

NAFLD, Metabolic Syndrome, and the Fight That Will Define Clinical Practice for a Generation of Hepatologists

Elliot B. Tapper, M.D.¹⁻³ and Rohit Loomba, MD, MHSc⁴⁻⁵

1. Division of Gastroenterology and Hepatology, University of Michigan
2. Institute for Healthcare Policy and Innovation, University of Michigan
3. Veterans Affairs Hospital, Ann Arbor
4. Division of Epidemiology, University of California at San Diego
5. NAFLD Research Center, Division of Gastroenterology, University of California at San Diego

Corresponding author:

Rohit Loomba, MD, MHSc
ACTRI Building, 1W202
9452 Medical Center Drive
La Jolla, CA 92037
Ph: 858-246-2201
Email: roloomba@ucsd.edu
Web: <http://fattyLiver.ucsd.edu>

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Nonalcoholic Fatty Liver Disease (NAFLD) is a global epidemic.(1) Worldwide, 1 in 4 people have NAFLD. (2) Further, increasing in parallel with the rising prevalence of obesity and metabolic syndrome, the prevalence and public health impact of NAFLD will worsen.(3) In the coming post-hepatitis C era, NAFLD will be the hepatologist's greatest foe; NAFLD is the fastest growing cause of cirrhosis and hepatocellular carcinoma.(3) At the same time, as is well known, the presence of NAFLD is inextricably linked to cardiovascular risk.(4, 5) Indeed, for patients with NAFLD, cardiovascular complications may prove more common and impactful than liver-related morbidity. Associations between NAFLD and cardiovascular risk, however, have been established with observational data that have neither the power to discern causality nor disentangle cross-sectional from longitudinal effects. Study design matters. At present, the relationship between NAFLD and cardiovascular risk represents a classic chicken-vs-egg problem.

Data are needed to clarify the temporal interaction between NAFLD, advanced liver disease, and cardiovascular risk. Such understanding will guide both the focal points of preventative efforts and the structure of our collaborative relationship with colleagues in primary care, endocrinology, and cardiology for patients at various stages of NAFLD. To this end, Allen and her colleagues present the new data to date from 3,869 patients with NAFLD defined by diagnosis codes with careful exclusion of patients with any codes consistent with viral hepatitis, alcohol use disorder and other liver diseases, matched to 15,209 controls included in the Rochester Epidemiology Project database (1997-2014). At first glance, like all retrospective observational cohort studies, any conclusions are intrinsically limited by selection and information biases. In this case, however, each variable using data that integrates not only billing

codes but also laboratory values (e.g. FIB-4, hemoglobin A1C) and medication utilization (e.g., anti-hypertensives, insulin secretagogues). These features enhance the accuracy of exposure and outcome ascertainment substantially. By combining longitudinal, population-based data with rigorously defined comorbidities, these data raise the bar for epidemiological associations and provide a better picture of how NAFLD and comorbidities fit into a sequence.

This study advances the epidemiology of NAFLD in 2 principal ways. First, the study suggests that NAFLD may be an accelerant for cardiovascular risk. The authors confirm that NAFLD is associated with increased overall mortality but that this risk is driven by the burden of metabolic comorbidities. However, in patients with limited-or-no metabolic comorbidities, NAFLD is significantly associated with death and the development of new comorbidities. Although all patients are more likely to advance through the states of metabolic comorbidity as they age, they show that NAFLD decreases the 'time-in-state' spent by afflicted patients with lower stages of metabolic comorbidity. As comorbidities accrue, the independent effect of NAFLD on mortality declines. Notably, these associations hold when stratified by the presence of cirrhosis. This multi-state transition model is helping in assessing the impact of cardiovascular comorbidities on the mortality associated with NAFLD.

Second, the incidence of NAFLD has risen a staggering 6-fold in less than 20 years. Portending worse outcomes to come, these trends are most acute for adults aged 18-39. Retrospective cohort studies are at risk for trends in clinical practice that may lead to increased detection (e.g more ultrasounds) or increased awareness and resultant case-finding. Importantly, the authors show that the increasing NAFLD incidence was distinct from steady rates of

abdominal ultrasound utilization. The average body mass index of patients with incident NAFLD rose from 1999-2005. This could indicate clinicians actively ordering or interpreting liver enzyme or ultrasound results in the context of increasing awareness of NAFLD in obese patients owing to practice standards modelled by local (Mayo Clinic) hepatologists. However, the average BMI in the population rises from 2005-2014 but not for NAFLD patients, suggesting that, overall, diagnostic trends may not be the sole feature behind these findings. NAFLD may also present in patients with other primary liver diseases and thus the exclusion criteria may underestimate these trends. The patient with cleared hepatitis C and NAFLD, for example, though excluded from this study could experience all the same risks as the included subjects.

