European Journal of Internal Medicine 94 (2021) 6–14

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Should we continue surveillance for hepatocellular carcinoma and gastroesophageal varices in patients with cirrhosis and cured HCV infection?

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ARTICLE INFO

Keywords:
Direct-acting antivirals
Viral hepatitis
Hepatitis C
Cirrhosis
Surveillance
Variceal bleeding

ABSTRACT

Hepatocellular carcinoma (HCC) and variceal bleeding are among the most common causes of liver-related mortality in patients with hepatitis C virus (HCV)-induced cirrhosis. Current guidelines recommend HCC and gastroesophageal varices (GEV) surveillance in patients with HCV infection and cirrhosis. However, since the recent introduction of direct-acting antivirals, most patients with cirrhosis are now cured of their chronic HCV infection. As virological cure is considered to substantially reduce the risk of cirrhosis-related complications, this review discusses the current literature concerning the surveillance of HCC and GEV in patients with HCV-induced cirrhosis with a focus on the setting following sustained virological response.

1. General introduction

Hepatitis C virus (HCV) infection is a major global health problem. In 2019, approximately 58 million people were chronically infected worldwide, and their overall survival is substantially impaired [1,2]. This mainly results from the progressive development of hepatic fibrosis, due to the presence of chronic hepatitis, which may result in cirrhosis. At this universal end-stage of chronic liver disease, patients are at risk of clinical complications such as hepatocellular carcinoma (HCC) and variceal bleeding [3–5]. Therefore, surveillance and primary prophylaxis strategies have been developed to optimize patient outcomes. In case of HCV eradication, patients have shown an improved clinical course [6]. In the past, PEG-interferon and ribavirin combination therapy was used. For patients with cirrhosis, this resulted in sustained virological response (SVR) rates of, on average, 30% for genotype 1/4 and 50% for genotype 2/3 [7]. Nowadays, two to three months of therapy with direct-acting antivirals (DAAs) results in SVR in >95% of patients with compensated liver disease and ~80% of those with decompensated cirrhosis, with minimal side effects [8]. The general risk of post-SVR liver-related complications increases now that DAAs are more often used in patients with more advanced liver disease. Therefore, the optimal management of patients with cirrhosis and cured HCV infection should be evaluated as studies with prolonged follow-up after DAA-induced SVR are surfacing.

2. Hepatocellular carcinoma

Based on older natural history studies, the annual risk of HCC among patients with cirrhosis and ongoing HCV infection ranges from 3% to 7% [9,10]. The incidence of HCV-related HCC has increased over the recent decades, and the peak of HCV-related cirrhosis still lies ahead of us [11,12]. If not diagnosed at an early stage, HCC has an extremely poor 5-year survival [13]. A recent Swedish national cohort including over 3000 patients with HCC demonstrated median survival rates of 4.6 years following resection, 3.1 years after ablation, 1.4 years after trans-arterial chemoembolization, 0.5 years with sorafenib and 0.3 years with best supportive care [14]. Those who qualified for liver transplantation had the best outcome with 75% survival at 5 years. Although high-level evidence is absent, HCC surveillance in patients with HCV-related cirrhosis is therefore currently advised to detect HCC early, when curative therapy (i.e. resection, ablation or liver transplantation) is still possible [3,4].

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https://doi.org/10.1016/j.ejim.2021.08.023
Received 17 May 2021; Received in revised form 2 August 2021; Accepted 27 August 2021
Available online 23 September 2021

Abbreviations

AFP	alpha-fetoprotein
CSPH	clinically significant portal hypertension
CT	computed tomography
DAAs	direct-acting antivirals
EBL	endoscopic band ligation
FIB-4	Fibrosis-4
GEV	gastroesophageal varices
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HVPG	hepatic venous pressure gradient
ICER	incremental cost-effectiveness ratio
LSM	liver stiffness measurement
MRI	magnetic resonance imaging
NPV	negative predictive value
NSBB	non-selective beta-blocker
SVR	sustained virological response
US	ultrasound

2.1. Detection of HCC

Current guidelines recommend HCC surveillance using abdominal ultrasound (US) as imaging modality [3,4]. Although safe and inexpensive, the operator-dependent accuracy of US is a disadvantage. Furthermore, especially in patients with a nodular transformed cirrhotic liver it can be difficult to distinguish small malignant lesions from benign histological changes (e.g. regenerative nodules). A recent meta-analysis including 13,367 patients with cirrhosis indicated that the sensitivity of US for HCC of any stage was 84%. However, US was found to be less accurate for the detection of early HCC, with a sensitivity of only 47% [15]. The addition of alpha-fetoprotein (AFP) (at a frequently used cut-off of 20 ng/mL) to US improves the sensitivity to detect HCC in a curative stage compared with US alone (63% vs. 45%, respectively) [15]. However, false-positively elevated AFP levels due to HCV-induced inflammation reduce surveillance specificity [15,16]. Therefore, current guidelines are not conclusive about the value of adding AFP in HCC surveillance [3,4].

