Comparing interferon-free with interferon-based regimens in HCV patients: Rogers phenomenon and Simpson's paradox

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i. TITLE

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ii. RUNNING TITLE

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Study concept and design: Carrat, Hejblum; acquisition of data: Nahon, Fontaine, Pol; analysis and interpretation of data: Carrat, Hejblum; drafting of the manuscript: Carrat, Hejblum; critical revision of the manuscript for important intellectual content: Nahon, Fontaine, Pol.

vi. ABSTRACT AND KEYWORDS

Abstract:

Comparisons of time-to-event clinical outcomes between patients with or without a sustained virological response (SVR) after treatment of chronic hepatitis C infection have been repeatedly reported for emphasizing the potential clinical impact of treatment. Combining recently published data from different therapeutic eras with simple examples, we show that comparisons of incidence rates by SVR status between patients treated with Interferon-based and Interferon-free regimens are flawed by confounding by prognosis. The relevant analysis for evaluating and comparing the clinical impact of these regimens should be a comparison between randomized treatment groups, irrespective of the SVR status.

Keywords:

Antiviral Agents; Carcinoma, Hepatocellular; Hepatitis C, Chronic; Sustained Virologic Response; Treatment Outcome;

vii. MAIN TEXT

Direct-acting antiviral (DAA) therapies have recently revolutionized treatment of chronic hepatitis C virus (HCV) infection.[1] 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.[2] 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.[3] 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 a SVR, and thereby, to suggest the potential clinical benefit of treatment.[4] However, SVR is strongly associated with other risk factors also known to influence disease progression,[5] and such a confounding by prognosis may lead to striking findings when comparing the rates of clinical outcomes issued 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.[6] 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 topic here concerns the order between incidence rates by treatment groups in the different SVR subgroups). Similarly, the HCC incidence rates in the non-SVR subgroups were higher than the rate observed in untreated patients. However, a reverse pattern, i.e. a lower HCC incidence rate in the interferon-free compared with

interferon-based groups or the untreated group was observed when considering total patients. These results are simply caused by confounding by prognosis and a combination of 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 i.e. 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 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 favorable 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 Rogers phenomenon,[7] is sufficient for 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 favorable effect on outcome-free survival in patients with SVR, i.e. 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, e.g., 2 years (scenario B3 in panel B of Figure 1). In both subgroups of patients, the incidence rate observed with a 90% SVR rate is still higher than that observed with a 30% SVR rate (6.3 versus 4.5 and 25.0 versus 10.0 per 100 person-years in patients with or without SVR, respectively), while in contrast, the incidence rate observed on the total is lower with a 90% SVR rate than with a 30% SVR rate (6.8 versus 7.4 per 100 person-years). This paradoxical finding, known as Simpson's paradox,[8] is also a consequence of the confusion by prognostic factors of survival. The above-detailed example explains why the pattern of HCC incidence rate comparison between treatment groups is reversed when the with and without SVR subgroups of patients are combined.

This example illustrates why a comparison between treated patients with and without SVR would not be relevant for assessing treatment impact on clinical outcomes. Even if treatment has no impact, comparing SVR to non-SVR patients will always favor SVR simply because patients with favorable 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 less than 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 that comparing the outcomes of treated patients who do and do not develop 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 non-debatable 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 here also be biased by confounding by prognosis and would not fulfill 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 for performing appropriate comparisons. However, prognostic factors associated with treatment initiation are likely easier to identify and to integrate in analyses (e.g., 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 favor treatment since treatment was prioritized in patients with less favorable 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.

viii. REFERENCES

1. Chung RT, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. *N Engl J Med.* 2014;370(17):1576-1578.
2. Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. Guideline on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-evaluation-direct-acting-antivirals-treatment-chronic-hepatitis_en.pdf. Accessed June 6, 2019.
3. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis.* 2011;52(7):889-900.
4. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med.* 2013;158(5 Pt 1):329-337.
5. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet.* 2019;393(10179):1453-1464.
6. Li DK, Ren Y, Fierer DS, et al. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study. *Hepatology.* 2018;67(6):2244-2253.
7. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med.* 1985;312(25):1604-1608.

