Direct-acting antiviral (DAA) therapies have recently revolutionized treatment of chronic hepatitis C virus (HCV) infection. All DAAs have received approval based on trials reporting sustained virological response (SVR) as the primary endpoint, defined as undetectable HCV RNA in the serum at least 12 weeks after stopping treatment. SVR is considered as ‘a cure’ of HCV infection. SVR rates obtained with DAAs are higher than 95% in 2017, whereas such rates were 30%-50% ten years earlier when the treatment relied on pegylated interferon and ribavirin. Rates of a given clinical event such as hepatocellular carcinoma (HCC), liver decompensation, or all-cause or liver-related deaths, observed in patients with and without SVR, have been frequently compared to highlight the benefit of achieving SVR, and thereby, to suggest the potential clinical benefit of treatment. However, SVR is strongly associated with other risk factors also known to influence disease progression. Such a confounding by prognosis may lead to striking findings when comparing the rates of clinical outcomes from two very different eras of SVR rates, as illustrated below.

The panel A of Figure 1 reproduces HCC incidence rates by treatment group according to SVR status in patients with cirrhosis, extracted from the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database. Strikingly, the HCC incidence rates observed in the SVR and non-SVR subgroups were both consistently higher in the interferon-free than in the interferon-based treatment groups (although the differences reported in the paper were not significant due to a lack of power, our issue here concerns the order between incidence rates by treatment groups in the different SVR subgroups). Similarly, the HCC incidence rates in the non-SVR groups were higher than the rate observed in untreated patients. However, a reverse pattern, that is a lower HCC incidence rate in the interferon-free compared with interferon-based groups or the untreated group was observed when considering total number of patients.
of patients. These results are simply caused through confounding by prognosis and a combination of the Rogers phenomenon\(^7\) with Simpson's paradox.\(^8\)

To explain, let us consider 10 patients with hypothetical outcome-free survival times (thereafter referred to as survival times; panel B of Figure 1)—for the sake of simplicity we will assume that every patient will experience the outcome (HCC) but our explanation will remain valid in case of censored observations.

Without treatment (scenario B1 in panel B of Figure 1), the observed incidence rate is 7.7 per 100 person-years. Let us assume that exactly the same 10 patients are treated, with no effect of treatment on survival, that is the survival times are not modified neither in patients with SVR nor without SVR (scenario B2 in panel B of Figure 1). If SVR is negatively associated with risk factors of outcome, then SVR will occur more frequently in patients with longer survival times, as shown in our example: assuming a 30% SVR rate, the relative risk of outcome in patients with SVR as compared to those without SVR is 5.0 per 100 person-years/10.0 per 100 person-years = 0.5. However, the relative risk of outcome in treated versus untreated patients will be 7.7/7.7 = 1 since the treatment has no effect on survival. Assuming a 90% SVR rate, all other parameters remaining unchanged, a single patient will not achieve SVR (most likely, the patient with the worst prognosis). The relative risk of outcome in patients with SVR as compared to those without SVR is 7.1/25.0 = 0.3. Nevertheless, here again, the relative risk of outcome in treated versus untreated patients will remain at 1 (7.7/7.7). Thus, in two different situations of distinct SVR rates where the treatment has no effect on survival, the comparisons of survival between the subgroups of patients with and without SVR do not demonstrate at all any effect of SVR on survival but rather reflect the fact that SVR is a surrogate marker for patients with favourable prognoses. In addition, when SVR rates increase, the incidence rates increase in both subgroups of patients (from 5.0 to 7.1 and from 10.0 to 25.0 per 100 person-years in patients with or without SVR, respectively): such an observation, known as the Rogers phenomenon,\(^7\) is sufficient in explaining the higher incidence rates of HCC observed in patients with and without SVR treated with interferon-free therapies than corresponding rates observed in patients treated with interferon-based therapies.

