

**Title: Predictors of early and late hepatocellular carcinoma recurrence**

**Point by point response to reviewers**

**Reviewer 1**

**In this work, the authors explored the recurrence predictors of HCC and the differences between predictors of early and late recurrence. However, there are minor specific points in this manuscript as shown in following comments:**

**1. The content of the article was too long to reflect the novelty which needs to be refined.**

We wish to thank the reviewer for the comment. The review is currently about 7000 words. It includes extensive literature and aims to address each topic in an exhaustive manner, rather than providing recent news on the issue. We therefore believe that further cuts would deplete the manuscript. Furthermore, no word limits have been indicated by the Editor.

**2. It is recommended that the authors focus on clinicopathological factors or molecular markers to study predictors of HCC.**

We wish to thank the reviewer for the comment. In accordance with what was expressed by the reviewer, the manuscript is focused on the clinical (related to the patient and the type of treatment) and pathological (related to HCC) factors potentially predictive of recurrence. Among the biomolecular markers, AFP and PIVKA-II have sufficient data in the literature to provide an additional indication on the risk of recurrence. To our knowledge there are no other markers in this regard.

**3. It is recommended to provide references in the past 5 years.**

Thanks for the comment. We agree with the reviewer on the extreme importance in a review article of an extremely up-to-date bibliography. All the latest works available in the literature are included in this manuscript. In fact, over 40% of the citations refer to manuscripts from the last five years and about 75% to manuscripts from the last 10 years. As suggested by the reviewer, where possible, several references have been updated. However for some topics the latest data available are not recent but still deserve to be included.

### **Reviewer 2**

**The manuscript "Predictors of early and late hepatocellular carcinoma recurrence" is well written and is recommended for publication.**

We wish to thank the reviewer for the comments on our work.

### **Reviewer 3**

In this review, Nevola et al. have summarized predictive factors for early and late recurrence of hepatocellular carcinoma (HCC) and potential guidelines to manage the risk of the recurrence. The article is overall well-written and provides useful information for clinicians and those interested in the topic. However, in addition to minor misspellings and grammatical errors, I have a few concerns/suggestions as followed:

1. The summary of predictors of early and late HCC recurrence in Table 1 and 2 are helpful for readers. However, a side-by-side comparison of the early and late predictors will allow readers to identify factors that are unique for each type of recurrence especially there are several characteristics common in both recurrences such as multifocality, high AFP, male sex, and liver cirrhosis (Table 1 and 2). With this

observation, is it true to state “Due to the different pathogenesis, early and late recurrence show non-overlapping predictive factors”? (Pg. 3) In addition, later in the article, the authors suggest “These data suggest that the dichotomy between early and late recurrence is probably not so clear-cut, and pathogenetic mechanisms and clinical features may overlap.” (pg. 16). The authors should pay an attention to address these contradictory statements.

We wish to thank the reviewer for the comment. Although apparently contrasting, the same concept was intended to be expressed both on page 3 and on page 16. However, in accordance with what has been suggested, the sentence has been reformulated in order to avoid a misunderstanding.

**2. A table/figure/flow chart that summarizes therapeutic strategy and post-treatment surveillance for patients with early and late predictors could be useful for the readers.**

We wish to thank the reviewer for the comment. A flow chart able to indicate the ideal treatment in relation to risk factors for early and late recurrence would be desirable. However, at present there are no data which compare the weight of the single risk factors or which allow us to quantify the recurrence risk using a score. Furthermore, in choosing the optimal treatment, other factors must be taken into consideration (e.g. age, comorbidities, performance status, hepatic functional residual) and therefore the current treatment cannot be generalized only in relation to the predictors of recurrence. Accordingly, a figure focused on the cornerstones in the decision-making process of optimal HCC therapy has been added and the text has been adjusted.

**3. Details of literature search and criteria of the selected studies should be discussed.**

We wish to thank the reviewer for the comment. Although the literature search is extremely thorough, this manuscript qualifies as a narrative review (and not a systematic

review). Therefore, in our opinion, specifications of the search and selection criteria do not appear necessary.

#### **Reviewer 4**

The authors provide detailed review of the predictive factors as well as recurrence risk stratification guides, focused on the recurrence of hepatocellular carcinoma. The authors further differentiate these predictors between early and late recurrence. This is a review article aiming to summarize the available information in literature, and does not involve any new experiment. The manuscript is of good quality, the efforts from the authors are noticeable, and I commend them for their work. As the authors do not provide the detailed regarding the search criteria or the time-period from which the literature was reviewed, it does limit the impact of the publication long-term. Future directions described in the manuscript include further research regarding the same topics. The publication will likely assist the care provides including the specialists as well as primary care providers get a comprehensive understanding of the predictors for HCC recurrence. Minor Grammatical / Spelling errors noted, Please refer to the attached file for track changed suggestions. E.g. Introduction includes Aflotoxin -->Aflatoxin. Consider 1-2 re-reads of the manuscripts to identify if similar minor errors present and address please.

We wish to thank for the comments. Accordingly, the errors highlighted by the reviewer and those that emerged on a second reading have been corrected.