8. Hernan MA, Clayton D, Keiding N. The Simpson's paradox unraveled. *Int J Epidemiol.* 2011;40(3):780-785.

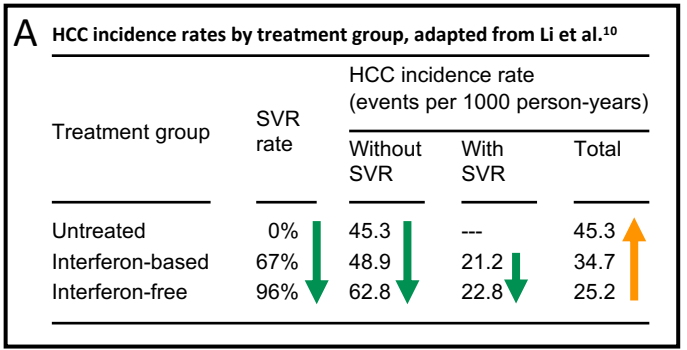
9. Koretz RL, Jakobsen JC, Hauser G, Nikolova D, Gluud C. Letter to Editor: Response to AASLD Editorial/Message from the President. *Hepatology.* 2019;69(5):2300.

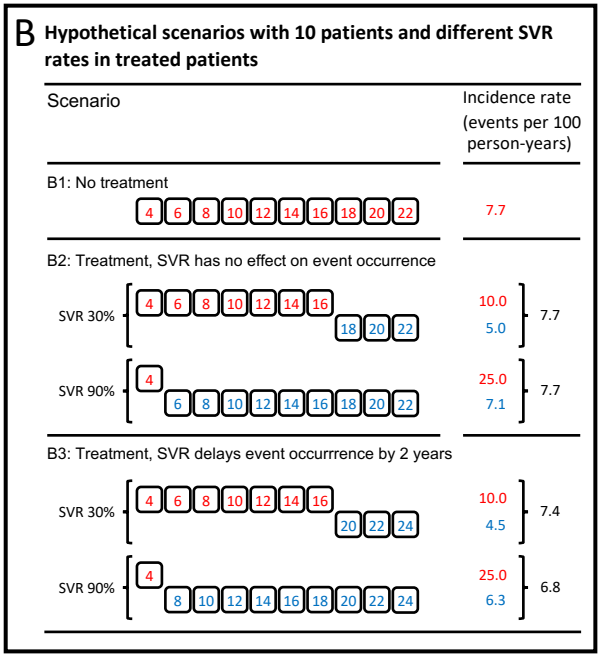
ix. TABLES

Non applicable (no Table)

x. FIGURE LEGENDS

Figure 1: Illustration of Rogers phenomenon and Simpson’s paradox in HCV patients.





Panel A: Incidence rate of HCC by treatment group, adapted from Li D.K. et al.[10].
Panel B: Hypothetical scenarios with 10 patients and different sustained virological response (SVR) rates in treated patients. Each cell represents a patient, the cell inner number indicates the corresponding patient outcome-free survival (in years), blue and red color refers to patients with and without SVR, respectively. Incidence rates are calculated by dividing the number of events by the total number of person-years of follow-up (e.g., in scenario B1, 10 deaths occurred during the (4 + 6 + 8 + 10 + 12 + 14 + 16 + 18 + 20 + 22) = 130 years of follow-up, that is (10 / 130) x 100 = 7.7 per 100 person-years). Panel B3, in which the scenario assumes that SVR achievement increases survival by 2 years but is confounded by prognosis factors, illustrates the patterns shown in Panel A.

Abbreviations used: HCC, hepatocellular carcinoma; SVR, sustained virological response.