher rates of COPD (2.2 vs 0% P = 0.001) than those who attended (Table 1). Also, patients who were lost to follow-up had lower transaminase values (AST 42 (29.5-54.8) IU / L vs 56 (36-86) IU / L p <0.001; ALT 43 (25-68) IU / L vs 53 (32-97.5) IU / L p = 0.010.

Loss of follow-up from hepatology consultations was higher in patients referred from PC than in patients referred from hospital consultations (66.5 vs 33.5% p <0.001).

In the multivariate analysis, predictors of non-attendance or loss of follow-up were: being on opioid replacement therapy (OR 2.11 (1.06-4.22), p = 0.034), not suffering hypertension (OR 1.98 ( 1.04-3.79), p = 0.039) , and primary care serology request (OR 1.67 (1.00-2.79), p = 0.049). In the multivariate analysis, not knowing the route of infection was shown as a predictor of attendance at the consultation (OR 0.45 (0.24-0.87 p = 0.018) (Table 3).

PWID who were undergoing opioid substitution treatment had a higher rate of loss of follow-up than those who did not undergo this treatment (81.4% vs 68.3%, p = 0.006).
DISCUSSION

The hepatitis C care cascade has been defined as HCV patient’s management process from anti-HCV+ to the beginning of antiviral treatment and the cure of the disease. In the last few years, barriers have been identified at different levels of this cascade. New DAAs allow greater access for infected people, guarantying a high likelihood of efficacy with almost no adverse effects. Therefore, we need additional efforts to implement diagnosis and referral to specialist care.

One of the main problems is found in the screening and diagnosis phase, with high rates of underdiagnosis. In Spain, according to recent data, it is estimated that approximately 22,500 of 200,000 people infected with HCV, are unaware of the diagnosis. A national seroprevalence study estimates that prevalence of HCV antibodies is 0.85% in the population aged from 20 to 80 years and the prevalence of active infection is 0.22%. Similar data are described in other European countries.

Hepatitis C risk groups (age groups, drug users, etc) are well known and several strategies have been developed to improve diagnosis and to provide treatment among them.

In this study, we assessed the second phase of the hepatitis C care cascade in our health area: referral to a specialist in order to confirm HCV infection and treatment administration (“link to care”). Our results show that more than 20% of patients with a known HCV diagnosis (anti-HCV+) had not been referred, and 22% of patients, had not completed the diagnostic process due to non-attendance to specialist consultations, despite being referred. Consequently, more than 40% of patients with a known HCV infection did not complete the cascade of care. Similarly, in a retrospective Swedish study up to two-thirds of patients with HCV diagnosis were lost to follow-up.

A recent Spanish study, including 4816 positive HCV antibody patients, between 2010-2018 with a 14.06% of not referred, showed that HCV monoinfection was the only risk factor associated with loss of follow-up. In our study, we also analysed patients who were lost from the system, but they were divided in two specific groups (not referred and lost to follow-up) and we collected demographic, clinical and biochemical variables, in order to detect predictive factors associated with non-referral or non-attendance to specialist consultations.
Compared with referred patients, non-referred and lost to follow-up had a higher rate of drug use, methadone therapy, and change of address. This data is not surprising, since patients with active drug use represent a population group normally associated with complex lifestyles\textsuperscript{19}, which generally results in low adherence to treatments and follow-ups. Similar data has been observed in other studies, where alcohol consumption, active drug use within six months, and absence of social support have been related as a risk factor both for not confirming HCV infection and to a lower referral to specialist care\textsuperscript{20–22}.

Our data shows that patients who had been referred to hepatology units, had higher rates of comorbidities, such as HBP, DM or CKD, probably due to a greater awareness of the disease in this population. On the contrary, in the multivariate analysis, the factors related to non-referral to hepatology consultations were the diagnosis of COPD, being institutionalized or in prison, normal transaminase levels and serological diagnosis made in PC.

A high rate of CHC has been described in the prison and institutionalized population, and it is estimated that a quarter of the world’s prison population has been exposed to HCV infection\textsuperscript{23}. However, there are significant difficulties in diagnosis and hospital referral\textsuperscript{19,20}. These results suggest the need of specific strategies with the aim of simplifying the referral circuit in this setting, similar to those carried out in other centers\textsuperscript{23–25}.

Suffering COPD was the factor with the highest OR in our study. It is necessary to keep in mind that respiratory pathology is not a contraindication for treatment with current DAAs, so it would be necessary to plan PCP and pneumology education to avoid gaps in the referral process.

In studies based on interferon therapies, it was already known that around 30% of patients with CHC had normal transaminase values. Incorrectly, transaminase values do not correlate with the degree of fibrosis or active infection; this idea can delay diagnosis\textsuperscript{20,26}.

