**Comparing predicted probability of hepatocellular carcinoma in cirrhosis patients to the general population to promote screening uptake**

AUTHORS: Hamish Innes1,2,3; Victoria Hamill1,2; Scott A McDonald1,2; Peter C Hayes4; Philip Johnson5; John F Dillon6; Jen Bishop2; Alan Yeung1,2; April Went2; Stephen T Barclay7; Andrew Fraser8,9; Andrew Bathgate5; David J Goldberg1,2; Sharon J Hutchinson1,2

AFFILIATIONS:

1. School of Health and Life Sciences; Glasgow Caledonian University. Glasgow UK.
2. Public Health Scotland, Glasgow, UK.
3. Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK.
4. Royal Infirmary of Edinburgh, Edinburgh, UK
5. Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK.
6. Division of Molecular and Clinical Medicine; School of Medicine, University of Dundee, UK.
7. Glasgow Royal Infirmary, Glasgow, UK.
8. Aberdeen Royal Infirmary, Aberdeen, UK.
9. Queen Elizabeth University Hospital, Glasgow, UK

WORD COUNT: 2,800 (excluding references, abstract and tables)

CONFLICTS OF INTEREST: There are no conflicts of interest to disclose.

FINANCIAL SUPPORT: This study has two main sources of financial support: a) Medical Research Foundation (Grant ID:C0825); and b) Public Health Scotland.

AUTHOR CONTRIBUTIONS: a) Study concept: all authors; b) study design: HI, SM, SJH, VH; c) acquisition of data: all authors; d) resources: all authors; e) Statistical analysis: HI, SM, SJH; VH; f) drafting manuscript: HI, SM, SJH, VH; g) critical revision of manuscript: all authors.

CORRESPONDING AUTHOR INFORMATION:

Dr Hamish Innes; Glasgow Caledonian University, George Moore Building, Room M403A; Cowcaddens Road; G4 0BA. <Tel:0141-5332950>; Email:Hamish.innes@gcu.ac.uk

DATA AVAILABILITY STATEMENT:

The data used in this study are not publicly available, but can be acquired through successful application to the Public Benefit and Privacy Panel for Health and Social Care (<https://www.informationgovernance.scot.nhs.uk/pbpphsc/home/for-applicants/> ).

ABSTRACT

BACKGROUND:

Risk scores estimating a patient’s probability of a hepatocellular carcinoma (HCC) diagnosis are commonplace, but are difficult to interpret in isolation. Here, we compared the predicted HCC probability for individuals with cirrhosis and cured hepatitis C to the general population (GP).

METHODS:

All cirrhosis patients achieving sustained viral response (SVR) in Scotland through to April 2018 were included (N=1803). The predicted three-year probability of HCC at time of SVR achievement was determined using the aMAP prognostic model. GP data on the total number of incident HCCs in Scotland, stratified by demographics, were obtained from Public Health Scotland.

Predicted HCC risk for cirrhosis SVR patients was compared to GP incidence using two metrics: 1) The three-year incidence ratio: i.e. three-year predicted probability for a given patient divided by the three-year probability in GP for the equivalent demographic group; and 2) The three-year absolute risk difference: the three-year predicted probability minus the three-year probability in the GP).

RESULTS:

The mean predicted three-year HCC probability among cirrhosis SVR patients was 3.64% (range: 0.012%-36.12%). Conversely, the three-year HCC probability in the GP was much lower, ranging from <0.0001% to 0.25% depending on demographics. The mean three-year incidence ratio was 410, ranging from 5 to >10,000. The mean three-year absolute risk difference was 3.61%, ranging from 0.012 to 35.92%. An online HCC-GP comparison calculator for use by patients/clinicians is available at: <https://thrive-svr.shinyapps.io/RShiny/>

CONCLUSIONS:

Comparing a patient’s predicted HCC probability to the general population may help clinicians communicate risk information and encourage screening uptake.

HIGHLIGHTS:

WHAT IS KNOWN?

* Cirrhosis patients are at high risk of hepatocellular carcinoma (HCC).
* Guidelines recommend HCC screening for all cirrhosis patients - however, uptake is very low.
* Validated risk scores are available for predicting a patient’s future probability of HCC.

WHAT IS NEW HERE?

