Modeling NAFLD-Related Disease Progression among the PITER SVR12 Cohort

C. Estes[1], L. Kondili[2], M.G. Quaranta[2], A. Craxi[3], S. Petta[3], M. Masarone[4], F.P. Russo[5], M. Siciliano[6], B. Coco[7], R. Filomia[8], H. Razavi[1]

[1]Center for Disease Analysis Foundation, Lafayette, United States; [2]Istituto Superiore di Sanità, Rome, Italy; [3]University of Palermo, Palermo, Italy; [4]Salerno University, Salerno, Italy; [5]University of Padua, Padua, Italy; [6]Catholic University of Rome, Rome, Italy; [7]University Hospital of Pisa, Pisa, Italy; [8]University Hospital of Messina, Messina, Italy

INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is frequent among patients with chronic hepatitis C virus (HCV) infection (1)
  - The cured HCV population may be susceptible to worsening of NAFLD and development of nonalcoholic steatohepatitis (NASH), due to advancing age (2) combined with high levels of obesity and metabolic risk factors (3)
- The prevalence of NAFLD is increasing across Europe (4) and relatively high rates of fibrosis have been observed in the general adult population of Italy, after excluding cases of viral hepatitis and excessive alcohol consumption (5)
- Liver disease among the Italian population is often multifactorial, with historically high levels of HCV infection, co-existing with metabolic disorder (3, 6)
- Prevalence of NAFLD and NASH in Italy is recognized as a cause of advanced liver disease (7), including hepatocellular carcinoma (HCC), and liver mortality (7, 8)
- An urgent need exists to understand risk factors for ongoing disease progression among patients cured of HCV infection
- Modeling can help assess how continued liver disease progression would alter the outcome of HCV cure

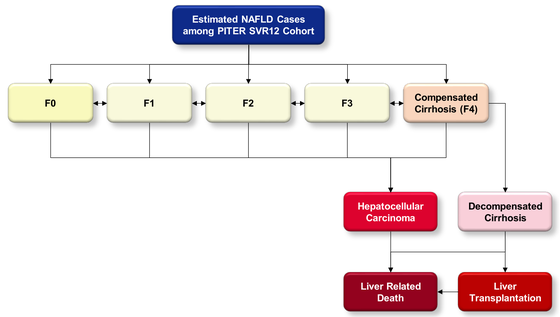
AIM

- Use NAFLD modelling to simulate morbidity and mortality among a representative cohort of HCV cured patients

METHOD

- A model of NAFLD-related disease burden was applied to participants in the PITER cohort (9) who achieved sustained viral response at 12 weeks (SVR12) to quantify potential continued disease progression
- Estimated prevalence of NAFLD in the cohort was based on previous estimates (10), and adjusted for the increased age of the cohort as compared to the general Italian population
- Estimated prevalent NAFLD cases entered the model based on PITER cohort data for sex, age group, disease stage and year at the time of SVR12 achieved after DAA therapy, and were followed over time through 2030
- Cases were tracked by fibrosis stage (Figure 1) with mortality tracked at every stage classified as background, excess cardiovascular and liver-related
  - Model fibrosis transition rates varied by sex, age group, and BMI class of PITER cohort participants
  - Background mortality rates were adjusted to account for incremental increased mortality related to cardiovascular disease (11, 12)
  - NASH cases were estimated based on the modeled distribution of NAFLD cases, with most F0 cases assumed to be simple steatosis, and the likelihood of NASH increasing with advancing fibrosis stage
  - Continued fibrosis progression was followed, and subsequent morbidity and mortality were estimated
    - Cumulative incident cases of decompensated cirrhosis, HCC, and liver-related deaths were calculated for the cohort

Figure 1. NAFLD Disease Progression Model



CONTACT INFORMATION

info@cdafound.org

RESULTS

- 2394 patients achieved SVR12 during 2014-2018 in the PITER cohort dataset, after excluding cases with excessive alcohol consumption
- An estimated 670 patients were classified as NAFLD based on modeled prevalence for Italy during 2014-2018 (30% of cohort)
  - 46% were male due to higher rates of exclusion among males due to alcohol consumption
- Over 80% of the cohort entered the model at fibrosis stage ≥F2 and 65% were classified as F4
- Modeled NAFLD cases peaked at 640 cases in 2017, declining 40% to 380 cases by 2030
- Median age was estimated at 66 years in 2018, increasing to 74 years by 2030
- The proportion of model cases classified as NASH peaked in 2015 at 97% as large numbers of advanced cases entered the model, declining to 84% in 2030 due to mortality among advanced fibrosis cases
- F0-F1 cases comprised 14% of the modeled cases in 2018, increasing to 22% by 2030, due to lower rates of disease progression and related mortality among this population (Figure 2)
  - In 2018, 86% of cases were classified as ≥F2 (530 cases), 77% as ≥F3 (480 cases) and 64% as F4 (400 cases), reflecting the high burden of disease attributable to previous viral infection
  - By 2030, the proportion of cases classified as ≥F2 declined to 78% (300 cases) of total prevalent NAFLD, due to lower mortality among participants with no/mild fibrosis. Likewise, the proportion of cases estimated as ≥F3 declined to 70% and F4 cases declined to 56% of the total
- There were an estimated 140 incident decompensated cirrhosis and 15 incident HCC cases from 2014-2030 (Figure 3)
  - Incident decompensated cirrhosis decreased 48% from 12 cases in 2018 to 7 cases in 2030
  - Incident HCC decreased 48% from 1.3 cases in 2018 to 0.7 cases in 2030
- There were an estimated 320 total deaths among the model cohort by 2030
  - 160 deaths were classified as background mortality (including excess cardiovascular mortality)
    - 13% of background deaths were classified as excess cardiovascular mortality
  - 160 deaths were classified as liver-related mortality, largely due to the advanced stage at which patients entered the NAFLD model
  - Liver deaths peaked at 24 deaths in 2019, declining 34% to 8 deaths in 2030