Computed tomography (CT) is not advised as general HCC surveillance strategy. While an improved sensitivity of CT over US for HCC detection is debated, additional downsides include potential contrast-induced nephrotoxicity and repetitive radiation exposure [17]. Magnetic resonance imaging (MRI) is time-consuming and associated with higher costs. Nevertheless, in a prospective study among 407 patients with a high annual risk of HCC (>5%), MRI did show a significantly higher HCC detection rate (86% vs. 28%) with fewer false-positives than US [18]. Especially in case of severe steatosis, which substantially reduces the reliability of US for the detection of HCC, MRI can be considered. Prospects include shortened MRI scanning protocols, which might overcome the limited availability while preserving a high sensitivity [19].

2.2. Efficacy of HCC surveillance in cirrhosis

A large controlled trial with cluster-randomisation showed that HCCs detected through surveillance were more frequently treated with surgical resection and these patients had a substantially better outcome than those diagnosed with HCC outside of a surveillance program [20]. However, the trial was performed over 20 years ago among Chinese patients with predominantly hepatitis B virus (HBV) infection and a median age of ~40 years. Current practices in patients with HCV-related cirrhosis in Western countries are therefore mainly based on the results of cohort studies. A pivotal meta-analysis included 15,158 patients with cirrhosis (of any aetiology) and HCC from 47 studies [19]. The 3-year survival rate of 51% following surveillance-detected HCC was significantly higher than the 3-year survival of 28% following HCC detected outside of surveillance (pooled OR 1.9, 95%CI 1.7–2.2), which remained in studies that adjusted for lead-time bias. Increasing the uptake of curative therapy for early HCC may represent a route through which the benefit of surveillance can be maximized. Whereas in a meta-analysis and a more recent cohort study 63–71% of HCC detected through surveillance was early stage HCC, uptake of curative therapy was only 35–52% [19,21]. In multiple European cohorts the median survival after HCC diagnosis was indeed higher among those compliant with the biannual surveillance recommendation, while reducing the imaging interval to three months was not found to be beneficial [22–25]. Still, there remains controversy regarding the clinical benefit of HCC surveillance in patients with cirrhosis, as not all cohort studies reported positive outcomes [26]. This might partly explain the low uptake of the clear surveillance recommendations in society guidelines [27].

At present, HCC surveillance with biannual abdominal US with or without AFP is considered to be cost-effective in patients with an average annual HCC risk of 1.5% [4]. While a recent study suggested that MRI-based surveillance might be even more cost-effective among patients with a sufficiently high risk of HCC [28], those with cirrhosis and ongoing HCV infection are already well above this threshold. However, among patients with HCV-related cirrhosis and successfully treated HCV infection this should be re-assessed as both the average HCC rate and the risk of other cirrhosis-related complications are substantially reduced by curative treatment.

2.2.1. Should SVR influence the surveillance strategy?

While viral eradication might not influence the performance of abdominal US for the detection of HCC in patients with HCV-related cirrhosis in the short term, this may be different for AFP due to decreased hepatic inflammation. Successful antiviral therapy was shown to reduce AFP with hardly any patients remaining above 10 ng/mL in absence of HCC [29]. Repeating prior studies on the performance of US and AFP for HCC detection following successful DAA therapy is thus relevant. Considering the impact of SVR on liver-related clinical endpoints, cost-efficacy of HCC surveillance for patients with cirrhosis after HCV eradication should be assessed separately as well. This was recently done in a Canadian modelling study, which described a strong and exponential relation between the annual HCC risk and the incremental cost-effectiveness ratios (ICER) of biannual US [30]. The ICER was estimated to be below the commonly suggested willingness to pay threshold of 50,000 Canadian dollars from an annual HCC risk of 1.3% onwards. The assumptions driving these analyses should, however, be reviewed when interpreting its results in light of other health care systems. Furthermore, several developments could have lowered the risk cut-off for cost-effective HCC surveillance post-SVR. First, the clinical efficacy of surveillance might have increased over time as improved US quality could have eased the detection of HCC, although this can be challenged by an increase in fatty liver disease [16]. Second, there are potentially more life-years to be gained following an early diagnosis due to better HCC management options today [31]. Third, two multicenter studies indicated that DAA therapy among patients with successfully treated early HCC was independently associated with a lower risk of death (adjusted HR 0.4-0.5) [32,33]. Finally, future risk stratification tools could further improve the cost-efficacy of HCC surveillance.