* We compared predicted HCC probability to the general population (GP), in a national cohort of cirrhosis patients with cured hepatitis C.
* The predicted HCC probability was higher than the GP in every single case.
* On average, the predicted probability was 410 times greater than equivalent probability in the GP.
* Thus, GP comparisons may help clinicians convey HCC risk and promote uptake of screening.

INTRODUCTION:

Patients with hepatitis C related cirrhosis remain at risk of hepatocellular carcinoma (HCC) even after virological cure [1-6]. Cohort studies indicate the average risk is between 1.5 and 2.7 HCCs per 100 person-years of follow-up.[1-6] Detection of HCC at an incipient stage is the most critical factor governing survival after HCC diagnosis, and thus, clinical guidelines recommend all cirrhosis patients receive biannual screening.[7-9] Despite robust observation evidence associating screening uptake with longer post-HCC survival,[10] adherence to this recommendation is poor.[11.12] For example, in a recent systematic review of population-based studies, Woolf et al reported that only 9.8% of patients received two screening events per year. [12]

Prognostic models are now available that can estimate a cirrhosis patient’s future probability of HCC occurrence.[13-16] Some of these models have been externally validated in independent datasets [13,17], which is the acid test of a model’s performance and a pre-requisite for clinical use [18]. In theory, this presents an opportunity to tailor clinical management to a patient’s specific risk profile. In practice, interpreting an individual’s probability of HCC (i.e. as “low” or “high”) is challenging, especially given variable risk literacy levels among patients and clinicians [19,20]. For this reason, comparing an individual’s HCC probability against the equivalent probability in the general population (GP) - i.e. a relatable benchmark - may aid clinical interpretation of HCC risk. Another open question is whether GP comparisons could identify a subset of patients for whom screening is not justified. For example, it is conceivable that some cirrhosis patients, after being cured of their HCV, could have a predicted HCC incidence that is equivalent or similar to the GP. In this scenario, such patients would be unequivocal candidates for avoiding HCC surveillance. This question is pertinent to the ongoing debate around individualised screening for HCC [21,22].

Differences between HCC risk in cirrhosis patients and the general population have not been well explored by previous studies, and there are no risk tools available to facilitate individual-level comparisons Thus, the goals of this study were two-fold. Firstly, to compare the predicted three-year probability of HCC in a representative cohort of Scottish cirrhosis patients with cured hepatitis C to the GP. Second, to create an online GP comparison tool to enable individual patient and clinicians to compare a predicted HCC probability to the equivalent probability in the GP.

METHODS:

1.0 STUDY DESIGN:

We performed a cross-sectional study to compare the predicted HCC 3-year risk in cirrhosis SVR patients to the background risk of HCC in the GP.

2.0 DATA SOURCES:

2.0.1 CIRRHOSIS PATIENTS WITH CURED HEPATITIS C:

The Scottish hepatitis C virus (HCV) clinical database is a retrospective cohort study >25,000 patients in Scotland who have attended a specialist liver clinic appointment for care/management of chronic HCV infection. [23,24] This data source records information collected during routine clinical care such as details of antiviral treatment episodes and the results of laboratory tests. It has also been linked to national health registries in Scotland, including the in-patient hospitalisation (SMR01), cancer (SMR06) and mortality registers. Approval to link these registries to the Scottish HCV clinical database was granted by the Privacy Public Benefit Panel for Health and Social in NHS Scotland (application number:1516-0457).

2.0.2 GENERAL POPULATION DATA

HCC incidence in the Scottish GP was ascertained using data provided by Public Health Scotland. Specifically, an anonymised dataset comprising of all HCC-related deaths, hospital admissions and cancer registrations in Scotland between 1990 and 2020 was obtained from Public Health Scotland. This file also included corresponding information on the individual’s age, gender and the year of event. HCC-related events were identified by the presence of an ICD10:C22.0 or ICD9:155.0 code in any causal/diagnostic position. These data were used in conjunction with mid-year population estimates to generate annualised probability of HCC in the GP

3.0 INCLUSION/EXCLUSION CRTIERA:

All cirrhosis patients achieving sustained viral response (SVR) in Scotland through to April 2018 were included in this study (N=1803). Where a patient had more than one treatment episode resulting in SVR, then the first episode was selected. Patients with a diagnosis of HCC before SVR achievement were excluded. Participants were also excluded if they were missing the data for one or more components of the aMAP score (i.e. age, gender, bilirubin, albumin or platelet count).

