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Built-in bias in HCV clearance in acute HCV infection

To the Editor:

We read with interest the recent paper about hepatitis C virus (HCV) clearance in patients with acute HCV infection [1]. We are wondering why authors did not calculate risk ratio instead of odds ratio (OR) when they have run a cohort study? They can present how much is the incidence of HCV clearance and relative risk (RR) of factors affecting on such clearance, which is more precise than OR and real actual estimation of the strength of risk factor. Reporting RR besides OR in univariate analysis and then multivariable OR based on logistic regression makes it easy to interpret multivariable (adjusted) OR regarding "built-in-bias." When the condition of interest has a high incidence and prospective data are available, like the study by Mangia *et al.* [1], it is usually better to report the RR instead of OR. Implementing OR as an estimate of the RR biases it in a direction opposite to the null hypothesis; that is, it tends to exaggerate the magnitude of the association. This is called built-in bias which is negligible when the disease is relatively rare [2]. When the incidence is high; like spontaneous HCV clearance and non-responders to treatment in the present study, the bias can be substantial [2]. In other words, built-in bias is responsible for the discrepancy between the RR and OR estimates.

The value of this bias is equal to:

$$\frac{1-q_{-}}{1-q_{+}},$$

when q_+ is the incidence (probability) in exposed and q_- the incidence in unexposed individuals. For instance, regarding response to treatment and *IL28B*, 31 out of 40 *IL28B* CC carriers *vs.* 27 out of 40 *IL28B* XT carriers were responder; in this way q_+ and q_- would be 77.5 and 67.5 percent respectively, indicating built in bias of 1.4, which means OR overestimates RR estimation up to 1.4 fold. Regarding relationship between spontaneous HCV clearance and Jaundice or *IL28B*, built in bias is lower (about 1.3).

This shows that the value of bias may be considerable in this study and similar researches and we should consider this issue for future studies as a common mistake which is undertaken by most researchers.

Moreover, multivariate OR reported for HCV genotype and *IL28B* (15.6 and 8.7, respectively) as predictors of SVR are not correspondent to the results in the Table 3! Their value cannot be influenced very much after adjustment specifically considering such low number of sample size and event rate (outcome). On the other hand, according to their multivariable analysis treatment timing (OR 0.94, 95% CI 0.89–0.97) and adherence (OR 1.06, 95% CI 1.02–1.11) resulted independent predictors of SVR. The question here is why these ORs have such a narrow confidence interval despite so much adjustment in addition to such low sample size; while ribavirin use with a high OR had a wide confidence interval in that model simultaneously (OR 15.1, 95% CI 2.19–103.99, $p = 0.006$)?

There are some other imperfect reportings in the article like percent of clearance for "No jaundice" in Table 2 (82.6 instead of 17.4) and using "univariate analysis" term instead of multivariable analysis after using baseline characteristics as covariates.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

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Ali Kabir*
Department of Epidemiology, Faculty of Public Health, Shahid Beheshti University of Medical Sciences, and Center for Educational Research in Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran
*Corresponding author.
E-mail address: aikabir@yahoo.com

Davood Khalili
Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Reply to: "Built-in bias in HCV clearance in acute HCV infection"

To the Editor:

We would like thank our colleagues for their insightful notes on basic epidemiology. We agree with them that researchers and clinicians sometimes forget the different nature of the risk metrics. Undoubtedly, odds ratios (OR) and relative risks (RR) have different definitions and, therefore, different interpretations. The RR, computed as the ratio of two risks, is a natural way to compare risk proportions: a RR of 1.60 indicates a higher risk of 60% in

Table 1. Standardized mean difference of ribavirin use, adherence and treatment timing between *IL28B* and HCV genotype groups.

