



UNIVERSITA' DEGLI STUDI DI MESSINA
POLICLINICO UNIVERSITARIO
Unità di Hepatologia Clinica e Biomolecolare
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Microbiologia e Scienze Biomediche

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6940-review.doc).

Title: Occult hepatitis B virus and hepatocellular carcinoma

Author: Teresa Pollicino, Carlo Saitta

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6940

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1 (n. 00069423)

(1). To our knowledge no longitudinal study evaluating HCC occurrence in patients with OBI has been performed so far. However, in the "Occult HBV and HCC Clinical Evidence" section of the review we reported the data from a very recent observational cohort study in which it has been evaluated the clinical evolution of patients with chronic hepatic C according to OBI status. In particular, in the previous version of the review we reported ...". In fact, OBI positivity was associated with HCC development ...". Now, in accordance with the suggestion, we modified the sentence as follow..: "In particular, HCC development occurred more frequently in OBI positive than OBI negative patients (35% OBI positive vs. 8,7% OBI negative patients, respectively, $P < 0.01$).

Concerning the percentage of OBI in HCV associated HCC, a new sentence has been added at lines 33-34 of the same review section: "In most of these studies, the prevalence of OBI in HCV patients with HCC was as high as 60%-70%..."

(2). We agree with the reviewer that the presence/absence of antiHBc and/or antiHBs antibodies identify two different type of OBI, and the important evidence coming from immunological studies (Zerbini et al 2008 *Gastroenterology* and Bess et al 2012 *J Virol*) strongly support this hypothesis. However, no data are available concerning the possible different impact of positivity/negativity for HBV antibodies on the outcome of the liver disease and the risk of HCC development as well as on the HCC outcome once it has developed.

(3). Analogously, there is no evidence concerning possible differences in terms of clinical outcomes between patients who developed anti-HBV antibodies after an acute self-limited hepatitis or after the recovery from a



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long-lasting CHB. We think that the lack of scientific support does not allow to provide any suggestion to the physicians on possible different behaviors to be adopted in these two subsets of OBI patients.

Reviewer 2 (n. 02567528)

- (1) The text has been modified accordingly.
- (2) The text has been modified accordingly.
- (3) As suggested, we are now providing a new figure (figure 1) in which the different HBV profiles and their incidence in OBI are represented.
- (4) The text has been modified accordingly
- (5) The text has been modified accordingly
- (6) Both the text and the figure (now, figure 2) have been modified accordingly
- (7) and (8) Typing mistakes have been corrected

3. Format has been updated

4. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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