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Reply to: "Non-enhanced magnetic resonance as a surveillance tool for hepatocellular carcinoma: Many unresolved issues"

To the Editor:

We would like to thank Dr. Choudhary and colleagues for their interest in our article, "Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: Comparison with ultrasound".[1] It is our great pleasure to respond to their comments.

In our study, non-enhanced magnetic resonance imaging (MRI) missed 9 HCC cases out of the 43 high-risk patients on 3 surveillance rounds, thus showing a per-exam sensitivity of 79.1%. In the original PRIUS study (Surveillance of Patients with Cirrhosis at High Risk of Hepatocellular Carcinoma by MRI with Liver-Specific Contrast, ClinicalTrials.gov ID NCT01446666)[2] that compared gadoxetic acid-enhanced MRI with ultrasonography (US) in the same study population, the sensitivity of MRI was 86.0% (37/43); the 6 HCCs were missed even on full-sequence MRI using gadoxetic acid. In other words, gadoxetic acid-enhanced MRI only detected 3 more lesions than non-enhanced MRI. Non-enhanced MRI made a false positive detection in 38.2% (21/55). Given that multiphase contrast-enhanced images provide crucial information for differentiating focal hepatic lesions, false positivity may be unavoidable in non-enhanced MRI. However, the goal of our study was not to compare the diagnostic performance of non-enhanced MRI with that of contrast-enhanced MRI, but to assess the potential utility of non-enhanced MRI as a surveillance tool, endorsed by the current clinical guidelines for HCC. In our study, US had a per-lesion sensitivity of 27.9% (12/43) and a false positive rate of 82.4% (56/68), a notably poorer performance than non-enhanced MRI.

We completely agree with the concern that the per-exam sensitivity of US (27.9%) in our study seems very poor. As Dr. Choudhary and colleagues mentioned in their letter, a meta-analysis in 2009 reported that the pooled sensitivity of US for detecting early-stage HCCs is 63%;[3] however, a more recent meta-analysis reported that the sensitivity of US for detecting early-stage HCCs was as low as 47% while ranging from 21% to 89%.[4] Also, it should be noted that tumor size is an important factor in lesion detection on US;[5] in our study, the mean size of HCC was only 1.6 cm, and the majority (66.7%) of the HCCs were at very early stages (*i.e.,* single nodules <2 cm), while previous studies targeted larger or multiple lesions at early stage (*i.e.*, single lesions of 2–5 cm or 2–3 lesions each <3 cm). Moreover, according to a study that included HCCs at a very early stage in patients due to be treated with radiofrequency ablation, 29.3% of them were not clearly visible on US as they were inconspicuous or located in the blind area, even though their presence and the location were already known.[6] Thus, very early-stage HCCs are difficult to detect due to their poor conspicuity on US. In addition, the low sensitivity of US in our study can be partly attributed to the study design. As we included patients at high risk of HCC (annual HCC risk >5%), our study population may have had advanced liver cirrhosis with severely distorted and heterogeneous liver parenchyma that could hamper the detection of HCCs. Moreover, as this study had a single-arm design, the exclusion of patients with lesions only found on non-enhanced MRI in the preceding surveillance rounds might have further impaired the performance of US.

The benefits of gadolinium-based contrast agents (GBCA) in liver MRI cannot be over-emphasized and their safety profiles have been favorable for over 30 years. Lately, however, there has been a growing concern regarding the long-term accumulation of gadolinium in the human body, including in the central nervous system. Food and Drug Administration and international guidelines published safety alerts[7,8] and indicated that they are actively investigating the risk and clinical significance of gadolinium deposits. Given the repetitive nature of surveillance studies and the high probability of exposure to GBCA in their clinical course, patients at high risk of HCC are likely to require multiple doses of GBCA and thus develop significant amounts of gadolinium deposits. Thus, it would be reasonable to reserve the use of GBCA for patients who are suspected to have focal hepatic lesions on surveillance tests instead of using GBCA for surveillance tests.

The recently revised international guidelines for HCC have allowed for the use of alternative imaging modalities in selected patients with inadequate US results. In this regard, our study explored the role of non-enhanced MRI as a potential surveillance tool for HCC. Along with the present study[1] and the PRIUS study[2] as a starting point, several ongoing prospective studies are testing various MRI techniques including abbreviated MRI using gadoxetic acid (Clinical Feasibility of Abbreviated MRI for HCC Surveillance in High-risk Group, ClinicalTrials.gov NCT03731923) and non-enhanced MRI (MAGNUS-HCC, ClinicalTrials.gov NCT02551250; MIRACLE-HCC, ClinicalTrials.gov NCT02514434) for use as alternative surveillance tools for HCC. We appear to be heading into an exploratory period when it comes to new imaging techniques for HCC surveillance.