This is the time to invest in efforts towards increased awareness, early lifestyle intervention, and optimal multidisciplinary management to identify those at increased risk of death from liver disease as well as cardiovascular disease. The hope, though prospective studies are needed, is that early interventions will reduce the risk of death from both liver disease and cardiovascular disease. Two barriers may obstruct progress. One, though the finding of NAFLD may lead to referral to our clinics, few hepatologists practice in a clinical program equipped to modify cardiovascular risk.⁽⁶⁾ Models for multidisciplinary clinics, effective lifestyle interventions, and efficient collaboration with other specialists in cardiology, endocrinology, and bariatric surgery are rare but needed. Two, it is not clear whether the association between NAFLD and cardiovascular risk has been sufficiently disseminated in the community. This study suggests that NAFLD is increasing in the young and is a marker of impending cardiovascular risk but it is not clear whether this finding is an effective trigger for intensified risk-factor management at the level of community. A referral to Hepatology may be the best

opportunity to start early if we are sufficiently prepared for those who have the progressive form of NAFLD. However, it is likely that minority of these patients will be seen or referred until we study and develop a population-based screening program for advanced fibrosis using non-invasive biomarkers. Outreach to young, asymptomatic, well patients with risk-factors that aim to increase the amount of care provided can be challenging. Physicians may be unaware, patients may not be motivated, and the system may not be prepared. Efforts to increase awareness of and act upon these data are essential but without the infrastructure to address the problem, such efforts may not deliver the desired results.

In our **conceptual diagram**, we lay out how Hepatologists can maximize their impact for populations with and at risk for NAFLD. To address our clinical preparedness for the expected increased volume of referrals for NAFLD, we outline a minimum set of clinical resources including fibrosis risk assessment (including vibration-controlled elastography and magnetic resonance elastography), nutritional consultation or detailed support through carefully selected smartphone apps, and, because patients are less likely to respond to vague exhortations to increased activity, pre-prepared specific recommendations for exercise.⁽⁷⁾ Where multidisciplinary clinics are not feasible, efforts to cultivate steady relationships with specific clinicians in bariatrics/endobariatrics and preventative cardiologists or endocrinologists will serve to streamline referrals and standardize clinical evaluation and recommendations. Finally, hepatologists must be advocates for patients with NAFLD. This will include performing outreach to referring clinicians and securing resources from the hospital system for clinical support and electronic decision supports to facilitate case-finding and linkage to care based on, for example, elevated liver enzymes or radiographic hepatosteatosis.

Now that Allen and colleagues have shined their spotlight on the impact of NAFLD, the next steps are clear. We need to organize, build a team, and fight.

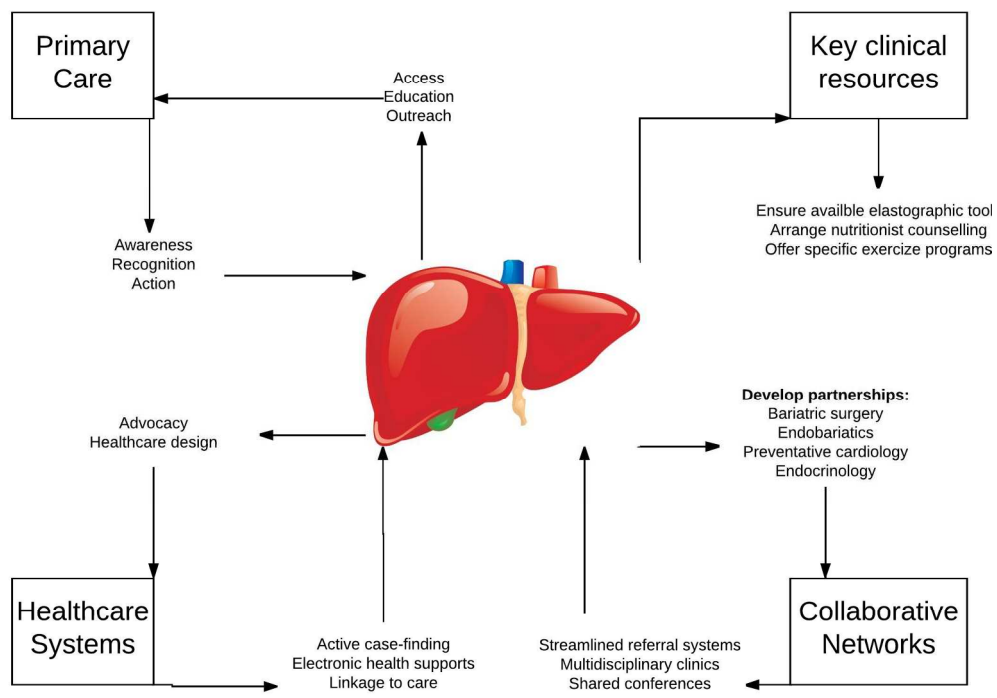
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Figure: The Central Role of the Hepatologist in Coordinated Care for Nonalcoholic Fatty Liver Disease (NAFLD)

Hepatologists are uniquely positioned in the healthcare system in order to optimize the management of patients with NAFLD. In this conceptual diagram, we describe the resources needed and the relationships that should be cultivated in order to enhance clinical care for patients with NAFLD.

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