Covariate	Category	*IL28B* non-CC	*IL28B* CC	Standardized mean difference	HCV genotype 1	HCV genotype 2 + 3	Standardized mean difference
Ribavirin use				55.38			-20.85
	No	8 (20.00)	18 (45.00)		17 (36.96)	9 (27.27)	
	Yes	32 (80.00)	22 (55.00)		29 (63.04)	24 (72.73)	
Adherence		90.30 ± 27.32	91.75 ± 24.90	5.55	90.44 ± 26.33	91.58 ± 26.23	4.34
Treatment timing		12.66 ± 14.67	16.35 ± 21.07	20.31	12.18 ± 13.36	18.01 ± 23.19	30.79

Table 2. Model building for sustained virological response (SVR).

		IL28B CC carriers			HCV genotype (2 + 3 *vs.* 1)		
Model		OR	95% CI	*p* value	OR	95% CI	*p* value
A	Univariate	1.658	0.614-4.482	0.319	2.987	0.966-9.232	0.057
B	Both	1.726	0.609-4.895	0.305	3.181	1.013-9.990	0.048
C	B + ribavirin use	2.725	0.809-9.185	0.106	3.433	1.019-11.564	0.047
D	C + adherence	3.708	0.844-16.296	0.083	5.116	1.116-23.442	0.036
E	D + treatment timing	8.716	1.442-52.674	0.018	15.610	2.023-120.45	0.008

exposed subjects *vs.* non-exposed ones to develop an event. The OR, computed as the ratio of two odds, is a less intuitive risk measure: an OR of 1.60 does not suggest a higher risk of 60% but a higher odds in exposed subjects. In our study, the crude OR of *IL28B* (exposure) for clearance (outcome) is 4.22 (Table 1), while the correspondent crude RR is equal to 2.95. The so called built-in bias could only occur if one reads this OR interpreting it as an RR. Therefore, why is RR not always used in cohort studies as in our case? The reason stems from the need to perform a multivariable analysis in an observational (i.e., non-randomized) study, in which it is necessary to adjust for potential confounders. To estimate an adjusted RR, binomial or Poisson regressions are usually used. However, as is commonly known, none of them are satisfactory [1,2]. Convergence problems very often arise with binomial regression models failing to provide an estimate of RR. While Poisson regression models provide conservative results (Poisson distribution is typically used for rare events). Also the conversion method proposed by the authors has been proven to be invalid [3]. For these reasons, multivariable logistic regression models, and therefore the OR, have been widely used and still are even when events are not rare.

We presented in our original article the well-established crude and adjusted ORs as the measure of the associations, aware that Journal of Hepatology readership bears in mind that an OR must be not interpreted as a RR. In our paper we never discussed ORs as RRs, and, even when comparisons were reported, they referred to crude frequencies and percentages. Multivariable models were simply used to adjust for potential confounders.

Furthermore, it seems that the results of the multivariable analysis on sustained virological response (SVR) left the authors at least perplexed, as the use of the exclamation mark suggests. However, here we provide some useful epidemiological explanations about confounding. The univariate ORs for *IL28B* CC carriers and for HCV genotype were 1.658 and 2.987, respectively. On the other hand, in the multivariable model, the possible clinical confounders, i.e. ribavirin use, adherence and treatment timing, resulted highly predictive of SVR. Furthermore we observed (see Table 1) that these very covariates were strongly unbalanced in the two *IL28B* groups and the two HCV genotype groups, as shown by their large standardized mean differences (an absolute value greater than 5% indicates between-group imbalance). Indeed this proves their key role as confounders, which was sufficient to move the ORs from 1.658 to 8.716, and from 2.987 to 15.610, for *IL28B* and HCV genotype, respectively. A key paper on sensitivity analysis for residual confounding serves as reference [4]. For sake of completeness we also reported in Table 2 the model building, which shows how the ORs moved toward higher values and more significant *p* values. As a further proof, we estimated the same multivariable model using a Bayesian exact approach, implemented in WinBugs, to verify whether in the previous approach estimation problems occurred. The Bayesian exact logistic regression model, which appropriately handles zero cells strata in the adjustment process, provided overlapping results (Table 3).