2.2.2. What is the risk of HCC after SVR?

Long-term follow-up studies including patients with advanced hepatic fibrosis who were treated with interferon-based therapy indicated that the risk of HCC was reduced approximately 4-fold following SVR [34,35]. Still, successful treatment did not eliminate the HCC risk, as the annual incidence of HCC was still 1.1–1.4% depending on the background population studied [6,36]. Regarding DAAs, the first small and uncontrolled studies alarmed the field because of a high rate of HCC

occurrence and recurrence after successful DAA therapy. Larger and better-designed cohort studies hereafter soon indicated that the higher HCC rate following DAAs was predominantly observed because DAAs cure patients with more advanced liver disease and inherently higher HCC risk [37–39]. Importantly, in the largest cohort study including 62, 354 chronic HCV-infected patients, the HCC risk reduction with SVR was similar in those cured with DAAs (adjusted HR 0.3, 95%CI 0.2–0.4) and those cured with interferon-based therapy (adjusted HR 0.3, 95%CI 0.3–0.4) [38]. Nevertheless, we should expect to encounter HCC after SVR more frequently in the upcoming years since patients with more advanced cirrhosis and higher HCC risk are now treated and cured. Based on current short-term follow-up studies, the annual HCC risk after DAA-induced SVR ranges between 1.0% and 4.3% (Table 1) [35,37-60]. While the annual HCC risk did not decline sufficiently during the first 4 years after DAA-induced SVR, the long-term experience following interferon-induced SVR learned us that there was no further reduction of the annual HCC risk over 10 years of follow-up [6,46,62].

2.2.3. Can non-invasive tools be used to select patients for post-SVR HCC surveillance?

While the optimal surveillance protocol might vary depending on the HCC rate, the most prudent question is whether risk stratification can reliably identify SVR patients with a negligible risk of HCC. Apart from lacking cost-efficacy, HCC surveillance might be more likely to harm such patients [63]. The harms of surveillance require more attention but include emotional distress, financial costs, and physical injuries as a result of invasive diagnostics or even treatment of false-positive nodules. Parameters most frequently associated with HCC risk after interferon-induced SVR included age, ethnicity, features of the metabolic syndrome and non-invasive markers of liver disease severity. In line, a recently developed risk model among American Veterans with HCV-related cirrhosis and SVR showed that such readily available and objective clinical parameters prior to antiviral therapy could accurately assess the risk of HCC after SVR [58]. Although the mean follow-up of two years was limited, this cohort registered 344 HCC cases among 7, 689 patients with cirrhosis.

While external validation needs to be awaited before implementation in daily practice, further attention goes towards the predictive relevance of the evolution of non-invasive markers of liver disease severity following DAA-induced SVR [46,47,62]. The largest study included 7, 553 patients with cirrhosis and SVR, of whom 619 were diagnosed with HCC during a mean follow-up of 3.0 years [62]. Those with a decline in their Fibrosis-4 Index (FIB-4; score to assess hepatic fibrosis based on age, platelet count, AST and ALT) from ≥3.25 prior to treatment, which indicates a high likelihood of cirrhosis, to <3.25 at SVR showed an HCC incidence of 2.5% per year. This was far above the threshold for cost-effective surveillance. Nevertheless, it was approximately half the incidence of patients with a FIB-4 that persisted ≥3.25 (5.1%/year) [62]. The annual HCC risk in patients with cirrhosis and a FIB-4 <3.25 before and after successful DAA therapy was 1.2%, which is still around the cut-off for cost-effective surveillance. While efforts continue, there is currently no validated method to identify patients with HCV-related cirrhosis and SVR who have a low enough HCC risk to omit surveillance [51]. Important to consider is that non-invasive liver disease parameters have yet to be validated following HCV eradication, so that the stage of liver disease should be assessed based on pre-treatment values. So far, the diagnostic accuracy of non-invasive tests for assessment of liver fibrosis in patients with SVR has been shown to be suboptimal [64]. To illustrate, liver stiffness measurement (LSM) with Fibroscan®, a non-invasive tool with an accurate diagnostic value for advanced fibrosis or cirrhosis in patients with ongoing HCV infection, may lower or even normalize post-SVR while additional liver biopsy frequently reveals persistent cirrhosis [65,66]. As the readily available clinical parameters may have insufficient discriminative ability to exclude patients from surveillance, it is important that novel molecular biomarkers and genetic factors are actively explored through innovative

Table 1
Studies reporting incidence of hepatocellular carcinoma after DAA-induced SVR in patients with HCV-related advanced liver disease.

