The third year

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We are now in our third year of publishing and *JHEP Reports* has achieved some significant milestones, including being listed in PubMed and other indices. Continuing on with the tradition of the editors preparing an editorial for each issue, this month's editorial will cover some of our recently published articles.

Several themes have emerged in this issue, including fatty liver disease and bile acids, hepatocellular carcinoma (HCC), cirrhosis and liver failure. The articles were not specifically chosen to highlight these themes, but rather reflect current research interests. Not surprisingly, viral hepatitis no longer dominates published articles. Nonetheless, there are two articles that concern viral hepatitis, one to do with hepatitis C in children and one describing a mouse model of hepatitis B infection. This editorial will not discuss all the published articles but will broadly deal with some of the themes mentioned above.

Two studies report an evaluation of prognostic biomarkers. Blaya *et al.*[1] report on the use of microRNAs (miRNAs) in cirrhosis. They measured the concentration of several miRNAs and showed how the miRNAs are dysregulated in acute-on-chronic liver failure. They also suggested that dysregulation increased along with progression of chronic liver disease, and was associated with hepatic and extrahepatic organ dysfunction, and thus may indicate poor outcome. The second biomarker study suggested that the relative concentrations of macrophage migration inhibitory factor and sCD74 in patients with acute decompensation of cirrhosis also predicted outcome.[2]

Biomarkers can be used for surveillance, for assessing response to treatment, assessing prognosis before and after treatment, and as risk factors. In studies looking at biomarkers for early detection of disease, the clinical usefulness really depends on sensitivity and specificity and on ease of use of the particular test being studied. A large number of biomarkers have been proposed, *e.g.* for HCC, but apart from AFP, AFP-L3 and DCP, none have gained traction because the necessary studies have not been done. For a putative biomarker to be clinically useful there must be evidence that the marker is predictive in prospective studies, and that it is better than currently used markers. Similarly, studies looking at biomarkers as prognostic indicators have not been widely performed or validated. Although biomarkers may indicate a better or worse prognosis, they do not give a timeline for survival. Patients want to know the life expectancy. "How much time do I have left?". Telling a patient that he/she has a poor prognosis is less useful than giving a timeline. Some studies have suggested that a particular biomarker or set of biomarkers can be used to decide different treatment strategies, *e.g.* whether a patient is a candidate for transarterial chemoembolization or not. However, unless this hypothesis is tested in a prospective manner, the value of the marker(s) is questionable. This is not to say that biomarker studies should not be done. However, as an editor I must assess whether a biomarker being reported has a potential to be clinically useful. If not, unless the study has other important findings (as is the case with the miRNA study), the study is unlikely to be published in *JHEP Reports.*

There are 5 articles dealing with public health and epidemiology. In particular the articles deal with deficiencies in public health responses to liver disease. Dr. Lazarus and colleagues[3] have constructed an index to assess how prepared European countries are to deal with the coming substantial increase in liver disease related to non-alcoholic fatty liver disease (NAFLD). Countries are graded on four variables according to whether the preparedness level is high, low or something in between. The value for each variable was based upon questionnaires filled out by teams in each country. Most countries were either somewhat prepared or unprepared for the increase in liver disease. Only the United Kingdom and Spain scored above 50/100. 16 of the 29 countries scored below 25/100. This analysis speaks to the need to improve preparedness in many European countries, but the analysis could probably equally well be applied to other countries where NAFLD is a growing problem, such as the US and Canada. On the same theme, Dr. Goosens and colleagues[4] show that HCC related to fatty liver disease is increasing in incidence, particularly in women. It seems that, in this respect, fatty liver disease might be the great equalizer. Once again, these results speak to the need to improve understanding of the incidence and management of NAFLD.

The response to the impending increase in incidence of NAFLD and its complications is the responsibility of both government and medical professionals. However, given the intractability of NAFLD, it is not clear that being aware of what's coming is necessarily going to make a major difference to the incidence of disease or the incidence of complications. It will also take work on the part of the medical community to convince governments to dedicate funds to the management of NAFLD.

Dr. Younossi and colleagues[5] report that hospice care of patients with HCC is associated with longer survival and lower costs. In the US, patients frequently die without having had the support of hospice care. The situation is not likely to be much different in other Western countries. It is not clear whether the fault lies with physicians who do not refer patients, or if

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resources are lacking. However, this also speaks to how unprepared many countries are to deal with liver disease.

Dr. Burton and colleagues[6] looked at the incidence of HCC and associated mortality in the UK. They found that while the incidence of HCC is still increasing, the rate of increase is slowing. They attribute this to treatment of hepatitis C. They also describe the risk factors that lead to HCC in their population. As expected, the usual culprits are all present, viral hepatitis, NAFLD, alcohol-related liver disease and chronic liver diseases of other causes. They also point out that more than half of those diagnosed with HCC are dead within a year. This speaks to late diagnosis and missed opportunities for early intervention and possible cure. It is also likely that these findings are applicable to many, if not all, Western countries, and perhaps many in Asia as well. Only in Japan and perhaps South Korea is there a very high awareness of HCC, and government mandated programs for early detection.

These 3 articles harp on the theme of inadequate facilities and care for patients with liver disease in general, and late-stage liver disease in particular. It is not discussed in any of these articles, but one must wonder whether liver transplantation has sucked up resources that might have otherwise gone to the care of patients with end-stage liver disease, or if the availability of transplantation has detracted decision maker's attention away from the management of end-stage liver disease.

Dr Kudo and colleagues describe the use of the ALBI score in evaluating HCC patients on treatment with ramicirumab.[7] The results of this study are, to me, less interesting than the fact that they are using the ALBI score. The use of this score is becoming widespread. Among others, it has been used to assess disease in acute-on-chronic liver failure,[8] to predict portal pressure,[9] hepatic reserve,[10] outcomes after cancer treatment[11] and outcomes after liver transplantation.[12] There are many comparisons between the ALBI score and the Child-Pugh score, but more are retrospective studies or studies with small numbers. It is probably time to assess the ALBI score more formally as a replacement for the Child-Pugh score in assessing risk for liver resection, HCC staging, and other situations where the Child-Pugh score is commonly used.

Dr Shepherd and colleagues[13] investigated whether inhibition of ketohexokinase could inhibit fructose-induced fatty liver disease. Ketohexokinase is responsible for clearing fructose from the circulation. Fructose is a major factor in the genesis of liver fat. Fructose is commonly used as a sweetener in commercially prepared foods to the extent that it may constitute up to 10% of calorie intake in some diets. Fructose is converted to fat because it bypasses two enzymes that are rate limiting for glycolysis and gluceoneogenesis. This drives synthesis of hepatic fatty acid. Inhibition of ketohexokinase reduces the formation of fructose-1-phosphate, thereby reducing lipogenesis. This points to a novel approach for managing fatty liver disease, which, given the failure or incomplete testing of several agents under development (*e.g.* selonsertib, elafibrinor and cenicriviroc) is worthwhile. Whether the agent used to inhibit ketohexokinase in this study can be used on humans remains to be seen, but at least this points to the possible development of other small molecule inhibitors of this enzyme as possible treatments.

This brief summary of some of the articles appearing in the journal this month indicate that although *JHEP Reports* is new and still "earning its spurs", it is aiming high, with ambitions of becoming an equal companion to the *Journal of Hepatology*.

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