Figure 2. Prevalent NAFLD Cases by Fibrosis Stage – SVR 12 PITER Cohort, 2014-2030

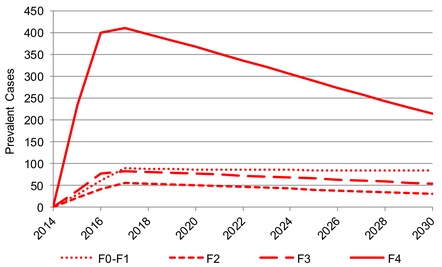
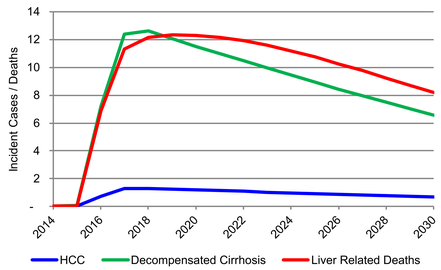


Figure 3. Incident HCC, Decompensated Cirrhosis, and Liver Deaths – SVR 12 PITER Cohort, 2014-2030



CONCLUSIONS

- In the presence of NAFLD, liver disease progression may continue among a portion of the cured HCV population
- Achieving SVR results in better health outcomes, but more research is needed to identify patients at risk for continued liver disease progression (13, 14)
- Liver disease progression was evaluated according to the specific fibrosis stage of each patient at the time of SVR
  - A limitation of this modeling is the uncertainty around the likelihood of continued fibrosis progression among cured cases with advanced fibrosis and metabolic risk factors
  - Improved diagnostic technologies are needed to quantify the probability of NASH and related disease among post-SVR cases
- Results support increased screening and prevention efforts for HCV patients who achieve SVR but in whom other risk factors for liver disease progression could not be excluded
- NAFLD modeling strongly supports the impact of HCV treatment among early stage (F0-F2) cases on preventing potential progression to advanced disease, which are associated with high rates of mortality and economic costs (15, 16)

REFERENCES

1. Sanyal AJ. Review article: Non-alcoholic fatty liver disease and hepatitis C - Risk factors and clinical implications. Alimentary Pharmacology and Therapeutics, Supplement. 2005;22(2):48-51.
2. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver International. 2011;31(SUPPL. 2):30-60.
3. ISTAT. Italy in figures, 2015. Italian National Institute of Statistics 2015.
4. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69(3):718-35.
5. Petta S, Di Marco V, Pipitone RM, Grimaudo S, Buscemi C, Craxi A, et al. Prevalence and severity of nonalcoholic fatty liver disease by transient elastography: Genetic and metabolic risk factors in a general population. Liver international : official journal of the International Association for the Study of the Liver. 2018.
6. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet Gastroenterology and Hepatology. 2017;2(3):161-76.
7. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology. 2005;42(1):44-52.
8. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis. 2010;28(1):155-61.
9. Kondili LA, Vella S. PITER: An ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy. Dig Liver Dis. 2015;47(9):741-3.
10. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018;69(4):896-904.
11. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Nonalcoholic Fatty Liver Disease and Risk of Incident Cardiovascular Disease: A Meta-Analysis of Observational Studies. J Hepatol. 2016.
12. Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, et al. Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity. Clin Gastroenterol Hepatol. 2017;15(10):1604-11.e1.
13. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. Clin Infect Dis. 2015;61(5):730-40.
14. Tachi Y, Hirai T, Miyata A, Ohara K, Iida T, Ishizu Y, et al. Progressive fibrosis significantly correlates with hepatocellular carcinoma in patients with a sustained virological response. Hepatol Res. 2015;45(2):238-46.
15. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43(4):682-9.
16. Kondili LA, Romano F, Rolli FR, Ruggeri M, Rosato S, Brunetto MR, et al. Modeling cost-effectiveness and health gains of a "universal" versus "prioritized" hepatitis C virus treatment policy in a real-life cohort. Hepatology. 2017;66(6):1814-25.