Liver cirrhosis was defined as compensated or decompensated cirrhosis diagnosed during routine clinical investigation. Cirrhosis diagnoses were typically made following liver biopsy; transient elastography; abdominal ultrasound; clinical examination; and routine liver function tests, according to clinical guidelines at that time.

4.0 PREDICTED HCC RISK AT SVR ACHIEVEMENT

The aMAP prognostic model was used to generate the 3-year predicted risk of HCC at the time of SVR achievement for each patient in our dataset. [13]

Thus 3-year risk was calculated according to the following formula: 1-S0(t)exp(aMAP linear predictor)

Where t= 3 years, and S0(t) refers to the baseline survival estimate at 3 years, which is 0.992 as specified in the original publication [15]. The aMAP linear predictor is calculated by the formula: ((0.06\*age) +(0.89\*sex) +(0.48\*ALBI score) -(0.01\*platelet count)). In this formula, “sex” is 1 for males and 0 for females. ALBI refers to the albumin-bilirubin score [25]. Data on age, sex, ALBI and platelet count, were all derived from the Scottish HCV clinical database. For routine liver blood tests (i.e. albumin, bilirubin and platelet count etc), we selected the most recent test on or prior to the start of antiviral treatment. Tests conducted more than twelve months before initiating treatment were excluded. Individuals with an unknown/missing aMAP score were excluded from our final study population (i.e. a listwise deletion approach).

In this study, we used *predicted* risk at time of SVR achievement rather than *observed* risk. This is because observed risk, by definition, is not known at the time of SVR achievement. Thus, HCC screening decisions must be made on the basis of predicted risk. Nevertheless, in previous work on this cohort, we showed that aMAP exhibited close agreement between predicted and observed HCC risk [17]. As a result, predicted and observed risk can be considered essentially equivalent to one another.

5.0 HCC INCIDENCE IN GENERAL SCOTTISH POPULATION

HCC incidence in the Scottish GP was ascertained using data provided by Public Health Scotland, in conjunction with publicly available mid-year population estimates.

Specifically, an anonymised dataset comprising of all deaths, hospital admissions and cancer registrations occurring in Scotland between 1990 and 2020 that were related to HCC was obtained from Public Health Scotland. This file also included corresponding information on the individual’s age, gender and the year of event. HCC-related events were identified by the presence of an ICD10:C22.0 or ICD9:155.0 code in any causal/diagnostic position.

We calculated the number of first time HCC presentations per year, according to age group (<40; 40-49; 50-59; 60-69;70-79; and 80+ years), gender (male and female), and calendar period (2000-2004; 2005-2009; 2010-2014; 2015+). In the common scenario where a patient had multiple HCC presentations, only the index (i.e. first) presentation was included to avoid double counting.

Data on mid-year population estimates were then downloaded from National Records of Scotland website. The number of incident HCC presentations in each age, sex and calendar period group, were divided to by mid-year population estimates for that particular group to yield the annual probability of HCC in the GP. This was then multiplied by three to obtain the 3-year HCC probability in the GP.

6.0 COMPARING PREDICTED RISK TO GENERAL POPULATION RISK

Each patient’s predicted three-year HCC probability was then compared with the expected three-year probability in the GP for someone of the equivalent age group, sex and calendar year period. In this way, all comparisons are like-for-like with respect to age, sex and calendar period.

Two specific metrics were used to compared predicted risk with expected risk (i.e. risk from GP):

1. The three-year incidence ratio: The 3-year predicted probability divided by equivalent probability for the GP.
2. The three-year absolute risk difference: The 3-year predicted probability minus the equivalent probability in the GP.

These metrics were assessed using descriptive statistics, scatter plots and percentile plots.

7.0 DEVELOPMENT OF ONLINE TOOL:

An online web-based tool was developed using R Shiny [26] to support individual-level comparisons between predicted and GP-expected risk. The user inputs information on albumin, bilirubin, gender, age and platelet count. Based on this information, the tool calculates the patient’s aMAP score, and uses icon array diagrams [27,28] to convey their HCC risk relative to the corresponding risk in the GP.

