Reviewer's report

Title: Prevalence and sequelae of viral hepatitis C infection estimated from routine data in at-risk groups

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Reviewer: Maria Oliveira

Reviewer's report:

This manuscript presents data on the prevalence of HCV infection among different exposure categories in an Italian region from 1997-2001. In addition, the frequency of hepatic and extra-hepatic disorders associated with hepatitis C is explored. Before deciding about acceptance or rejection, a major compulsory revision is advisable, in order to improve the present study.

Major Compulsory Revisions

1-I would strongly recommend that, prior to acceptance, English should be carefully revised.

2-References should be updated, revised and adequately formatted.

3-The study was approved by any Institutional Review Board? This should be stated.

4-Suggestion for title: Hepatic and extra-hepatic disorders, and HCV prevalence among different exposure categories: estimation from routine data.

5-Abstract: should be re-written, according to the revised manuscript

6-Introduction:

a. A literature update, with inclusion of recent publications is strongly recommended. Introduction and discussion should be re-written accordingly. For example, it is suitable to include current findings on the prevalence of HCV infection in risk groups as well as for HCV genotypes (about half of cited references date from the late 90’s);

b. A clear association between HCV infection and diabetes has been described in the literature (correct the last paragraph, page 3) [see, for example, White et al (2008) J Hepatol, 49(5); Negro and Alaei (2009) World J Gastroenterol, 15(913)];

c. Revise literature for other extrahepatic disorders;

d. What does “the probability of hepatic and extrahepatic sequelae was assessed” mean (page 4)?

7-Methods
a. The methods were not adequately described, see comments below.

b. Which Italian region was studied?

c. The study design was not mentioned

d. In the end of page 4 you mention “follow up”. Isn’t it a cross-sectional study?

e. In the end of page 6 you state that “diseases were hypothesized to be a consequence of viral infection…” Unless it’s a longitudinal study, causal relation between exposure and outcome cannot be estimated. Could you please make it understandable?

f. Since you did not assess acute HCV infections (at least, it was not mentioned), one cannot estimate incidence neither relative risk, like described. Text must be corrected accordingly.

g. For repetitive exposures as drug abuse and hemodialysis, HCV prevalence increases with longer duration. Therefore, it is advisable to state the period under exposure (ever, once a lifetime, last year, last 6 months?). Usually, HCV infection is associated with blood transfusion prior to the introduction of compulsory screening, which varies between countries. Which were the criteria established for this study (before 1994, as informed by you in page 11)?

h. Drug users also included IDU. Preferably, this category should be clearly divided as injectors and non-injectors, since prevalence varies significantly within subgroups. Please, correct the current and proposed tables.

i. Estimation of HCV prevalence: HCV infection is a silent chronic disease in such a way that identifying the date of infection is not a trivial task, as properly mentioned. From this perspective, age of detection (detection could had happened anytime in the course of infection) does not seem to be suitable to be used as age of infection. Why did you use the first as a proxy for the second?

j. “New HCV diagnosis” was used as a proxy for incidence among drug users and renal patients to assess temporal trends (see other comments in l). Could you please explain the rationale to use incidence as a measure?

k. In page 6, could you explain better the paragraph “Laboratories that reported …to the observed data”?

l. “Defining a time interval consistent… follow-up for detecting sequelae ended…”. Again, did you measure the prevalence of HCV infection and its association with intra-/extra-hepatic disorders or did you assess the incidence of these manifestations? Depending on design, relative risk cannot be estimated...

m. You state that risk factors cannot be individually assessed. Could you please explain it better?

n. You assessed the mortality registries but data was scantily described (only showed in the graphics). It is recommendable to describe it in the text or present
it in a table.

o. Statistical analyses and respective software must be included

p. Which trend analyses were carried out?

q. Which tests were used to evaluate associations?

r. How significance was established?

8-Results

a. For continuous variables, standard deviations should be added.

b. Include the odds ratio values and respective significance (95%CI or p-value=x) for each comparison assessed.

c. In the text, drug users were regarded as the youngest, but in the table 1, the youngest group is shown as surgery patients who were submitted to appendectomy. Please proceed to correction.

d. HCV prevalence was higher in males, except for DU (see table)

e. Page 8, Trends. Explain “fewer new HCV diagnoses and increasing mortality” (dialysis patients) and the opposite scenario for DU. Mortality data is not described for any group, neither if changes in rates were statistically significant.

f. Describe cluster analyses for transplant patients? Methods and Results sections;

g. “Sequelae of HCV infection”. Disorders occurred more frequently among HCV-positive subjects, when compared with their counterparts. It should be interesting to describe the associations between HCV infection and disorders, including multivariate analyses, depending on the findings of bivariate analyses.

9-Discussion

a. Mortality data and putative statistical analyses as presented in the manuscript do not support the current discussion.

b. Review literature, including current data (for example, many western countries show HCV prevalence lower than 2%. Among Italian blood donors, Piro et al (Blood Transf 2008, 6) found an HCV frequency of 0.2% in a prospective study carried out from 2000-2004).

c. To effectively suggest that drug use, hemodialysis, blood transfusion and/or others are risk factors/behaviors for HCV infection statistical analyses must be performed. In the text or table, statistical results were not shown to sustain existing observations.

d. Page 11, 1st paragraph: “The HCV prevalence…variable”. It is not clear why it was mentioned in the discussion.
Many factors contribute to reduction in HCV prevalence among drug users, especially among those who inject drugs. Between them, the positive role of harm reduction initiatives can be underlined [see Strathdee et al. (2006), AIDS and Behavior, 10; Des Jarlais et al. (2005) AIDS, 19(suppl3)]. In our experience, benefits from attendance in Syringe Exchange Programs were also perceived [Oliveira et al. (2009); J Clin Virol, 44]. Therefore, although it occurs in a lesser extent when compared to HIV infection, this observation does not clash with recent literature.

Limitations. After appropriate statistical analyses (including multivariate analyses to identify independent predictors for HCV infection and/or disorders), limitations should be re-written.

In the end of the manuscript, proposals/perspectives based on the present findings should be considered.

10-Table and figures

a. Table 1:

i. For continuous variables, standard deviation values must be included
ii. Which was the p-value for trend for the allogenic transplant patients group?
iii. What does a frequency of 12.5% of drug use among children <1 yr mean?
iv. I suggest that table 1 should be split into 2 tables:

Table 1. Demographic characteristics, hepatic-/extra-hepatic disorders and HCV prevalence and mortality, according to exposure category among …, including the following variables: n. subjects (regarded as N); gender (male,%); HCV infection (%), HCV mortality, Non-Hodgkin lymphoma (%), cryoglobulinemia (%); portal hypertension (%), etc.

Table 2. HCV prevalence and mortality according to year of detection and exposure category among ….

In both tables, statistical analyses and significance must be mentioned in the footnote. In addition, other pertinent information should be added (for example, drug use in the last 6 months; hemodialysis in the last year, etc.). In the second table, the reference category must also be mentioned.

b. Figures 1-4 must be removed
c. Depending on the presented findings, instead of figure 4, a third table could be included: Hepatic- and extra-hepatic disorders according to HCV status, showing the frequencies in each HCV group and their respective OR and 95%CI values. Relevant multivariate results should be mentioned in the footnote.

11-After major revisions, minor essential and discretionary revisions can be carried out.
Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests