in the subgroup within the Milan criteria (Log-rank test, p <0.05). Similar results were obtained in the subgroup beyond the Milan criteria but within the up-to-seven criteria and the subgroup beyond the up-to-seven criteria (Log-rank test, all p <0.05).

Taken together, although we demonstrated the clinical significance of the response to TACE at an early time point, further studies are required for extended applications of surgical resection in patients with BCLC B stage HCC as well as those with BCLC A stage HCC and Child-Pugh A class liver function, but a morphologically cirrhotic liver.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Kim BK, Kim SU, Kim KA, Chung YE, Kim MJ, Park MS, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol 2015;62:1304–1310.
[2] Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol 2015;62:617–624.
[3] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
[4] Kim SU, Ahn SH, Park JY, Kim DOY, CHON CY, CHOI JS, et al. Prediction of postoperative hepatic insufficiency by liver stiffness measurement (FibroScan((R))) before curative resection of hepatocellular carcinoma: a pilot study. Hepatol Int 2008;2:471–477.
[5] Wong JS, Wong GL, Chan AW, Wong VW, Cheung YS, Chong CN, et al. Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. Ann Surg 2013;257:922–928.
[6] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.

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Reduced mortality due to phlebotomy in moderately iron-loaded *HFE* haemochromatosis? The need for clinical trials

To the Editor:

We read with interest the paper by Bardou-Jacquet and colleagues [1] examining mortality in *HFE*-associated hemochromatosis and the accompanying editorial [2]. Both the authors of the study and the writers of the editorial concluded that the observation that *HFE* p.C282Y homozygotes with a serum ferritin (SF) at diagnosis between the upper limit of normal (ULN) and 1000 μg/L have reduced mortality compared to the population at large is predominantly due to venesection therapy.

We are not convinced however, that this conclusion is supported by the data provided for the following reasons:

1. If normalization of SF resulted in reduced mortality then it would be expected that *HFE* p.C282Y homozygotes with normal SF at diagnosis would also have reduced mortality but this was not found to be the case.
2. There was no information about the amount of iron removed for 36% of subjects so there was likely to be a significant minority of individuals with SF between the ULN and 1000 μg/L who did not have normalization of SF.
3. The cohort had a follow-up mean duration of 8.3 ± 3.9 years. The average age at diagnosis was 45.2 ± 14.2 years. This means that it is likely that many subjects in the group with SF between the ULN and 1000 μg/L had a raised SF for many more years than they had a normalized SF. It is not at all clear how this balance would result in reduced mortality when this was not seen among those with normal SF at diagnosis. Of those who did have information about the amount of iron removed, there is no information about whether they continued venesection therapy in order to maintain a SF level <50 μg/L after a SF of <50 μg/L was achieved initially, or the extent to which follow-up data (number and volume of phlebotomies, clinical and biochemical indicators of tolerance and efficacy of venesection therapy) were available. Moreover, there is no information about a formal, standardized, consistent, cohort-wide protocol around advising participants to start, continue and potentially stop venesection therapy, which makes the claim that the results can be interpreted as "intention-to-treat" difficult to justify.

Reasons other than the benefit of normalization of SF that could explain the study findings include:

1. Having a mild excess of iron in the body reduces the risk of cardiovascular and extra-hepatic cancer. This is counter intuitive with data suggesting that iron is a pro-oxidant and therefore more likely to result in increased cancer incidence. In addition we found an increase in the incidence of breast and colorectal cancer in a large cohort of *HFE* p.C282Y homozygotes compared to a matched *HFE* wild-type control group, we did not, however, have sufficient data to examine the association of cancer occurrence with SF levels [3]. From the

cardiovascular standpoint, there is evidence that low hepcidin levels that are associated with *HFE* p.C282Y homozygosity, leads to low reticuloendothelial cell iron levels despite high total body iron and that this can lead to reduced levels of atherosclerosis (the so called "hemochromatosis paradox") [4].

2. As noted by the authors, those with SF between the ULN and 1000 μg/L had increased medical care compared to the average person and this may have resulted in other lifestyle changes that were beneficial. For example lifestyle changes in subjects with fatty liver disease such as diet and exercise, can improve liver function and morbidity. No information is given by the authors on body mass index and any changes in this following appropriate intervention.
3. Individuals with SF between ULN and 1000 μg/L are less prone to iron deficiency anemia and this may result in health benefit.

The only way to answer the question of the role of venesection therapy in *HFE* p.C282Y homozygotes with SF between ULN and 1000 μg/L is to do a randomized study with half the cohort having normalization of SF and the other half not being treated. Until such data are available, the question of benefit from treating *HFE* p.C282Y homozygotes with SF between ULN and 1000 μg/L remains, in our view, unproven.

Conflict of interest

The authors who have taken part in this letter to the editor declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Bardou-Jacquet E, Morcet J, Manet G, Laine F, Perrin M, Jouanolle AM, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. J Hepatol 2015;62:682–689.
[2] Zoller H, Finkenstedt A. Should C282Y homozygotes with mild iron overload be treated? J Hepatol 2015;62:510–511.
[3] Osborne NJ, Gurrin LC, Allen KJ, Constantine CC, Delatycki MB, McLaren CE, et al. HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. Hepatology 2010;51:1311–1318.
[4] Sullivan JL. Do hemochromatosis mutations protect against iron-mediated atherogenesis? Circ Cardiovasc Genet 2009;2:652–657.

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Reply to: "Reduced mortality due to phlebotomy in moderately iron-loaded HFE Haemochromatosis? The need for clinical trials"

To the Editor:
Australian colleagues raise concerns about our study [1], and the accompanying editorial [2]. We showed that *HFE* C282Y homozygotes with initial serum ferritin (SF) between the upper limit of normal and 1000 μg/L had significantly lower overall mortality than that of the general French population. Delatycki *et al.* disagree with our conclusion that this could be due to early management of patients, and putatively to the maintenance of low body iron stores through iron removal.

With respect to their comments about methodological aspects, we would like to stress the following points:

- We were able to provide the amount of iron removed in 64% of our patients. This high proportion demonstrates the efficacy of our recommendations. However, we agree that, for a significant number of patients, we had no reliable information about long-term maintenance therapy. Therefore, we have been cautious when discussing the putative role of venesection therapy in lowering mortality rate.
- Since the early 1990s, we deliver written guidelines and a personal follow-up notebook to every C282Y homozygote. With time, our recommendations did not vary with respect to the indications and management of initial and maintenance of