Editorial

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Signed, SEALed, detected I'm your patient with advanced fibrosis or cirrhosis!

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Today, many patients with chronic liver disease are not diagnosed until they present with complications of cirrhosis, such as ascites or hepatocellular carcinoma (HCC). A key challenge in the hepatology community, as articulated by the EASL-Lancet Commission and endorsed by others,[1] is to identify patients with advanced fibrosis or cirrhosis earlier, so that preventive treatments and screening for HCC can be considered. This month's issue of the *Journal of Hepatology* presents the results of a German liver screening programme - "Structured Early detection of Asymptomatic Liver cirrhosis" (SEAL) - which highlights the potential benefits, but also the barriers that need to be overcome.[2]

There are two main challenges to effective early cirrhosis detection: Firstly, there is little evidence that earlier diagnosis of advanced fibrosis or cirrhosis leads to a longer and/or better life.[3–5] Secondly, there seems to be a lack of engagement from patients and general practitioners. This latter challenge was demonstrated in the SEAL study, where alarmingly only 49.2% of patients identified to be at high risk of advanced fibrosis or cirrhosis actually showed up for their follow-up outpatient hepatology appointment.[2] This disappointing lack of interest or appreciation of importance was similarly reported in a Welsh study presented at the ILC in 2020.[6] In that study of "reflex" AST testing, patients who had an elevated ALT measured in primary care had AST measured too, and the AST:ALT ratio was computed and presented to the general practitioner. If the ratio was >1, the ratio was accompanied by a recommendation to offer the patient further workup with a fibroscan examination. Of 2,117 patients who met that criterion, only 750 (35%) were referred, and only 348 (46%) of referred patients attended the fibroscan examination.[6] Clearly, many patients are lost along the "cascade of care" in hepatology, which we need to firstly recognise, but also understand, if we are to improve our implementation of care.[7]

The SEAL study presented in this issue of the *Journal of Hepatology* provides important evidence relating to key steps in our cascade of care. It examines the prevalence of advanced fibrosis or cirrhosis among people in the Rhineland-Palatinate and Saarland regions of Germany who held a particular insurance (24% of the population), did not have "clinically obvious complications of cirrhosis", and presented to their general practitioner for a health check-up program (Check-up 35).[8] The benefits of Check-up 35 are stated as: "Quick and simple; gives you an overview of your physical condition; and provides early detection of susceptibility to diabetes, cardio-pulmonary ailments and renal conditions."[8] The check-up is offered every two years from the age of 35 and includes a consultation with a review of the medical history, a physical examination, a urine analysis, a blood sample examining cholesterol levels and blood-sugar, a blood-pressure reading, and finally a conclusion with advice on a healthy lifestyle. There is no mention of alcohol.[8]

Within Check-up 35, a prospective consenting patient cohort of 11,859 patients from over 200 different general practices were enrolled for an additional check on liver health. This check included measurement of ALT and AST. If one or both were increased, the APRI score (AST to platelet ratio index) was calculated, and patients with an APRI score >0.5 were offered workup for liver disease by specialists. The outcome of that workup determined the prevalence of newly diagnosed advanced fibrosis or cirrhosis in the SEAL cohort. Ultimately, of the 11,859 SEAL-exposed patients (median age 60 years), 488 (4.1%) met the criteria for specialist workup. Of those, 240 (49.2% of the screen-positive patients) attended the appointment with the specialist, and 45 were subsequently confirmed to have advanced fibrosis or cirrhosis, corresponding to a prevalence of 0.38%. We do not know the aetiology of liver disease in these patients, but they are a subset of 245 patients diagnosed with chronic liver disease of any severity (prevalence of 2.1%). In this wider group, 60% had non-alcoholic fatty liver disease, 17.6% had alcohol-related liver disease, 4.1% had chronic hepatitis C, 1.6% had chronic hepatitis B, 2.4% had autoimmune hepatitis, 1.2% had primary biliary cholangitis, and 1.6% had liver cancer. The control cohort comprised 349,570 retrospectively identified participants of the regular Check-up 35, who had attended their general practitioner at least once between 2016 and 2017. The prevalence of newly detected advanced fibrosis or cirrhosis in the control cohort was 0.34% based on ICD-10 codes. The difference in prevalence between the SEAL and control cohorts (0.38% and 0.34%, respectively) was not statistically significant, and the number needed to screen to find one extra patient with advanced fibrosis or cirrhosis was 2,115.[2] Clinical significance may well be viewed differently from statistical significance, but costs still have to be considered. If the additional 1 of 2,115