Author, year	Study Design	Patients with SVR and cirrhosis (n)	Mean/ median Follow-up (years)	HCC cases (n)	(Calculated) Annual HCC Incidence Rate[#]
Cheung 2016* [50]	Prospective	317	1.3	17	4.3%
Kanwal 2017 [39]	Retrospective	7495	1.0	139	1.8%
Mettke 2018 [56]	Prospective	158	1.3	6	2.9%
Innes 2018 [37]	Retrospective	272	1.7	12	2.5%
Romano 2018 [57]	Prospective	2497	1.4 (IQR 1.0-1.9)	31	1.0%
Ioannou 2018 [58]	Retrospective	7689	2.0	344	2.2%
Calvaruso 2018 [59]	Prospective	2140	1.2 (Range 6-24)	64	2.6%
Kozbial 2018 [60]	Retrospective	393	1.3 (IQR 0.3-3.0)	16	3.3%
Nahon 2018 [61]	Retrospective	274	1.8 (IQR 1.1-2.2)	7	1.4%
Ioannou 2019 [62]	Retrospective	7533	3.0	619	FIB-4 <3.25: 0.5-1.4% FIB-4 ≥3.25: 2.4-3.8%
Mariño 2019 [40]	Retrospective	1070	1.6 (IQR 1.4–1.9)	56	3.1%
Park 2019 [41]	Retrospective	1218**	1.2 (SD 0.7)	17**	1.2%
Degasperi 2019 [42]	Retrospective	546	2.1 (range 0.3–3.3)	28**	3.4% (first year)
Carrat 2019 [43]	Prospective	2329	2.8 (IQR 1.8-3.4)	166**	2.2%
Piñero 2019 [44]	Prospective	653	1.3 (IQR 0.8-1.9)	28	2.8%
Shiha 2020 [45]	Prospective	1734	2.0 (SD 0.7)	101	2.9%
Tani 2020 [53]	Retrospective	191	1.2	10	1.9% (first year)
Kanwal 2020 [46]	Retrospective	6938	2.9 (SD 0.6)	NA[+]	1.3-2.3%
Pons 2020 [47]	Prospective	572	2.9 (range 0.3–3.8)	25	1.5%
Degasperi 2020 [48]	Retrospective – prospective	452	3.6 (IQR 0.3-4.8)	36	2.3%
Tanaka 2020 [49]	Retrospective	390	2.5	29	3%
Alonso Lopez 2020 [51]	Observational	993	3.8 (IQR 1.1-4.4)	35	1.5%
Ogawa 2020 [52]	Observational	443	3.5	69[$]	2.9%
	Retrospective	188	3.6	19	2.9%

(continued on next page)

Table 1 (*continued*)

Author, year	Study Design	Patients with SVR and cirrhosis (n)	Mean/ median Follow-up (years)	HCC cases (n)	(Calculated) Annual HCC Incidence Rate[#]
Abe 2020 [54]					
Tamaki 2021 [55]	Retrospective	1000	3.0	148[$]	3.4%

*Only patients with decompensated cirrhosis were included. **Reported number in all DAA-treated patients (not specifically those with SVR). #When the annual HCC rate was not reported, this was calculated based on the presented data. ¥Analyses performed in all DAA-treated patients (not specifically those SVR). +In the entire cohort of 18,076 patients with DAA-induced SVR there were 544 patients who were diagnosed with HCC. The adjusted hazard ratio of cirrhosis with respect to HCC was 4.2 (95%CI 3.3-5.1). [$]Number of HCC cases not specified for patients with cirrhosis.
Abbreviations: DAA: direct-acting antivirals. SVR: Sustained Virological Response. HCV: Hepatitis C Virus. HCC: hepatocellular carcinoma. NA: not available. IQR: interquartile range.

translational research [67,68].

3. Portal hypertension and gastroesophageal varices

Elevation of the pressure within the mesenteric circulation (i.e. portal hypertension) as a result of cirrhosis is a multifactorial syndrome. Driving factors are increased intrahepatic vascular resistance and increased portal venous blood inflow due to splanchnic vasodilatation. Portal pressure can be estimated by measuring the hepatic venous pressure gradient (HVPG) through catheterisation of the hepatic veins. An HVPG $\geq$10 mmHg indicates clinically significant portal hypertension (CSPH) [5]. Many of the clinical complications of cirrhosis can be attributed to portal hypertension, including the development of gastroesophageal varices (GEV). GEV are shunts between the portal and caval venous systems through which portal blood can bypass the cirrhotic liver. While ectopic varices also exist, variceal bleeding is mostly encountered in case of GEV.