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Conflict of interest

The authors declare no conflicts of interest pertaining to this work.

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Authors' contribution

Hyo Jung Park wrote the first draft, Hye Young Jang and So Yeon Kim made critical revisions.

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References

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[1] **Park HJ**, **Jang HY**, Kim SY, Lee SJ, Won HJ, Byun JH, et al. Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: Comparison with ultrasound. J Hepatol 2019;72:718–724.

[2] Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol 2017;3:456–463.

[3] Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37–47.

[4] Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154:1706–1718.e1.

[5] Liu WC, Lim JH, Park CK, Kim MJ, Kim SH, Lee SJ, et al. Poor sensitivity of sonography in detection of hepatocellular carcinoma in advanced liver cirrhosis: accuracy of pretransplantation sonography in 118 patients. Eur Radiol 2003;13:1693–1698.

[6] Min JH, Lim HK, Lim S, Kang TW, Song KD, Choi SY, et al. Radiofrequency ablation of very-early-stage hepatocellular carcinoma inconspicuous on fusion imaging with B-mode US: value of fusion imaging with contrast-enhanced US. Clin Mol Hepatol 2014;20:61–70.

[7] McDonald RJ, Levine D, Weinreb J, Kanal E, Davenport MS, Ellis JH, et al. Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. Radiology 2018;289:517–534.

[8] FDA Drug Safety Communication. FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI). Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluating-risk-brain-deposits-repeated-use-gadolinium-based. [Accessed 17 February 2020].

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Incidence of chronic kidney disease in patients with non-alcoholic fatty liver disease

To the Editor:

We read with great interest the article by Byrne *et al.* who summarized recent advances in the association between non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD), and reported that the prevalence rate of CKD in patients with NAFLD ranged from 20% to 55%.[1] Given a high cardiovascular disease-specific mortality among NAFLD populations (4.79 per 1,000 person-years, 95% CI 3.43–6.70), NAFLD-related cardiovascular events have filtered into people's minds.[2] By contrast, although CKD is another closely related extrahepatic disease, the burden of CKD, especially the incidence of CKD, has not been systematically described and quantitatively assessed in patients with NAFLD, with and without diabetes mellitus.

Recently, we searched PubMed, Web of Science, Cochrane Library, and Scopus for original studies published before 12 February 2020, seeking to specify the incidence rate of CKD among NAFLD populations. Eligibility criteria were (a) population: NAFLD patients without CKD at baseline, and NAFLD was defined as histological (biopsy), or radiological evidence of hepatic steatosis in the absence of significant alcohol consumption and other known causes of liver disease; (b) outcome: the incidence of CKD during follow-up, and CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, or macroalbuminuria; (c) study design: observational longitudinal study; (d) necessary information to calculate the annual incidence: mean/median follow-up time, number of participants. Alternatively, the annual incidence was available.

Finally, we included 4 studies in which 20,030 individuals were diagnosed with NAFLD, and 2 studies in which 1,420 individuals were diagnosed with both NAFLD and diabetes mellitus (Table 1).[3–8] All 6 studies were assessed as high-quality using the modified Newcastle-Ottawa scale. In the 4 studies reporting incident CKD in patients with NAFLD, participants were recruited from 4 distinct regions of the world between 1978 and 2013.[3–6] The regional incidence rates of CKD varied widely, and were 16.6, 12.3, 4.7, and 8.6 per 1,000 person-years for Sweden, the United States, South Korea, and Japan, respectively. The pooled overall incidence of CKD in NAFLD was 9.2 per 1,000 person-years (95% CI 5.7–14.6; I^2 = 96.2%; $P_{heterogeneity}$ <0.01), according to the logit transformed proportions and random-effects model. Since none of the included studies had a site in Africa, South America, and Oceania, we appeal for globally coordinated efforts to clarify the CKD burden of NAFLD in mixed populations. Moreover, a higher incidence rate of CKD (63.0 per 1,000 person-years; 95% CI, 58.2–68.2; I^2 =0%; $P_{heterogeneity}$ =0.61) was found in patients with

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