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patients benefited from an intervention that was life-transforming, the costs may be justified. The estimated 10.9% of patients with viral hepatitis, autoimmune liver disease, or liver cancer would likely benefit from the earlier diagnosis, but the benefit to the estimated 77.6% with non-alcoholic fatty liver disease or alcohol-related liver disease is presently uncertain. While the lack of striking differences in detection was disappointing, the detail of this study – including its limitations – sheds additional insight that is beneficial.

The SEAL investigators acknowledge that the reliance on ICD-10 diagnostic codes to diagnose advanced fibrosis or cirrhosis in the control cohort was a limitation. The controls may have received incorrect diagnostic codes, and some correct diagnoses may have been left unrecorded or excluded from the investigators' definition of advanced fibrosis or cirrhosis.[9] Furthermore, the investigators used coded diagnoses given in the period from one year before to one year after the Check-up 35 examination to determine whether a diagnosis of advanced fibrosis or cirrhosis was new, with this arbitrary timeframe leading to some existing diagnoses being falsely attributed as new diagnoses.[2]

Despite its limitations, the SEAL study is important in that it firstly gives us an estimate of the prevalence of previously undetected chronic liver disease (2.1%) and advanced fibrosis or cirrhosis (0.38%) in members of the general population who choose to attend a general health check-up and a subsequent specialist workup. These estimates are on par with previous studies.[3] Second, it suggests that we can diagnose a few additional patients with otherwise undiagnosed chronic liver disease if we offer a non-invasive screening test in primary care—it remains possible that other non-invasive tests could perform better.[10] Third, it confirms that we cannot expect anything resembling 100% attendance to outpatient hepatologist workup of patients with a positive screening test in primary care—50% is a more realistic estimate. It was unfortunate that the SEAL trial ran during the COVID-19 pandemic, which may have impacted patients' willingness to attend their outpatient appointments, but the widespread non-attendance underscores that we still have some way to go to convince patients, general practitioners, and policy-makers that early detection of liver disease is important. Perhaps they would be more engaged if we had stronger evidence for the benefits of an earlier diagnosis, be it in terms of treating the cause of chronic liver disease; treating the hepatic fibrosis, steatosis, and/or inflammation; treating the complications of cirrhosis; or offering HCC surveillance. Surely, an earlier diagnosis of chronic hepatitis C infection is a wonderful thing because we can cure the infection, but what about the patient with non-alcoholic fatty liver disease or alcohol-related liver disease? How much can he or she expect to gain from an earlier diagnosis of advanced fibrosis or cirrhosis in terms of quantity or quality or life? And at what cost? These are questions that we will eventually be able to answer, but at this point we hepatologists may read the evidence more favourably than outsiders do. A recent example of the incongruence between hepatologists and generalists comes from EASL's efforts to gain the EU Commission's recommendation for HCC screening in patients with cirrhosis: We hepatologists find that there is convincing evidence for such a recommendation, but the EU's Group of Chief Scientific Advisors do not.[11]

In summary, the SEAL investigators must be complimented for their efforts and insights. Hopefully the SEAL study will keep on giving. Maybe long-term follow-up of the SEAL participants will demonstrate that those who were diagnosed with advanced fibrosis or cirrhosis through the SEAL pathway live longer or better than the controls with similar diagnoses. Maybe we can learn why so many patients do not attend specialist workup. As yet, the SEAL investigators have not examined this question, but it will be important for us to understand where and why we lose patients along the cascade of care if we want to reduce inequalities in hepatology.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

PJ drafted the manuscript. Both authors revised the manuscript and approved the final submission.

Supplementary data

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