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Reply to "Hepatocellular Carcinoma in Thalassemia and other Hemoglobinopathies"

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To the Editor:

We thank Dr. Mancuso and colleagues for their knowledgeable comments on our study. In particular, one point raised is that it does not address the question on the rate of patients with hepatocellular carcinoma (HCC) with and without concomitant cirrhosis.

This information is important because several studies have revealed a significant rate of HCC in thalassemia in non-cirrhotic liver and mainly in non-transfusion dependent thalassemia (NTDT) (1-3). However, as clearly stated in Supporting Information – Table 1, out of 80 patients who developed HCC, 63 of 75 for whom the data was available (i.e. 84%) had a concomitant diagnosis of cirrhosis. We have not been able to develop this issue in depth in the published article for reasons of space, but we would like to take the opportunity offered by Dr.Mancuso to clarify some further specifics.

Only for 30 of the patients with cirrhosis do we have the date of the diagnosis: 25/30 (83%) had a previous diagnosis, 5/25 (17%) had a simultaneous diagnosis.

In patients with previous diagnosis of cirrhosis, the median number of years between diagnosis of cirrhosis and diagnosis of HCC was 7.5 years (IQR: 5.2-13.1).

In addition, although we could not assess the role of cirrhosis as a risk factor for the development of HCC because we did not have this data in the control population that did not develop cancer, in our population cirrhosis was present in the majority of patients who developed HCC, without differences according to the type of hemoglobinopathy.

In further detail, cirrhosis was present in 83% of patients with transfusion dependent thalassemia (TDT) (45/54), in 92% of patients with NTDT (12/13), and in 75% of patients with sickle cell disease (6/8), (p=0.5). Notably, 9 of the patients who developed HCC in the absence of cirrhosis were still antiHCV positive.

Finally, Dr Mancuso and colleagues claim that our study does not help in solving the debate about treatment of HCC in thalassemia and other hemoglobinopathies because it does not contain specific data (4).

Seven patients with hemoglobinopathy and HCC underwent liver transplantation in our population (data already present in Supporting Information – Table 1). Apart from two who had a history of heart disease, the others had no major comorbidities. They were diagnosed with HCC after 2001 (between 2001 and 2020), and the transplant was performed 2.1 years (median value) after the HCC diagnosis. The number is too small to say whether, as desirable, there has been an increase in the number of transplantable patients over time. However, 5 of them were still alive at the last follow up (6.4 years after liver transplantation as a

median, min-max 0.1-17.2). The remaining two patients died because of liver failure and sepsis, 1.9 years and 8 months after transplantation, respectively.

Although larger studies are needed to clarify the role of liver transplant in patients with hemoglobinopathies, our work also contributes to reinforcing the concept expressed by Dr Mancuso and colleagues that liver transplantation can be a therapeutic option to be considered in selected cases and increases the published cases in this regard (5-6).

We would like to conclude by pointing out that even the proper management of liver cancer in a person with hemoglobinopathy and the eventual choice of transplantation cannot disregard a multidisciplinary evaluation in which the expert in hemoglobinopathies plays an important role in giving proper weight to the patient's clinical situation, life expectancy related to the underlying pathology, iron status, and past comorbities.

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