In general, patients without CSPH do not have GEV [5]. However, patients with compensated cirrhosis develop *de novo* GEV at a rate of approximately 7% per year [69–71]. Progression from small to large GEV (cut-off 5 mm) is seen in about 10% each year [71]. When GEV are present, the annual variceal bleeding rate ranges between 5% and 15%, and mainly depends on variceal size, presence of red wale sign (indicating thinning of the variceal wall) and Child-Pugh class as a measure of liver disease severity [5,69,71,72]. In contrast, variceal bleeding is seldom seen in patients with an HVPG <12 mmHg [73].

3.1. Primary prophylaxis of variceal bleeding

Variceal bleeding is a severe cirrhosis-related complication. The 6-week mortality in patients with decompensated cirrhosis is in the range of 10–25%, while mortality in patients with compensated cirrhosis is low [5,72,74,75]. Multiple randomized clinical trials have assessed the clinical efficacy of primary bleeding prophylaxis in patients with high-risk GEV. Both non-selective beta-blockers (NSBB) and endoscopic band ligation (EBL) are effective methods to reduce bleeding incidence (RR 0.6 and 0.4, respectively, when compared with no prophylaxis) [76,77]. Both primary prophylaxis strategies also improved all-cause mortality (RR 0.55-0.85 [76,77]) as most important clinical endpoint. Direct comparison between both primary prophylaxis strategies does not show differences in all-cause mortality [78]. Therefore, the type of primary prophylaxis should be an individual consideration based on local possibilities, patient preferences, contraindications and adverse events [5]. In contrast, secondary prophylaxis after a bleeding episode necessitates combined NSBB and EBL treatment [5].

The high mortality of variceal bleeding and effective bleeding prophylaxis justify endoscopic monitoring of the development of GEV, which is thus recommended for patients with cirrhosis [5]. In recent years, research efforts have focussed on sparing redundant endoscopies. This has led to establishment of the Baveno criteria [5]. These indicate that screening can be safely omitted in patients with ongoing HCV infection in case of a LSM value <20 kPa and a platelet count >150 $\times$ 10^9/L [5], as these patients have a low probability of high-risk (i.e. large) GEV. Applying these criteria saves approximately 26% of endoscopies, at the cost of missing only 3% of large GEV [79]. Although small GEV are missed in a larger proportion of patients, these have a low bleeding risk. Moreover, as there is no data supporting the efficacy of primary bleeding prophylaxis in small GEV, this is not recommended by current guidelines [5]. Important to consider, is that most data on portal hypertension and GEV originate from a clinical setting in which there is an ongoing etiological cause of liver disease.

3.2. Does clinically significant portal hypertension resolve after SVR?

Successful interferon-based treatment in patients with HCV-related cirrhosis reduces the HVPG and decreases long-term risk of GEV development [80–82]. Data regarding the effect of DAA-based HCV eradication were mostly limited to studies reporting short-term post-treatment HVPG measurements (Supplementary table 1) [83–87]. However, prior long-term observations regarding the platelet count, as an alternative non-invasive marker of portal pressure with the possibility of repeated measurements, indicated an ongoing amelioration over the years after interferon-based SVR among patients with cirrhosis [88]. Importantly, the main HVPG study including 226 DAA-treated patients with CSPH recently reported their 2-year follow-up results. CSPH prevalence dropped to 78% at 24 weeks post-SVR and further decreased to 53–65% at 96 weeks [86]. Still, as many as 17% of the patients in this prospective study showed an HVPG increase at 24 weeks following cessation of successful DAA treatment [89]. Along with previous decompensation, a high baseline HVPG was independently associated with the persistence of CSPH following HCV eradication. Indeed, 2 years after successful antiviral therapy CSPH remained in 93% of patients with a baseline HVPG $\geq$16 mmHg versus 40% in those with a baseline HVPG <16 mmHg (p<0.01). This finding is supported by a prior paired HVPG measurement study [87] and might explain the lack of a clear improvement in clinical outcome following SVR in patients with decompensated HCV-related cirrhosis [8]. More studies with longer follow-up in larger numbers of patients are needed to further elucidate the long-term effects of HCV eradication on the HVPG, which remains one of the best validated surrogate markers for clinical outcome in hepatology.

