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SEAL: Why was this approach not effective?

To the Editor:

We read with great interest the study recently published by Labenz *et al.* in *Journal of Hepatology*.[1] We congratulate the authors for undertaking such an initiative. However, we were astonished with the marginal advantage of the SEAL approach compared to the standard of care in the control group in the detection of compensated advanced chronic liver disease (cACLD). Several aspects could explain these results. One reason that the authors propose is that this study was performed in the general population and not focused on patients with high risk, such as patients with metabolic risk factors or with non-alcoholic fatty liver disease (NAFLD), where similar studies have shown a greater benefit in the detection of cACLD.

In the SEAL study, the evaluation of transaminases was embedded in the Check-up 35, which is a general health check-up offered to people over 35 years of age which is covered by many insurance companies in Germany. One of the characteristics of this check-up is that participants need to proactively make a specific appointment for it. This may lead to a selection bias in the study population, by selecting patients who take more care of their health. Although performed in 2004, a previously published study reports a lower participation in Check-up 35 of females with lower socioeconomic status.[2]

Individuals with lower socioeconomic status have a higher burden of health problems.[3] Therefore, it could be that the population that undergoes Check-up 35 is not only not a high-risk population, but is actually a lower risk population than the general population.

Another source of bias is the use of the APRI (aspartate aminotransferase-to-platelet ratio index) score. Different scores have been developed to detect advanced liver fibrosis; however, almost all studies have been performed in patients under hepatological care, a setting associated with a higher prevalence of liver disease. In the general population, FIB-4 and the NALFD fibrosis score have also been shown to have a low accuracy for screening for cACLD using liver stiffness as the gold standard.[4] The recently proposed CLivD score has been developed and validated in the general population and is more precise, although its calculation is more complex.[5] Focusing on high-risk groups (*i.e.* chronically elevated transaminases, metabolic syndrome, alcohol consumption) with an increased pre-test possibility could improve the predictive value of the tests and be a more efficient approach.

Finally, and most astonishingly, approximately 50% of individuals did not receive specialized care evaluation as foreseen in the trial, although a cACLD was suspected. It is unclear whether this is due to the lack of liver health awareness on the patient level or the primary care level. Indeed, given the avalanche of cases with NAFLD, the relevance of NAFLD may be downplayed. Furthermore, patients may have comorbidities which may be perceived as more important and therefore prioritized by patients and their general practitioners. The recently launched EASL-Lancet Liver Commission is aimed at increasing liver health awareness and reducing liver-associated mortality.[6] Yet it remains to be clarified whether increasing liver health awareness and early identification of individuals with cACLD leads to a reduction in liver-associated mortality.[7] Nevertheless, measures which lead to an increase in survival in individuals with compensated cirrhosis and clinically significant portal hypertension have recently been reported.[8] Whether this applies to those identified non-invasively in the general population remains to be demonstrated. The first step though, is to identify these individuals, who are mainly in the realm of primary health care.

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Authors' contributions

CR and AZ had the idea to write the letter. CR developed the letter. JB and AZ provided important intellectual input. All authors have approved the final manuscript.

Supplementary data

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Reply to: "SEAL: Why was this approach not effective?"

To the Editors:

We would like to thank Professor Ripoll and colleagues for their interest and their commentary on our SEAL study published in the *Journal of Hepatology*.[1,2] Ripoll *et al.* raise some important points and potential limitations of SEAL that we would like to take the opportunity to reply to.

We agree with our colleagues who point out that people of lower socioeconomic status are less likely to participate in a preventive health care program such as the German Check-up 35 program, as targeted in SEAL. This is a non-negligible circumstance that leads to a potential selection bias and should be taken into account when interpreting the results of SEAL. However, it should be noted that all SEAL participants were members of AOK, the largest general medical insurance in Germany, excluding patients from alternative insurance companies and all with private insurance, who have in general higher socioeconomic status.

Notwithstanding this shortcoming, it is an important finding for the hepatology community that screening for compensated advanced chronic liver disease (cACLD) even in a population with a potentially higher degree of health awareness is feasible and provides benefit. On the other hand, SEAL suggests that future studies could specifically target populations at highest risk of chronic liver disease. Though, these populations may be more difficult to approach, since the awareness of liver health in these populations is lower than in Check-up 35 participants, and appointments with a liver specialist in SEAL were only attended by about 50% of cases. Therefore, we agree that awareness of liver health needs to be raised in all parts of our society.

Ripoll *et al.* proposed the recently published CLivD score to identify a high-risk population in the general population that deserves detailed screening for cACLD.[3] We argue that a stepwise approach with defined strategies that help primary care physicians to identify patients at high risk for liver disease might indeed improve the care for patients with cACLD. Because this is another lesson that SEAL and other studies have taught us: Screening in the general population using traditional and simple non-invasive tests may not be sufficient and lacks positive predictive value.[1,4,5] However, it has to be acknowledged that scores such as the CLivD are frequently developed in retrospective cohorts. Therefore, studies testing the benefits of these algorithms as well as alternative methods (*e.g.*, transient elastography) prospectively are needed before implementation. In this context, we believe that SEAL can serve as a blueprint for these studies by demonstrating not only what is possible in terms of patient recruitment and involvement of multiple levels of care, but also the future needs.

In summary, we believe that we have only reached the tip of the iceberg in the early detection of cACLD and are eagerly awaiting the results of additional screening studies.

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