Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder globally with an increasing burden of liver-related events and cardiovascular disease (CVD). In the past decades, this epidemic has progressed quickly, particularly in regions with rapid Westernization. Currently, NAFLD represents a clinical field possessing several unmet needs. These needs include at least the following: (1) while NAFLD is a metabolic disorder per se, it presents with different phenotypes across gender, age, body mass index, genetic predisposition, race and ethnicity, and other characteristics; (2) there is no reliable biomarker for disease severity or outcome measurement; (3) there are currently no approved drug therapies and no confirmed therapeutic targets; (4) the disease course and outcome remain elusive in terms of disease progression or regression, occurrence of liver-related events or CVD, and the associated survival. In addition, NAFLD is commonly associated with metabolic abnormalities, with CVD as its leading cause of death. Therefore, adverse outcome prediction, including liver- and non–liver-related events, is the major challenge in a clinical setting. The clarification of the outcome prediction will pave the way not only for assessing the risks for disease progression but also for disease surveillance programs. The effort is no doubt beyond the lessons learned from viral hepatitis infection.

Chhatwal and colleagues present their estimates of mortality using a simulator including age, sex, and fibrosis score. The construction of the method was based on the current evidence and clinical trial data. The simulator incorporated liver-related mortality, non–liver related mortality, and background mortality. It then provided the estimated long-term outcomes in a graphical format. The authors validated the results with the largest-ever study of biopsy-proven NAFLD from Europe with satisfactory correlation, indicating that fibrosis stage had the strongest association with long-term outcomes and mortality. In addition, they found a nonlinear increase in adverse outcomes with increasing fibrosis stage. The largest increase in mortality—both liver and non-liver—was observed when patients progressed from F3 to F4. They concluded that the NAFLD Simulator can be used as an educational tool to increase awareness of the health consequences of NAFLD among patients and practitioners.

The first implication of the study was that it demonstrated fibrosis stage was the major factor associated with long-term adverse outcomes and survival. The results of the mathematical model were concordant with previous large observational studies. In addition, the greatest increase in mortality in those patients progressed from F3 to F4 may elucidate the disease course. The finding also provided evidence for surveillance design among the high-risk patients. Second, taking the risk evaluation for CVD an example, several calculators have been developed to estimate long-term adverse outcomes for CVD, including coronary heart disease and cerebrovascular disease. To advance the preventive and potential treatment goals in NAFLD, it is necessary to calculate the long-term risks for liver and non-liver events by using a validated risk calculator. Third, the simulator could be used as an educational tool for patients and practitioners to increase disease awareness. This is an important consideration for a metabolic liver disorder that is mostly without overt symptoms.

Some issues remain despite the achievements of the study. The disease spectrum of NAFLD includes different states, namely from simple steatosis, nonalcoholic steatohepatitis (NASH), NAFLD-related fibrosis stages to decompensated cirrhosis and hepatocellular carcinoma. The transition between disease states has not been fully clarified, which may mainly affect the performance of the simulator. Some assumptions of the study remain to be rigorously validated. For example, those patients with F4 stage were not assumed to have disease regression or NASH.

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resolution. In addition to age, gender, and fibrosis stage, several factors associated with long-term outcome also exist, such as race and ethnicity, geographic location, other concomitant diseases, and lifestyle modifications. Therefore, the vigorous and active validation of the model is mandatory for extending the scope of risk stratification in NAFLD. Moreover, current surveillance of liver-related events and CVD for patients with NAFLD is lacking, particularly among those with F4 stage. The exploration of evidence-based surveillance programs in patients with NAFLD is essential for clinical management.

REFERENCES