

Dear Jing Yu, Science Editor

We appreciate reviewers' comments that give us the opportunity to ameliorate the paper

(Manuscript NO: 27935. WJG).

Please find enclosed a copy of the new version of our article, revised according to these comments and a letter with the point by point responses. All revisions in the updated version of the manuscript are highlighted in yellow.

Thank you for your kind consideration

Best regards

Response to reviewers

Reviewer #1 (03536885)

Answers

- 1) We have not included any patient in the period 2007-2012 due to the fact that the outpatient clinic has changed location (in another side of Turin). During this change, part of data have not been collected in a standard style and homogeneously, due to logistic problems.
- 2) We chose the approach to analyze the triennial prevalence of different causes of liver disease in our cohort, with the rationale that using this range to detect early eventual changes in etiological trends it is easier. The cohort 2012-2014 has been included to confirm, also in recent years, the previous trend.
- 3) We have re-written all sentences where was originally reported “with respect to”. These were replaced with “in comparison”.
- 4)
 - a) In the result section, table numbers were inserted.
 - b) The decrease in HCV incidence is likely due to the amelioration of hygiene and social conditions in Italy, with the adoption of preventive measures able to notably reduce the acquisition of HCV. Since for the purpose of this study, only patients with the first evidence of increased liver enzymes were included, the etiology was unknown and none had been previously treated.
 - c) Table 3. We think that the significant increase in metabolic etiology in the period 2012-2014 is a warning of the impairment in eating habits of Italian people. This trend started

already before this period (see the period 2004-2006 with a P value [0.06] near the statistical significance).

- 5) We have modified the conclusion deleting the part regarding the proposal of a national surveillance program.

Reviewer #2 (03646816)

- 1) The sample size has not been determined with respect to the power of a formal statistical comparison, but rather on the basis of resources available for in-depth review of the physical medical records. We clarified this point in the statistical analysis section as suggested. A sample of 1163 medical records (in order to obtain approximately 100 patients per year) have been extracted according to an ordered sequence generated using a uniform distribution. To explore an updated trend in more recent years, an additional sample of 281 charts (period 2012-2014) was included in the analysis.
- 2) We have not included any patient in the period 2007-2012 due to the fact that the outpatient clinic has changed location (in another side of Turin). During this change, part of data have not been collected in a standard style and homogeneously, due to logistic problems. We have added this fact as a limitation of our study.
- 3) We selected cases with a "first" hepatologic consultation, indicated for the increase in liver enzymes. These were found increased at least in 2 times. We agree with the consideration that over half of NAFLD patients have normal aminotransferase levels and we commented it in the manuscript.
- 4) In the result section, table numbers were inserted. The last paragraph of the result sections was re-written.
- 5) Regarding the issue discussed by the reviewer, in our region has been performed an epidemiological study and among the authors there was G. Ciccone, who is also author in our work. In the previous work it has been shown that in healthy individuals the prevalence of undiagnosed metabolic syndrome was 5.2% in normal-BMI and 26.6% (23.3-30.2) and 45.3% (41.3-49.2) in overweight/obese individuals. Of the total cohort 52% were overweight/obese and they accounted for 85% of the cases of MS; a further 19% were normal weight with light physical activity. The authors concluded that more than 97% of unknown metabolic syndrome cases would be identified among apparently healthy individuals when overweight/obese, and normal-BMI subjects with low physical activity were screened (see: Bo S et al. Diabetes Res Clin Pract. 2007 Mar;75(3):362-5). In our cohort of patients with liver disease these data are not available due to the study design.
- 6) Since the new direct antiviral treatments for HCV were introduced in our region in January 2015, an impact in the drop of HCV prevalence could be excluded.

- 7) According to reviewer suggestion we have modified the conclusion deleting the part regarding the proposal of a national surveillance program.