3.3. Are GEV developing in patients with HCV-related cirrhosis after SVR?

As follow-up of patients cured with DAAs extends, more data concerning their effect on the development of GEV is emerging (Supplementary table 2) [90–96]. In a large French cohort including 246 patients with Child-Pugh A cirrhosis due to chronic viral hepatitis (70% HCV), the cumulative rates of *de novo* large GEV at 1, 3 and 5 years after SVR were 2%, 4% and 4%, respectively [92]. In contrast, incidences of *de novo* small or large GEV following viral eradication varied between 9% and 13% after 18 to 36 months of follow-up in three smaller studies, each including approximately 60 patients with cirrhosis [93,95,96]. Among 176 patients with Child-Pugh A cirrhosis who used a maximum tolerable NSBB dosage following ligation of their GEV, the reported recurrence of GEV (size not reported) following DAA-based HCV eradication was 30% after 4 years [94]. Estimates of post-SVR progression of pre-existing small GEV to large GEV ranged from 16% to 62% [91–93,95]. Several factors might explain this wide range. First, there are

differences in baseline liver disease severity. Factors associated with development of GEV included a platelet count $<100 \times 10^9$/L, higher LSM value and increased spleen size, which all indicate higher portal pressure [92,93]. Second, there might be differences in the presence of the metabolic syndrome and alcohol abuse, even though the first small and likely underpowered studies could not relate these comorbidities favouring liver disease progression to post-SVR GEV development [92, 93]. Lastly, results might be influenced by differences in the interval between baseline endoscopy and DAA-initiation, and random variation due to small sample sizes. More data from larger cohorts are required to identify clear risk factors and more precise incidence rates. A positive result at the other end of the spectrum is the regression of pre-existing GEV in up to 22% of patients after 2 to 3 years following HCV eradication [91,94]. Nevertheless, for now, it seems apparent that endoscopic surveillance cannot be generally omitted in patients with HCV-induced cirrhosis and SVR.

3.4. Can non-invasive tools be used to select patients for post-SVR varices surveillance?

In line with reports that found persistent biopsy-proven cirrhosis in patients with normalized LSM values after SVR [65,66], correlation between post-SVR LSM and portal pressure is limited [86,97]. In the main study reporting HVPG results of 226 patients with baseline CSPH successfully treated for HCV, post-SVR LSM cut-offs of <13.6 kPa and ≥21 kPa had moderate diagnostic value for the persistence of post-SVR CSPH [86]. Hence, the correlation between LSM alone and GEV development appears to be far from excellent and insufficiently reliable in clinical practice. Another surrogate marker for portal pressure is spleen stiffness measurement [98], however more data are needed in patients with HCV-induced cirrhosis to determine its value in post-SVR follow-up.

Recently, several studies have validated the Baveno criteria in the setting of HCV eradication [92,93,96]. In a cohort of 246 cases with HBV- or HCV-related cirrhosis (70% HCV), 28% of patients had a favourable Baveno status at the time of viral suppression and none of them harboured large GEV at 1, 3 and 5 years follow-up, compared with 3%, 8% and 8% of those with an unfavourable Baveno status [92]. In case of LSM >20 kPa and platelet count $<150 \times 10^9$/L, the number needed to surveil to detect one patient with high-risk GEV in 5 years would thus be 13. In this study, however, *de novo* small GEV were not considered, while these might be a precursor of large GEV. Furthermore, patients with Child-Pugh B/C cirrhosis or prior decompensation were excluded, while these have the highest risk of disease progression despite SVR. Among HCV patients with an unfavourable Baveno status prior to DAAs, Baveno status became favourable in 29% after SVR and none of these patients showed progression of GEV. In comparison, large GEV developed in 12% of those in whom the Baveno status remained unfavourable [92]. Another study confirmed the negative predictive value (NPV) of 100% for high-risk GEV in case of favourable Baveno status post-SVR, although only 15% fulfilled the criteria for a favourable Baveno status [93]. Extending the criteria to a platelet count $<110 \times 10^9$/L and LSM value ≥25 kPa (also known as the expanded Baveno criteria) increased the proportion of patients with favourable Baveno status to 38%, at the cost of a decline of the NPV to 91%. In summary, also following HCV eradication, the Baveno criteria remain a reliable tool to determine the need for GEV surveillance. Evidently, however, the clinical implication of GEV following HCV eradication is contingent on the incidence and implications of post-SVR variceal bleeding.

3.5. What is the risk of variceal bleeding after SVR?

Achieving SVR has been related to a reduced risk of variceal bleeding in patients with advanced liver disease [35,99]. Indeed, although GEV progression is often reported, variceal bleeding after DAA-based HCV eradication appears to be rare within the first years, especially in patients without GEV prior to antiviral therapy (Table 2) [47,86,87,90, 96,99–101]. The average bleeding rate from four prospective studies (including a total of 1323 patients with HCV-related cirrhosis) was 1% after a follow-up of approximately 3 years following SVR [47,86,87, 101]. One of these studies reported no bleeding in patients with favorable expanded Baveno criteria (39% of the cohort) [101]. Importantly, most of these studies excluded patients with a history of hepatic decompensation or HCC, as well as individuals with HBV co-infection. In a large retrospective analysis from the Veteran Affairs hospitals in the USA, with a mean follow-up of 3 years, the incidence rate of variceal bleeding was as low as 0.2 per 100 patient-years in patients with cirrhosis without GEV prior to DAAs [99]. This is remarkably low, especially considering the almost exclusively male study population with a high prevalence of comorbidities associated with progressive liver fibrosis. As expected, in patients with pre-existing varices variceal bleeding was more frequent, with incidence rates of 4 and 13 per 100 patient-years depending on whether the patient experienced a prior bleeding episode [99]. Other factors associated with an increased risk of variceal bleeding following SVR in this study were previous ascites, spontaneous bacterial peritonitis and a platelet count $<150 \times 10^9$/L, while obesity was not [99]. To consider, however, is that the low incidence of variceal bleeding could be due to adequate primary prophylaxis, even though population-based studies indicated that the compliance with guideline recommendations on endoscopic surveillance is far from optimal [102,103].

