Reply to: "Selection of MRI contrast agent and diagnostic criteria for HCC to maximize the advantages of contrast agents"

To the Editor:

We thank Dr Choi and colleagues for their interest in our work and their generous appraisal of our article. They have also made valuable comments, which we would like to respond to.

Dr. Choi and colleagues have first focused on the timing of "washout" using hepatobiliary contrast agent-enhanced MRI (HBA-MRI). We have evaluated the presence of washout on all phases: portal venous phase, transitional ("delayed") phase, and the hepatobiliary phase. Using the most restrictive criteria (2018 EASL)[1] that only consider the washout on portal venous phase, HBA-MRI achieved similar specificity to MRI with extracellular contrast agents (ECA-MRI) but with a significant decrease in sensitivity; while HBA-MRI had a similar sensitivity to ECA-MRI but significantly decreased specificity when extended washout was used (portal venous phase, or transitional phase, or hepatobiliary phase). These results were suggested by other studies. We agree with Dr. Choi and colleagues that the drop in sensitivity of HBA-MRI with EASL guidelines is not satisfactory but the drop in specificity using extended "washout" is also of concern, in particular when non-invasive imaging-based diagnosis of hepatocellular carcinoma (HCC) is sufficient for patient management.

The second comment regards ancillary imaging features. Indeed, we agree that MRI is multiparametric and we should take advantage of additional findings. Some findings have been incorporated in guidelines such as those from the AASLD.[2] While these ancillary findings may increase or decrease the likelihood of a lesion being HCC, they do not enable a definitive diagnosis of HCC or non-HCC. If the role of ancillary imaging features is further confirmed in large and prospective studies, guidelines might consider them as major features for the diagnosis of HCC.

We thank Dr. Choi and colleagues for their comment regarding the registration of the study in ClinicalTrials.gov and we have clarified this issue. This institutional study was built in 2008 and patient enrollment started in 2010, aiming at comparing the performances of EASL criteria for the diagnosis of small HCC using contrast-enhanced ultrasound (CEUS), CT and MRI. During this time HBA-MRI took on a growing importance and we decided to complete the study and to amend the study protocol. Therefore, this study has 2 parts. The first part (2008–2013) compared CT, ECA-MRI and CEUS in patients at risk of HCC[3] and the second part (2014–2017) compared ECA-MRI and HBA-MRI.[4] The patients included in the 2 studies were different.

Last, Dr. Choi and colleagues highlighted their recent study[5] showing that CT plus gadoxetic acid-enhanced MRI was associated with better survival than CT plus non-gadoxetic acid-enhanced MRI in patients with HCC and localized disease. This large nationwide retrospective cohort study from Korea is extremely interesting. Yet, the better performance of HBA-MRI is much more related to the improvement of HBA-MRI in tumor staging over ECA-MRI than the diagnostic performance itself.

In conclusion, we do not think that a single MR contrast agent is best for the diagnosis and staging of HCC. The diagnostic performance of HCC using MRI varies according to the contrast agent and the criteria used. The sensitivity/specificity expectations are clearly different around the world. Eastern countries prioritize a high sensitivity while Western countries consider a high specificity to be very important. Such differences are largely explained by the priority given to different therapeutic options around the world.

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Conflicts of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

This manuscript was co-written by Anita Paisant, Christophe Aubé and Valérie Vilgrain.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.045.

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No evidence for an increased liver uptake of SARS-CoV-2 in metabolic-associated fatty liver disease

To the Editor:

We read with interest the research article published by Ji and colleagues, in the *Journal of Hepatology*, showing that patients with metabolic-associated fatty liver disease (MAFLD) have a higher risk of COVID-19 disease progression and higher likelihood of abnormal liver blood tests from admission to discharge than patients without MAFLD.[1] Given the absence of data on medical history of these patients, this persistence of liver blood test abnormalities could be either a mere reflection of pre-existing abnormalities related to MAFLD or could alternatively be due to a higher susceptibility of the fatty liver to SARS-CoV-2 infection.

We therefore investigated whether MAFLD is associated with altered liver expression of SARS-CoV-2 critical entry proteins. SARS-CoV-2 attaches to cells by binding to angiotensin-converting enzyme 2 (ACE2). The cellular protease transmembrane protease serine 2 (TMPRSS2) cleaves the SARS-CoV-2 spike protein, allowing fusion of cellular and viral membranes.[2,3] Moreover, in the HEK293 cell line, overexpressing human ACE2, SARS-CoV-2 enters through endocytosis with critical roles played by endocytosis-regulating protein phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE).[4] Finally, as described for SARS-CoV and MERS-CoV, cathepsin L is also critical for priming of the SARS-CoV-2 spike protein in lysosomes following entry through endocytosis.[4]

We analysed the influence of MAFLD on liver gene expression of these 4 proteins implicated in SARS-CoV-2 infection by analysing public data from patients and from mice with MAFLD. In 2013, Ahrens and colleagues published microarray data obtained on human liver biopsies.[5,6] They made available transcriptomic data from 12 lean patients without MAFLD, 16 obese patients without MAFLD, 9 patients with simple steatosis and 17 patients with biopsy proven non-alcoholic steatohepatitis (NASH). Using these datasets, we observed that none of the genes necessary for SARS-CoV-2 infection was differentially expressed between lean or obese controls and patients with simple steatosis or with NASH (Table 1).

We performed the same analysis in a mouse dataset published by Xiong and colleagues.[8] Similarly, we observed no increase in liver gene expression of the 4 proteins implicated in SARS-CoV-2 infection between MAFLD mice and control mice (data not shown).

In conclusion, MAFLD is not associated with changes in liver expression of genes implicated in SARS-CoV-2 infection. The observed persistence of liver blood test abnormalities reported by Ji and colleagues is thus likely not explained by increased hepatic SARS-CoV-2 uptake.

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Table 1. mRNA expression of SARS-CoV-2 infection critical genes in human liver biopsy.

	Lean without MAFLD (n = 12) *vs.* NASH (n = 17)		Lean without MAFLD (n = 12) *vs.* simple steatosis (n = 9)		Obese without MAFLD (n = 16) *vs.* simple steatosis (n = 9)		Obese without MAFLD (n = 16) *vs.* NASH (n = 17)		Lean and obese without MAFLD (n = 28) *vs.* simple steatosis or NASH (n = 26)	
Gene name	Fold-change	adj. *p* value	Fold-change	adj. *p* value	Fold-change	adj. *p* value	Fold-change	adj. *p* value	Fold-change	adj. *p* value
ACE2	1.41	0.39	1.00	0.99	0.99	0.97	1.39	0.14	1.24	0.24
CTSL	0.98	0.96	1.10	0.69	1.04	0.73	0.92	0.67	0.99	0.95
TMPRSS2	0.85	0.72	0.78	0.57	0.87	0.64	0.94	0.95	0.88	0.60
PIKFYVE	1.03	0.93	0.77	0.94	0.85	0.11	0.92	0.64	0.94	0.53

Human microarray data[6] was made available by Ahrens and colleagues[5] and reanalysed by us using Geo2R[7] default settings. Geo2R is based on the "Linear Models for Microarray Data" R package that computes a moderated t-statistic for each gene and corresponding *p* value. Adjustment for multiple testing was performed using Benjamini and Hochberg's correction. *CSTL* gene encodes cathepsin L protein. Human transcriptomics data is available on GEO Dataset under the accession number GSE48452. MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis.

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