Finally, the absence of referral after serological diagnosis was more often observed in the Primary Care setting, as it has also been shown in other studies\textsuperscript{27,28}. Morales-Arraez et al, describe in the Canary Islands a lower confirmation of active infection among
PCP, as virological confirmation was not requested in more than a third of patients evaluated in PC\textsuperscript{20}. In our case, the high percentage of non-referral could also be due to the fact that most of these patients are diagnosed at Ambulatory Treatment Centers (ATC), where they cannot request tests or make direct referrals. Therefore, it is likely that many of these patients do not return to collect their results and, consequently, they are not referred. The simplification of the diagnostic process with the one-step diagnosis, the continuous educational activities and the simplification of the referral process, as well as the alert systems in clinical history could prevent the loss of patients at this point in the cascade\textsuperscript{28,30}.

Aleman et al, showed that lack of adherence to follow-up in hepatology units was related to age, lower educational level, and psychiatric disorders\textsuperscript{17}. However, in our study, the only factors associated with loss of follow-up during 2013-2018 were being on opioid substitution treatment and serological diagnosis performed in PC. In fact, we observed how those ex-PWID patients receiving opioid substitution treatment had higher rates of absence to specialized care compared to those who were not in treatment with this therapy. In an Australian cross-sectional study, the rate of specialized evaluation was also lower among patients on opioid therapy\textsuperscript{22}. This complex group of patients needs an individualized management and simplified assessment to ensure HCV treatment, such as treating HCV in non-hospital settings\textsuperscript{17,31}. The recent Spanish Association of Liver Study (AEEH) positioning document supports studies like ours that include retrospective search of patients in microbiology databases, in order to identify patients who have never been treated or have not achieved sustained virological response\textsuperscript{3}.

Our study has some limitations, mainly due to the retrospective design. The data was collected from medical records, which could lead to the loss of relevant information and therefore could induce bias, especially concerning the percentage of referrals, which could have conduced us to obtain a higher value of non-referrals than expected. In conclusion, a high percentage of patients with positive HCV serology are not referred or lose follow-up in our hepatology unit, mainly those belonging to high risk social populations, with higher comorbidities, normal transaminase values or diagnosed at PC. To achieve the WHO goal, it is necessary to develop both educational
activities and simplification of diagnostic and referral processes to improve treatment.