RESULTS:

DERIVATION AND CHARACTERISTICS OF FINAL SAMPLE:

2245 patients with cirrhosis and SVR were identified, of which 106 were excluded due to HCC onset before achieving SVR. A further 336 patients were excluded due to missing one or more components of the aMAP score (i.e. age, albumin, gender, bilirubin or platelet count). Thus, our final sample was comprised of 1803 patients (Figure 1).

In the final sample, the mean age was 50.3 years and 74.1% were males (see Table 1). The vast majority achieved SVR in the year 2015-2020 (77.3%) or 2010-2014 (16.3%). 59.0% achieved SVR via an interferon-free regimen. Roughly one patient in ten had decompensated cirrhosis at the time of achieving SVR (10.8%). Half the cohort had past HCV genotype 3 infection (51.0%), and about three-quarters had a history of injecting drug use (75.9%).

PREDICTED HCC PROBABILITY

The mean and median aMAP score was 57.1 and 57.5, respectively (range: 21.6-77.3). The mean and median predicted three-year probability was 3.64% and 2.37%, respectively (range was 0.1% to 36.1%) (Table 2).

There was considerable heterogeneity in predicted three-year HCC probability from one patient to the next (see Figure 1). For example, the mean three-year predicted probability was 18 times higher in the top quintile (9.8%) versus the lowest quintile (0.5%) (see Figure 2).

HCC INCIDENCE IN THE GENERAL POPULATION

A total of 9048 incident HCC events were identified in Scotland between the years 1990 and 2020. The three-year probability of HCC ranged from 2.4 x 10-6% in females under 40 years in 2005-2009, up to 0.20% in males aged 80+ in 2015-2020 calendar period (see Table S1).

HCC INCIDENCE IN CIRRHOSIS PATIENTS VERSUS GENERAL POPULATION

The mean and median three-year incidence ratio was 410 and 187, respectively. The ratio ranged widely from a minimum of 4.6 to a maximum of >10,000 (see Figure 3). The highest ratios were found in the under 40s age group where HCC incidence in GP at the lowest (see Table S2).

The mean and median three-year absolute risk difference was 0.0361 (i.e. 3.61%) and 0.0235 (i.e. 2.35%), respectively. However, this varied markedly from 0.00012 to 0.359.

Figure 4b indicates there a negligible difference between a patient’s three-year absolute risk difference and their three-year predicted risk. i.e. the mean difference between these two quantities was -0.00025, ranging from -2.4 x 10-6  to 0.002.

ONLINE RISK COMPARISON TOOL:

An online risk app is available at “<https://thrive-svr.shinyapps.io/RShiny/>”. It is intended for use by clinicians to convey HCC risk relative to the GP at an individual patient level (see Figure 5).

DISCUSSION:

As the prospect of HCV elimination approaches, a key challenge to the clinical community is the management of those who are cured (of HCV) but have a residual risk of HCC. Critical to this is ensuring that cured cirrhosis patients understand the risk of HCC and are provided with appropriate screening. To this end, we have developed a novel HCC-GP comparison tool, enabling clinicians to frame a patient’s three-year HCC probability against the equivalent probability in the GP. Our hope is that this tool will springboard patient-clinician discussions about HCC risk, and could mitigate low screening uptake (e.g. by highlighting what in most cases are starkly elevated risk profiles relative to the GP). In the future, the scope of our tool could be extended; for example, by incorporating GP data from countries beyond Scotland and by including other relevant benchmarks – all with a view to improving the interpretability of a patient’s predicted HCC risk profile.

Our results also shed light on the breadth of HCC risk profiles apparent among patients with cirrhosis and cured HCV. For example, we found that there is approximately a twenty-fold difference between the 3-year HCC probability for patients in the lowest risk quintile (i.e. 0.5%) and the 3-year HCC probability for patients in the highest risk quintile (i.e. ~10%). This risk diversity is incongruent with the uniformity of clinical guidelines, which recommend the same screening approach for all cirrhosis patients [7-9]. At the same time, what is clear from this study is that all patients – even those at lowest risk - have a considerably higher risk of HCC compared to the background population. Indeed, the minimum 3-year incidence ratio was 4.6 (mean of 410), and for the most part, a patient’s 3-year absolute risk difference was effectively the same as their 3-year predicted risk. Overall therefore, we were not able to identify a patient subgroup who exhibited a similar HCC risk profile to the GP – as was our hope when we started this study. Thus, our GP comparison tool cannot be used to rule out screening in selected patients (i.e. on the basis that a patient’s predicted HCC probability is no higher than the background population).

