Reviewer's report

Title: Microvessel density by automated analysis from regenerative nodule to small hepatocellular carcinoma - approach with CD105 and CD34 immunoexpression.

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Reviewer: George Tsirakis

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In the present manuscript, the authors investigated the immunohistochemical expression of CD105 and CD34 in various pathological liver tissues, as markers of neoangiogenesis. They found that CD34-MVD was increasing from RN to HCC, whereas CD105-MVD was higher in RN. Moreover, in tissues of RN and DN, CD105 expression was higher than CD34. These observations suggest that the expression of CD105, is closely related to cirrhosis, whereas CD34 is related to carcinogenesis. This is a quite well written manuscript.

Minor Essential Revisions

1. MVD should be steadily abbreviated as microvascular or microvessel density, not with both, suggesting that in title, key words and discussion “microvessel” should be replaced by “microvascular”.

2. In introduction, it is written that angiogenesis is increased in some pre-malignant lesions in cervical, lung and in adenoma-carcinoma colon sequence. I would also added that this is also happens in the evolution of MGUS to non-active and consequently to active multiple myeloma [Vacca A, et al. Bone marrow angiogenesis and progression in multiple myeloma. Br J Haematol. 1994 Jul;87(3):503-8].

3. I think that in methods section, the materials used are not completely clear. I suggested that all patients had cirrhosis (and if this is the case then it should be mentioned). Moreover, I did not understand if the biopsies were obtained from the initial or the transplanted liver.

4. In results, the values of CD105 and CD34 could be removed since they are shown in the tables. I would keep only the p values.

5. In discussion, it is written that soluble CD105 was higher in the serum of cirrhotic patients compared to healthy population, suggesting that cirrhosis is a state of increased angiogenesis [30]. Nevertheless, the same authors showed that serum levels of soluble CD105 was even higher when cirrhosis co-existing with HCC, compared to cirrhosis and cancer alone. If the patients of the study had cirrhosis, I would expect increased histological expression of CD105 in HCC biopsies. This has to do with the fact that serum levels of soluble CD105 have already been directly correlated to bone marrow MVD in Multiple Myeloma and with other markers of angiogenesis in various myeloid malignancies [Pappa C, et

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.