REFERENCES

1. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev*. 2014;13: 24-30.
2. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol*. 2017;15: 229-239.e5
3. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther*. 2015;41:613-623.
4. Hupé M, Rivière P, Nancey S, et al. Compared efficacy and safety of vedolizumab and infliximab in ulcerative colitis after failure of a first subcutaneous anti-TNF agent: a multicentre cohort study. *Aliment Pharmacol Ther*. 2020;51:852-860.
5. Sands BE, Peyrin-Biroulet L, Loftus EV, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381:1215-1226.
6. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol*. 2015;13:522-530.
7. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol*. 2014;109:1250-1256.
8. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y. AGA SECTION. *Gastroenterology*. 2017;153:827-834.

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Editorial: how widespread and serious is non-alcoholic fatty liver disease in the real world?

The prevalence of non-alcoholic fatty liver disease (NAFLD) is estimated to be 25% of the global population.[1] Yet, we still have a limited understanding of the natural history and the progression to liver-related outcomes and death. Previous estimates of disease occurrence are based upon simple serological measures and/or imaging[2] and its progression on dual liver biopsy studies.[3] While use of these cohorts has the clear advantage of describing large well-phenotyped samples this inevitably means the samples selected are biased and not representative of the majority of those with NAFLD in the general population or the 'real world'.

Loomba et al[4] performed a valuable retrospective analysis of a large real-world cohort in the United States using specified codes within a sample of Medicare records and calculated the prevalence of disease and the cumulative risk of progression of disease. Out of 10 million patients 5.7% had been diagnosed with NAFLD/Non-alcoholic steatohepatitis (NASH) alone. This is substantially lower than would be expected within the general population of a high-income country. While Medicare is a national health insurance program primarily providing cover for Americans aged 65 years or over it is not representative of the rest of the world population or their health care systems. Their approach to NAFLD ascertainment has not sought to identify those with asymptomatic advanced chronic liver disease, rather individuals have presumably been identified as part of clinical investigation. Additionally, use of the Medicare records introduces an inevitable selection bias due to the cohort being older and therefore more likely to have co-morbidities. These factors increase the risk of disease progression. Loomba et al[4] reported that 39% of patients initially diagnosed with NAFLD/ NASH alone had progression of disease and 12.6% had died after an 8-year period of follow-up. Consequently, the low prevalence they report coupled with the high rate of progression and death may not be representative of the majority of patients with NAFLD in the general population.

Diagnostic studies of early liver disease, using non-invasive tests of liver fibrosis, have demonstrated the feasibility of an alternative approach to measure the prevalence of undiagnosed advanced chronic liver disease. A European consortium is currently implementing a population-based study across eight countries with the aim to screen 21,000 participants to definitively answer this question.[5] Current estimates within the general[6,7] or at-risk community population[8-10] are reported to be between 5.6% and 21.2%.

However the rate of disease progression within this burden of preventable chronic liver disease is still unknown. Future studies reporting longitudinal follow-up of these community-based cohorts which recruited patients with access to free health care at the point of entry are likely to provide a more representative and generalisable estimate of disease progression. Concurrent studies measuring the effect of any intervention will determine if clinical outcomes can be altered in comparison to the natural history of early liver disease. Only following such studies may we have a greater understanding about NAFLD/NASH in the real world.

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LINKED CONTENT

This article is linked to Loomba et al papers. To view these articles, visit https://doi.org/10.1111/apt.15679 and https://doi.org/10.1111/apt.15694.

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REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence and outcomes. *Hepatology*. 2016;64:73-84.
2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274-285.
3. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13:643-654.e9; quiz e39–40.
4. Loomba R, Wong R, Fraysse J, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. *Aliment Pharmacol Ther*. 2020;51:1149-1159.
5. https://www.liverscreen.eu/. Accessed 8/3/2020.
6. Caballería L, Pera G, Arteaga I, et al. High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study. *Clin Gastroenterol Hepatol*. 2018;16(7):1138-1145.e5.
7. Koehler EM, Plompen EPC, Schouten JNL, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: the Rotterdam study. *Hepatology*. 2016;63:138-147.
8. Harman DJ, Ryder SD, James MW, et al. Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography. *Aliment Pharmacol Ther*. 2018;47:504-515.
9. Harris R, Card TR, Delahooke T, et al. Obesity is the most common risk factor for chronic liver disease: results from a risk stratification pathway using transient elastography. *Am J Gastroenterol*. 2019;114:1744-1752.
10. Roulot D, Roudot-Thoraval F, NKontchou G, et al. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. *Liver Int*. 2017;37:1897-1906.

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Editorial: how widespread and serious is non-alcoholic fatty liver disease in the real world? Authors' reply

We thank Dr Harris et al for their Editorial on our recent paper.[1,2] They provided additional context on the urgent need for greater understanding and awareness regarding the clinical burden of NAFLD. In support of this goal, we evaluated a representative sample of the over 50 million individuals with Medicare eligibility and provided a full characterisation of the demographics and comorbidity burden of the diagnosed NAFLD population. In our study, we highlight and contextualise how the real-world under-diagnosis of NAFLD and our focus on diagnosed patients led to inevitable bias in our assessment of the clinical burden of the disease. However, our findings are essential to understand the burden of patients diagnosed under current real-world clinical identification patterns and provide valuable insights on the high risk of disease progression and mortality associated with NAFLD in the elderly population. In addition, our analysis provides valuable data to inform algorithms to identify individuals at a high risk of NAFLD progression early in their disease course when interventions can be applied to reduce their future clinical burdens. This is especially relevant as promising medical interventions for NAFLD are currently under evaluation and review.[3,4]