This study is a preliminary attempt to bridge the gap between making a HCC risk prediction and translating this prediction into a clinical decision. More sophisticated methodological approaches and frameworks are urgently needed to support this translation process. One option is to use Markov simulation modelling to weigh the benefits of screening against the harms. This type of study has previously been used to help translate a predicted 10-year risk of cardiovascular disease into a decision rule for prescribing statin therapy [29]. The same principles could arguably be applied to a HCC screening context. Another option is to use health economics to inform HCC screening decisions. It is well known that the cost effectiveness of HCC screening is closely related to HCC incidence (i.e. screening becomes more cost effective as HCC incidence increases). Economic evaluations can pinpoint the HCC incidence threshold below which screening ceases to be cost effective, which could provide a basis for a screening decision rule. However, there are likely to be challenges around the acceptability and validity of this approach. For example, health related quality of life estimates used in current economic assessments do not relate very closely to contemporary cirrhosis patients or patients with HCC. [30,31] Further, existing attempts to estimate this incidence threshold appear to vary considerably – i.e. from 0.4% HCCs per year [30] to 1.5% HCCs per year [31].

Our study has a number of strengths. Firstly, it is the first study to compare predicted HCC incidence to the background population. Moreover, we have performed this comparison using a large and generalisable cohort of cirrhosis SVR patients from Scotland. The creation of an online App is also another strength, which may facilitate HCC risk discussions between patient and clinician. Notable limitations of this study are as follows. Firstly, comparisons to the general population were adjusted only for age, sex and calendar period. Unfortunately, we did not have data on HCC incidence rates in the GP according to the Scottish Index Multiple Deprivation. As a result, we may have slightly over-estimated the differences between HCC risk in cirrhosis patients compared to the GP. However, we think this is unlikely to change the broad picture or our headline conclusions. Secondly, our analysis was based on data from Scotland, and it is unclear how generalisable our findings will be to other countries and settings. Third, our analysis did not include pre-cirrhosis patients with Metavir F3 fibrosis, which EASL and APASL guidelines (but not AASLD) guidelines recommend should receive HCC screening after SVR achievement. [32] It would be worth repeating the present analysis on a cohort of F3 patients, as HCC incidence may be more comparable with GP levels in this patient group. Fourth, screening for HCC in our cohort of cirrhosis SVR patients will have been much higher than in the general population. This could have led to an ascertainment bias, particularly if there is a potential for HCC deaths to be misattributed to other causes. This issue is not well understood but could potentially have led us to overstate the difference in HCC incidence between our cohort and the general population.

In summary, patients with cirrhosis and SVR exhibit highly diverse risk profiles for HCC. Nonetheless, all patients – even those at lowest risk – have a higher probability of HCC than the general population. Thus, although GP comparisons cannot be used to identify a “low” risk subgroup that could avoid screening, they may still be useful for communicating risk information to patients and mitigating low screening uptake in high risk patients.

**REFERENCES:**

[1 El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in veterans with hepatitis C virus infection. Hepatology. 2016;64:130-7.

[2] Innes H, Barclay ST, Hayes PC, Fraser A, Dillon JF, Stanley A, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: Role of the treatment regimen. J hepatol 2018;68:646-654

[3] van der Meer AJ, Feld JJ, Hofer H, Almasio PL, Calvaruso V, Fernandez-Rodriguez CM, et al. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol. 2017; 66:485-493.

[4] Pon M, Rodriguez-Tajes S, Esteban JI, Marino Z, Vargas V, et al. Non-invasive prediction of liver-related events in patients with HCV-associated compensated advanced chronic liver disease after oral antivirals. J Hepato. 2020;72:472-480.

[5] Ioannou GN, Beste LA, Green PK, Singal AG, Tapper EB, Waljee AK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. Gastroenterology. 2019;157:1264-1278.

[6] Negro F. Residual risk of liver disease after hepatitis C virus eradication. J Hepatol. 2021;74:952-963.

[7] EASL clinical practice guidelines: management of hepatocellular carcinoma.. J hepatol. 2018;69:182-236.