4. Conclusion

While virological cure reduces the risk of HCC and variceal bleeding in patients with HCV-related cirrhosis, their risk of these complications is not entirely eradicated with SVR. As our experience following DAA-induced SVR in patients with cirrhosis increases, we will learn how to improve their management including the optimization of surveillance strategies for HCC and GEV. For now, the average risk of HCC in patients with cirrhosis post-SVR appears to remain high enough to justify continued surveillance (Fig. 1). As sufficiently validated prognostic tools to accurately identify patients with a low risk of HCC are not yet available, all patients with HCV-related cirrhosis should currently remain included in HCC surveillance programs irrespective of successful DAA therapy or improved non-invasive parameters of liver disease severity. Future research could result in a more tailored approach. A crucial precondition, however, is that patients are able to undergo HCC treatment with reasonable expectation of clinical benefit. This should thus be repetitively evaluated during the follow-up for each patient.

In contrast, endoscopic surveillance can be prevented in a substantial proportion of patients with compensated cirrhosis and SVR by applying the Baveno criteria (Fig. 1). In absence of signs of progression of liver disease, relevant GEV are indeed highly unlikely among patients with normal platelets and a LSM <20 kPa. This includes patients in whom these parameters were unfavorable prior to DAAs. In fact, as variceal bleeding after SVR seems uncommon and first variceal bleeding is associated with low mortality in case of compensated cirrhosis, future studies should elaborate on the clinical efficacy and cost-effectiveness of regular endoscopic follow-up following HCV eradication. Using the expanded Baveno criteria to further reduce the number of endoscopies might be considered. Importantly, the proportion of patients with a favorable Baveno status is at least likely to increase with time after SVR, as remodelling of the liver is a gradual process with an ongoing decrease of portal pressure. Of note, this process may be challenged by additional etiological causes of liver disease, of which metabolic syndrome and alcohol use are most prevalent. Further long-term follow-up data in patients with cirrhosis and SVR, also addressing co-factors and the evolution of liver disease parameters over time, are needed to establish optimal surveillance policies after HCV eradication.

Table 2
Studies reporting incidence of variceal bleeding after DAA-induced SVR in patients with HCV-related advanced liver disease.

Author, year	Study Design	Patients with SVR and cirrhosis (n)	Varices at baseline endoscopy* (no / SV / LV)	Previous variceal bleeding	BL CP-score (% A/B/C)	Mean/ median follow-up (years)	Variceal bleeding post-SVR	Bleeding incidence stratified for pre-treatment presence of varices
Romano 2018 [100]	Retrospective	37, decompensated cirrhosis	n.r.	35%	Median 7 (IQR 5-11)	1.0	2 (8%)	n.r.
Abadia 2019 [90]	Prospective	33	0 / 7 / 26	4 (12%)	76% / 24% / 0%	1.3 (IQR 1.2 – 1.7)	1 (3%)	Bleeding occurred in patient without prior bleeding
Moon 2019 [99]	Retrospective	7927	23% with varices, size n.r.	5%	n.r.	3.1	5% of patients with cirrhosis. Rate 1.6 per 100 patients years	No varices: 0.2 per 100 patient years Prior varices, no bleeding: 4 per 100 patient years Prior bleeding varices: 13 per 100 patient years
Mandorfer 2020 [87]	Prospective	90, BL HVPG≥6 mmHg	57 / 17 / 16	n.r.	72% / 28% / 0%	2.9	n = 1 (1%)	n.r.
Lens 2020 [86]	Prospective	226, BL HVPG≥10 mmHg	69 / 89 / 68	26	79% / 21% / 0%	3.7 (IQR 3.0 – 3.8)	n = 3 (1%)	n.r.
Pons 2020 [47]	Prospective	572	168 / 89 / 34	0	All CP-A	2.9 (range 0.3-3.8)	n = 2 (0.3%)	n.r.
Giannini 2020 [96]	Prospective	56	33 / 16 / 7	n.r.	n.r.	n.r.	0	
Corma-Gomez 2020 [101]	Prospective	435	SV or no varices: n.r. LV: 62	13	94% CP-A	3.7 (IQR 2.5 – 4.1)	n=10 (2%), 0.8 per 100 patient years	No prior bleeding varices: 0.6 per 100 patient years Prior bleeding varices: 3/13 (23%)