REFERENCES


Table 1: demographic characteristics of patients with positive HCV serology. Referred and not referred patients during 2013-2018 and those who attended the consultation and were lost to follow-up during 2013-2018 were compared.
<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Referred (983)</th>
<th>Non-referred (245)</th>
<th>P</th>
<th>Attend consultations (760)</th>
<th>Loss of follow-up (223)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Blood Pressure</td>
<td>54 (5.5%)</td>
<td>3 (1.2%)</td>
<td>&lt;0.001</td>
<td>35 (4.6%)</td>
<td>9 (4.0%)</td>
<td>0.227</td>
</tr>
<tr>
<td>DM</td>
<td>8 (3.3%)</td>
<td>0 (0.0%)</td>
<td>0.322</td>
<td>7 (3.1%)</td>
<td>0 (0.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Obesity</td>
<td>168</td>
<td>6 (2.4%)</td>
<td>0.011</td>
<td>3 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0.643</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>82 (8.3%)</td>
<td>0 (0.0%)</td>
<td>0.343</td>
<td>7 (2.2%)</td>
<td>0 (0.0%)</td>
<td>0.974</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>40 (5.0%)</td>
<td>1 (0.4%)</td>
<td>0.800</td>
<td>14 (1.8%)</td>
<td>0 (0.0%)</td>
<td>0.439</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (1.2%)</td>
<td>0 (0.0%)</td>
<td>0.322</td>
<td>5 (2.2%)</td>
<td>0 (0.0%)</td>
<td>0.227</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>42 (4.3%)</td>
<td>1 (0.0%)</td>
<td>0.007</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>5 (0.5%)</td>
<td>1 (0.0%)</td>
<td>0.001</td>
<td>4 (1.0%)</td>
<td>0 (0.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>10 (1.0%)</td>
<td>1 (0.4%)</td>
<td>0.274</td>
<td>20 (4.0%)</td>
<td>5 (1.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>42 (4.3%)</td>
<td>1 (0.4%)</td>
<td>0.322</td>
<td>3 (0.6%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic Cirrhosis</td>
<td>19 (1.9%)</td>
<td>1 (0.4%)</td>
<td>0.274</td>
<td>11 (2.0%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Analytical Data</td>
<td>19 (1.9%)</td>
<td>1 (0.4%)</td>
<td>0.274</td>
<td>20 (3.0%)</td>
<td>1 (0.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST median U/L (range)</td>
<td>356 (47.8%)</td>
<td>2 (0.3%)</td>
<td>0.001</td>
<td>74 (33.5%)</td>
<td>14 (6.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT median U/L (range)</td>
<td>54 (22.2%)</td>
<td>10 (4.3%)</td>
<td>0.274</td>
<td>196 (86.5%)</td>
<td>15 (6.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-requested viral load (n,n)</td>
<td>50 (34-79)</td>
<td>188</td>
<td>0.001</td>
<td>147</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Sending center</td>
<td>460 (47.7%)</td>
<td>188</td>
<td>&lt;0.001</td>
<td>147</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hospital PC</td>
<td>503 (52.1%)</td>
<td>503 (52.1%)</td>
<td>&lt;0.001</td>
<td>147</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>20 (2.0%)</td>
<td>20 (2.0%)</td>
<td>0.001</td>
<td>20 (2.0%)</td>
<td>20 (2.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2: Factors associated with non-referral. Univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Route of transmisión:</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>OR 0.49 (0.33-0.73) P &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Active drug users</td>
<td>OR 1.91 (1.06-3.45) P 0.033</td>
<td></td>
</tr>
<tr>
<td>Opioids replacement therapy</td>
<td>OR 1.95 (1.35-2.84) P &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>OR 2.69 (1.79-4.05) P &lt;0.001</td>
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</tr>
<tr>
<td>Homeless</td>
<td>OR 4.52 (2.44-8.36) P &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prisoners/ institutionalized</td>
<td>OR 5.93 (2.24-15.75) P &lt;0.001</td>
<td>OR 8.30 (1.10-62.85) P 0.040</td>
</tr>
<tr>
<td>Change of address</td>
<td>OR 4.75 (3.15-7.15) P &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diabetes (no)</td>
<td>OR 2.14 (1.09-4.19) P 0.027</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>OR 4.91 (1.49-16.23) P 0.009</td>
<td>OR 10.58 (1.92-58.34) P 0.007</td>
</tr>
<tr>
<td>AST (&lt; 40)</td>
<td>OR 5.81 (3.47-9.71) P &lt;0.001</td>
<td>OR 2.24 (1.16-4.36) P 0.017</td>
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<tr>
<td>ALT (&lt; 40)</td>
<td>OR 3.06 (1.91-4.90) P &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>OR 3.18 (2.29-4.42) P &lt;0.001</td>
<td>OR 2.97 (1.42-6.24) P 0.004</td>
</tr>
</tbody>
</table>

Table 3: Factors associated with non-attendance to hepatology unit. Multivariate and univariate analysis.

<table>
<thead>
<tr>
<th>Route of transmisión: Unknown</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 0.30 (0.19-0.48) P &lt;0.001</td>
<td>OR 0.45 (0.24-0.87) P 0.018</td>
</tr>
<tr>
<td>Active drug users</td>
<td>OR 3.05 (1.57-5.94) P 0.001</td>
<td></td>
</tr>
<tr>
<td>Opioids replacement therapy</td>
<td>OR 1.90 (1.24-2.92) P 0.003</td>
<td>OR 2.11 (1.06-4.22) P 0.034</td>
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<tr>
<td>Change of address</td>
<td>OR 2.29 (1.30-4.05) P 0.004</td>
<td></td>
</tr>
<tr>
<td>HBP (no)</td>
<td>OR 3.01 (1.78-5.08) P &lt;0.001</td>
<td>OR 1.98 (1.04-3.79) P 0.039</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (no)</td>
<td>1.99</td>
<td>(1.03-3.82)</td>
<td>0.040</td>
</tr>
<tr>
<td>AST</td>
<td>0.99</td>
<td>(0.98-0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (&gt;40)</td>
<td>1.94</td>
<td>(1.23-3.04)</td>
<td>0.004</td>
</tr>
<tr>
<td>ALT</td>
<td>1.00</td>
<td>(0.99-1.00)</td>
<td>0.029</td>
</tr>
<tr>
<td>PC</td>
<td>2.15</td>
<td>(1.57-2.95)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 1: Study flowchart**

- 1600 IgG+ serologies 2013-2018
- 1330
- Referred 1041
  - Attend specialized consultation 800
    - 40 exitus
    - 750 included in the analysis
  - Loss of follow-up / Non-attendance 241
    - 16 exitus
    - 223 included in the analysis (22.88%)
- Non-referred 289
  - 44 exitus
  - 245 included in the analysis (18.95%)

- 4 Pediatric Infectious Diseases
- 84 treated by Internal Medicine
- 221 Coinfected HIV-HVC
- 11 indetectable viral load