Also the ORs 95% confidence intervals troubled our colleagues. Please note that the two independent predictors, treatment timing and adherence, are continuous variables with their own metrics and results must be interpreted consequently. For example, in our study treatment timing was expressed in weeks and resulted, in the multivariable analyses, an independent predictor of treatment response with a OR = 0.937 (95% CI = 0.898–0.978, $p = 0.003$). If we express treatment timing in days, the association results in OR = 0.991 (95% CI = 0.985–0.997, $p = 0.003$). On the other hand, if we express treatment timing in months, the

Table 3. Multivariable model for sustained virological response (SVR) estimated using a Bayesian approach.

Variable	Median OR	95% CI
IL28B CC carriers	12.450	2.219-106.200
HCV genotype	24.290	3.624-293.800
Ribavirin use	16.720	2.762-149.100
Adherence	1.071	1.036-1.121
Treatment timing	0.934	0.890-0.975

Table 4. Correction of Table 1 in "Mangia A, *et al.* Treatment optimization and prediction of HCV clearance in patients with acute HCV infection. J Hepatol 2013;59:221–228".

Characteristics	Overall N, (% by column)	Clearance N, (% by row)	Viral persistence N, (% by row)	*p* value
Jaundice, n (%)	83 (49.1)	32 (38.6)	51 (61.4)	0.0023
No jaundice, n (%)	86 (50.9)	15 (17.4)	71 (82.6)	

association results in OR = 0.753 (95% CI = 0.625–0.907, $p = 0.003$). Therefore the narrowness of confidence intervals for continuous covariates measures of risk is only apparently misleading.

The authors correctly stated that an imperfect reporting is present in the manuscript, but not in Table 2 of the original manuscript, rather in Table 1, where the absolute counts for "No jaundice" have been inverted between Clearance and Viral Persistence groups. The corrected numbers are now reported in the following Table 4.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Massimiliano Copetti
Unit of Biostatistics, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy

Fabio Pellegrini
Unit of Biostatistics, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy
Unit of Biostatistics, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy

Valeria Piazzolla
Alessandra Mangia*
Liver Unit, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy
*Corresponding author.
E-mail address: a.mangia@tin.it

How to decide about liver transplantation in patients with hepatocellular carcinoma: Size and number of lesions or response to TACE?

To the Editor:

With great interest we read the paper by Otto *et al.* [1] retrospectively reviewing 136 patients with hepatocellular carcinoma (HCC) treated with 2 or more cycles of transarterial chemoembolisation (TACE) prior to liver transplantation over a period of 13 years. The authors of this single center study suggested that not preoperative staging (in or out of Milan criteria) but characterisation of tumour response to TACE allows for identification of patients most suitable for liver transplantation by identification of HCC patients with the most favourable tumour biology. The currently accepted concept of "downstaging" is defined by the reduction of intrahepatic HCC burden in order to achieve 5-year survival rates comparable to that of HCC patients to meet transplant criteria without downstaging [2,3]. Therefore, possible "downstaging" by response to TACE should not be confused with "favourable tumour biology".

We agree with the authors that clinical staging for HCC for "inside" or "outside" Milan criteria (MC) may differ in both directions in up to 25% of cases when compared to histopathology findings [4]. However, we believe that critical re-evaluation of the data presented is needed before response to repeated TACE can be adopted into clinical decision-making process or for changing allocation rules.

It seems, even though not clearly stated, that in this analysis only patients were included who survived the initial in-hospital phase after liver transplantation. Additionally, no data are provided on time from diagnosis to listing or waiting times or drop-outs on the waiting list. No lab-MELD data or match-MELD data at the time of diagnosis or transplant are provided. Specifically, it remains unclear whether patients who experienced downstaging by TACE got the benefit of HCC related match-MELD or were transplanted only after clinical deterioration or with expanded criteria donor organs directly allocated to the transplant center.

Seventy-five patients (55%) suffered from Child-Pugh A cirrhosis, 100 patients had only one or two lesions and/ or 120 out of 136 patients had UICC-T1/T2 tumours. Due to the scarcity of available organs, liver resection in Child-Pugh A cirrhotic patients may have