[8] Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.

[9] Kanda T, Lay GKK, Wei L, Moriyama M, Yu-M-L, Chuang W-L, et al. APASL HCV guidelines of virus-erradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. Hepatol Int 2019;13:649-661.

[10] Singal AG, Pillai A, Tiro J. Early Detection, Curative Treatment, and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis: A Meta-analysis. *PLoS Med*. 2014;11(4). doi:10.1371/journal.pmed.1001624

[11] Yeo YH, Hwang J, Jeong D, Dang N, Kam LY, Henry L, et al. Surveillance of patients with cirrhosis remains suboptimal in the United States. J Hepatol. 2021. 75: 856-864.

[12] Wolf E, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of hepatocellular carcinoma surveillance in patients with cirhrosis: a systematic review and meta-nalysis. Hepatology. 2021;73:713-725.

[13] Fan R, Papatheodoridis G, Sun J, Innes H, Toyoda H, Xie Q, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol. 2020;73:1368-1378.

[14] Sharma SA, Kowgier M, Hansen BE, Brouwer WP, Maan R, Wong D, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol. 2018;68:92-99.

[15] Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. J Hepatol. 2018;69:1088-1098.

[16] Ganne-Carrie N, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Nomogram for individualised prediction of hepatocellular carcinoma occurrence in hepatitis C virus cirrhosis (ANRS CO12 CirVir). Hepatology. 2016;64:1136-1147.

[17] Innes H, Jepsen P, McDonald S, Dillon J, Hamill V, Yeung A, et al. Performance of models to predict hepatocellular carcinoma risk among UK patients with cirrhosis and cured hepatitis C infection. JHEP Reports. 2021. 3:100384.

[18] Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162:W1-73.

[19] Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. BMJ. 2012; 15:344:E1602.

[20] Friedeerichs H, Birkenstein R, Becker JC, Marschall B, Weissenstein A. Risk literacy assessment of general practitioners and medical students using the Berlin numeracy test. BMC Fam Pract. 2020;21:143.

[21] Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. Gastroenterology. 2019;157:54-64

[22] Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol. 2018;68:526-549

[23] McDonald SA, Hutchinson SJ, Innes HA, Allen S, Bramley P, Bhattacharyya, et al. Attendance at specialist hepatitis clinics and initiation of antiviral treatment among persons chronically infected with hepatitis C: examining the early impact of Scotland’s hepatitis C action plan. J Viral Hepat. 2014;21:366-76.

[24] McDonald SA, Innes HA, Hayes PC, Dillon JF, Mills PR, Goldberg DJ, et al. What is the impact of a country-wide scale-up in antiviral therapy on the characteristics and sustained viral response rates of patients treated for hepatitis C? J Hepatol. 2015;62:262-268.

[25] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach – The ALBI grade. J Clin Oncol. 2015;33:550-558.

[26] Chang W, Cheng J, Allaire JJ, Siever C, Schloerke B, Xie Y, et al. Shiny: web application framework for R. 2021. Available at: https://CRAN.R-project.org/package=shiny

[27] Garcia-Retamero R, Galesic M, Giderenzer G. Do icon arrays help reduce denominator neglect? Med Decis Making. 2010;30:672-84.

[28] Fagerlin A, Zikmund-Fisher BJ, Ubei PA. Helping patients decide: ten steps to better risk communication. J Natl Cancer Inst. 2011;103:1436-43.

[29] Yebyo HG, Aschmann HE, Puhan MA. Finding the balance between benefits and harms when using statins for primary prevention of cardiovascular disease: A modelling study. Ann Intern Med. 2019;170:1-10.

[30] Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: An assessment of benefits and harms. Am J Gastroenterol. 2020:115:1642-1649.

[31] Zangneh HF, Wong WL, Sander B, Bell CM, Mumtaz K, Kowgier M, et al. Cost effectiveness of hepatocellular carcinoma surveillance after a sustained virologic response to therapy in patients with hepatitis C virus infection and advanced fibrosis. Clin Gastroenterol Hepatol. 2019;17:1840-1849.

[32] D’Ambrosio R, Ioannou GN. Hepatocellular carcinoma risk, outcomes, and screening after hepatitis C eradication. Hepatol Commun 2021;5:1465-1468.

















