

## **RESPONSES TO RIEVIEWERS**

ESPS Manuscript NO: 31417

Title: Mortality associated with Hepatitis C and Hepatitis B virus infection: a nationwide study on multiple causes of death data

In the revised manuscript, highlighted are changes made following reviewers' suggestions and professional language editing

### **Reviewer's code: 03488404**

#### Comment 1

Methodological issues (many undiagnosed and misdiagnosed cases) should be stressed in abstract.

#### Answer

The problem of incomplete reporting and misclassification of the etiology of liver disease is now mentioned in the Abstract (Conclusion) of the revised manuscript

#### Comment 2

Many citations can be considered outdated, more recent data available.

#### Answer

The new systematic review on hepatitis B and C prevalence in Europe from the European Center for Disease Control, issued in November 2016, is now cited in the revised manuscript. Three additional studies published are now cited on changing etiology of chronic liver diseases in clinical studies carried out in Italy [Sagnelli 2016, Saracco 2016], and on mention of HCV infection in records of a sample of Italian general practitioners [Lapi 2016]

## Overview

This 3 year analysis of nearly 2 million Italian death certificates provides important epidemiologic data on prevalence nationally, regionally, and by age and gender of hepatitis B (HBV) and C (HCV) infection among the decedents. Italian death rates with HBV or HCV infection were then compared to age-standardized EU death rates over age 20-59 years; deaths and country of origin of immigrants were also analyzed. As the authors acknowledge, death certificates provide incomplete or misclassified health condition data. Hence, their data likely underestimates HBV and HCV prevalence. With Italy's higher HCV prevalence, relative to other Western EU countries, the authors should state if there has been national or regional HBV or HCV population testing efforts – which would affect rates of identified infections. Despite these limitations, the study provides data not currently available in the literature which is immediately useful for clinicians and public health authorities to follow trends in HBV and HCV disease-related mortality.

## Answer

To date, in Italy HBV and HCV testing has been directed toward high-risk or convenience groups (including intravenous drug users, blood donors, pregnant women, hospitalized patients), whereas there have not been national or regional testing strategies at the population level. This is now specified in Introduction of the revised manuscript.

## Minor comment 1

Suggest changing the title, running title, and throughout the manuscript to: “Mortality associated to with Hepatitis C and Hepatitis B virus infection”

## Answer

The suggested change has been applied to the title, running title, and throughout the manuscript.

## Minor comment 2

For clarity, mortality rates should be expressed as a proportion – as 45/100,000 or 45 per 100,000: “HCV-related mortality rates were higher in Southern Italy among elderly people (45x/100,000 in subjects aged 60-79 and 125x/100,000 in subjects aged  $\geq 80$  years), ...

## Answer

The suggested change has been applied throughout the manuscript.

#### Minor comment 3

P. 7, paragraph 2 – suggest revising: Such a peak is already well-recognizable from mortality rates at least in the male gender, and must be strictly monitored in the future: progression of HCV-related liver disease progresses faster with aging, ...

#### Answer

The sentence has been rephrased according to the reviewer's suggestion.

#### Minor comment 4

Below the bar graph of Figure 3, two disease categories are missing descriptors, which are represented by small dots and solid gray on the graph (these likely represent 'circulatory diseases' and 'all other diseases' – and should be included)

#### Answer

Sorry for the error in including Figure 3 within the manuscript's file; the Figure has now been amended.

**Comment**

Dear Dr. Fedeli and colleagues, Thank you for the submission of your manuscript. I have now had the opportunity to carefully read your paper and the related literature. I have been aghast at your tremendous workloads using the Italian National Cause of Death Register. However I am afraid that there is a methodological shortcoming. Unfortunately, without functional data to support the findings and offer the kind of clinical relevance and significance, I am afraid that we find the study not fitting well our editorial requirements. Issues Death Certification is one of the good source to collect a variety of useful information. To avoid the limitation such as a misclassification, they have employed the MCOD methodology in this analysis. However the analysis of MCOD has also some limitations, for example, the authors have a direct measure of negative predictive value. Morbidity related to hepatitis virus infection is due not only to chronic liver disease, but also diverse extra-hepatic manifestations. Most of physician devotes considerable attention to degree of inflammation and severity of fibrosis in hepatitis virus infected liver. However, recent accumulation of expertise in extra-hepatic manifestations caused by hepatitis virus make certain us understands the importance of progressive systemic illness. I am afraid whether their sorting criteria is enough analyzable or not to provide a newly mortality data as highly value-added information.

**Answer**

The analysis of mortality data suffers from incomplete reporting and misclassification of the etiology of liver disease: physicians filling in death certificates can be unaware of HCV or HBV infection in the patient, or may not consider that the disease contributed to the patient's death. Furthermore, among elderly patients affected by multiple comorbidities, there may be no simple etiologic chain leading to the identification of a single underlying cause; death often results from a complex interaction between multiple factors. As a consequence, especially in the contest of ageing populations like in Italy, instead of relying only on the underlying cause of death, the analysis of any mention of the disease in death certificates allows a more complete identification of the burden of mortality attributable to viral hepatitis infection. The above comments have now been added at the beginning of the Discussion of the revised manuscript. Moreover, by means of MCOD analyses comparison of mortality data between different countries can be carried out (see reference 22), partially overcoming problems related to different certification practices (e.g., mention of a disease in different part of the death certificate).