*Small varices defined as <5mm or Paquet grade F1. Large varices defined as ≥5 mm or Paquet grade F2 or F3. Abbreviations: DAA: Direct-acting Antivirals. SVR: Sustained Virological Response. HCV: Hepatitis C Virus. SV: Small Varices. LV: Large Varices. BL: Baseline. CP: Child-Pugh. N.r.: not reported. IQR: interquartile range. HVPG: Hepatic Venous Pressure Gradient.

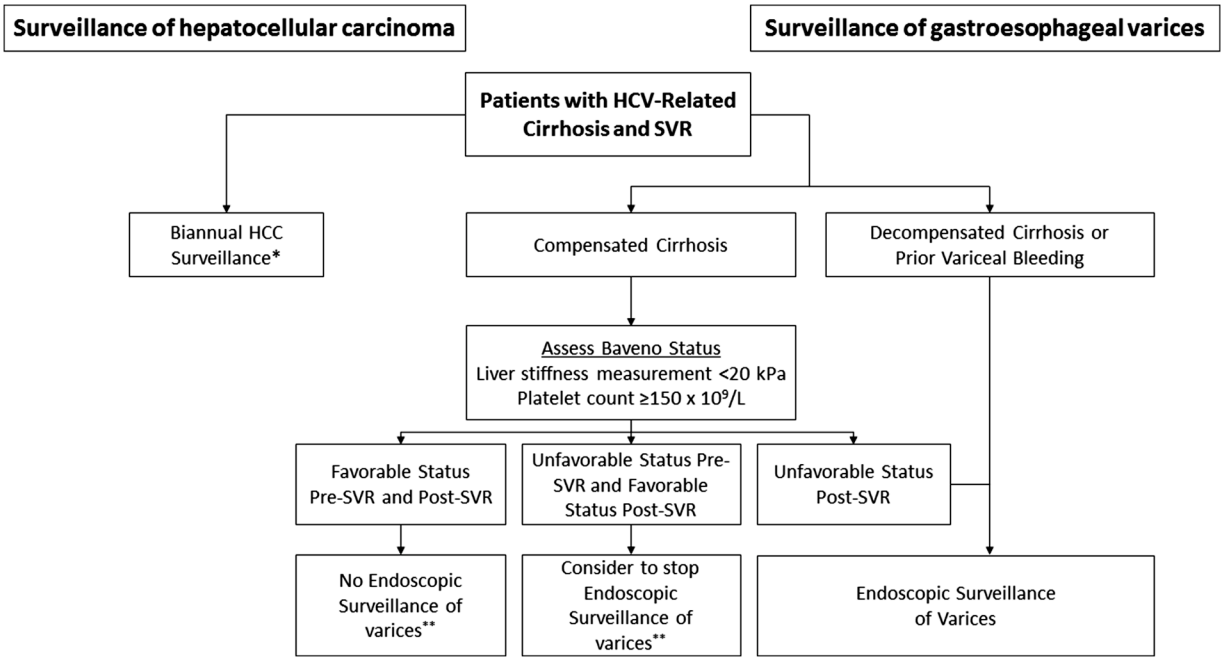

Fig. 1. Decisional flowchart for surveillance of hepatocellular carcinoma and gastroesophageal varices in patients with cirrhosis and cured HCV infection. **Legend:** *Consider to omit HCC surveillance in case of patients who are not expected to be able to undergo HCC treatment with reasonable expectation of clinical benefit. **In absence of signs of further progression of liver fibrosis. HCV: hepatitis C virus. SVR: sustained virological response. HCC: hepatocellular carcinoma.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Cas J Isfordink follows a PhD traject in the CELINE (hepatitis C elimination in the Netherlands) initiative sponsored by Gilead. Raoel Maan received financial compensation for consultancy from AbbVie. Robert A de Man has nothing to disclose. Karel J van Erpecum participated in advisory boards of Gilead, Janssen-Cilag, BMS, Abbvie, and MSD and received research grants from Gilead, Janssen-Cilag and the DutchCancer Society (KWF Kankerbestrijding). Adriaan J van der Meer received financial compensation for lecture activities from Zambon, research funding from Gilead, MSD, AbbVie and Zambon, and compensation for consultancy from AOP Orphan.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.08.023.

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