Suppose now that the treatment has a favourable effect on outcome-free survival in patients with SVR, that is that SVR is a valid surrogate criterion for this clinical outcome, but that the relationship between SVR and survival remains confounded by other prognostic factors. Let us assume that treatment increases survival in all patients with SVR by, for example 2 years (scenario B3 in panel B of Figure 1). If SVR is negatively associated with risk factors of outcome, then SVR will occur more frequently in patients with longer survival times, as shown in our example: assuming a 30% SVR rate, the relative risk of outcome in patients with SVR as compared to those without SVR is 5.0 per 100 person-years/10.0 per 100 person-years = 0.5. However, the relative risk of outcome in treated versus untreated patients will be 7.7/7.7 = 1 since the treatment has no effect on survival. Assuming a 90% SVR rate, all other parameters remaining unchanged, a single patient will not achieve SVR (most likely, the patient with the worst prognosis). The relative risk of outcome in patients with SVR as compared to those without SVR is 7.1/25.0 = 0.3. Nevertheless, here again, the relative risk of outcome in treated versus untreated patients will remain at 1 (7.7/7.7). Thus, in two different situations of distinct SVR rates where the treatment has no effect on survival, the comparisons of survival between the subgroups of patients with and without SVR do not demonstrate at all any effect of SVR on survival but rather reflect the fact that SVR is a surrogate marker for patients with favourable prognoses. In addition, when SVR rates increase, the incidence rates increase in both subgroups of patients (from 5.0 to 7.1 and from 10.0 to 25.0 per 100 person-years in patients with or without SVR, respectively): such an observation, known as the Rogers phenomenon,\(^7\) is sufficient in explaining the higher incidence rates of HCC observed in patients with and without SVR treated with interferon-free therapies than corresponding rates observed in patients treated with interferon-based therapies.

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no impact, comparing SVR to non-SVR patients will always favour SVR simply because patients with favourable prognosis are compared with patients with poor prognosis. Methods for controlling confusion by prognosis can be used (such as adjustments, weighting, matching...) but even if extensive multivariable analyses are carried out, concerns always remain about potential influences on outcome of additional unmeasured confounding factors. Moreover, considering previous periods during which <30% of patients were responding while more than 90% of patients are responding nowadays, these confounding factors may have changed over time, making intractable the comparisons between cohort data originating from such different therapeutic eras. Finally, it has also been argued that comparing the outcomes of treated patients who do and do not achieve SVRs shows that the SVR is a good prognostic sign, but cannot provide any insight into treatment because all of the participants were treated.9

Actually, the correct analysis for assessing the impact of a given treatment regimen on clinical outcomes would be a comparison of a group receiving this regimen with one or more control groups presenting with similar clinical profiles and prognosis distribution, irrespective of SVR status. Only a randomized clinical trial would constitute the nondebatable appropriate design to prove that the regimen is clinically superior to the control(s). Of note, subgroup comparisons such as SVR patients versus untreated patients (untreated individuals who would or would not have achieved SVRs, had treatment been provided) would be biased here also through confounding by prognosis and would not fulfil the intent-to-treat principle. Observational studies can only demonstrate associations between treatment and outcomes, and methods for controlling confusion by indication bias are therefore required in performing appropriate comparisons. However, prognostic factors associated with treatment initiation are likely easier to identify and to integrate in analyses (eg using propensity weighting or matching) than those associated with SVR, and the risk of residual confounding is accordingly decreased. Moreover, the proposed approach is more conservative as the direction of a residual bias, if any, should not favour treatment since treatment was prioritized in patients with less favourable prognosis. Finally, providing direct estimates of treatment effect on clinical outcomes, ideally through a randomized experiment, constitutes a much more meaningful and forceful perspective than providing estimates of SVR effect on clinical outcomes.

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CONFLICT OF INTEREST

None.

DISCLOSURES

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AUTHORS CONTRIBUTION

Carrat, Hejblum: conceived the study and design; Nahon, Fontaine, Pol: acquired the data; Carrat, Hejblum: analysed and interpreted the data; Carrat, Hejblum: drafted the manuscript; Nahon, Fontaine, Pol: critically revised the manuscript for important intellectual content.

ORCID

Fabrice Carrat https://orcid.org/0000-0002-8672-7918

Gilles Hejblum https://orcid.org/0000-0003-0127-1964

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