Reply to: “Prediction of liver-related mortality in a community setting”

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Published in:
Journal of Hepatology

DOI:
10.1016/j.jhep.2022.12.021

Publication date:
2023

Document Version
Author accepted manuscript

Mind the prevention paradox

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MANUSCRIPT INFORMATION: Word count= 710; Number of tables= 0; Number of figures=0

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CONFLICTS OF INTEREST: No conflicts of interest to disclose.

FUNDING: HI is supported by a viral hepatitis fellowship from the Medical Research Foundation (grant ID: C0825).

AUTHOR CONTRIBUTIONS: writing and editing manuscript: HI and ING.

To the Editor,

We thank Schneider et al [1] for their interest in our study [2]. Our objectives were two-fold. First, to assess if it is possible to estimate 10-year risk of cirrhosis morbidity using readily available scores. Second, we determined the extent to which these scores could be enhanced by incorporating information on germline genetic polymorphisms.

Onset of cirrhosis morbidity represents a watershed point in the natural history of chronic liver disease. [3] It heralds a downturn in patient quality of life, and an increase in health system expenditure. It is also of major interest to “at risk” individuals, who want to know their chance of developing life-impairing overt liver disease. Our decision to set incident cirrhosis morbidity as the primary outcome event was influenced by these factors.

Schneider et al’s analysis of UKB data suggests a sizeable proportion of liver deaths occur in individuals with lower FIB4/APRI/Cirrus values. [1] This is an interesting observation. Their results are supported by previous studies. [4,5] For example, in a study of FIB4 values from a community cohort in Sweden, Haagstrom et al reported that half of incident cases of severe liver morbidity occurred in patients with low FIB4 (<1.35). [5] At first glance, this does seem paradoxical. That is, if these risk scores really are so good at estimating 10-year risk, why do so many events occur in lower risk patients? To answer this point, we must think about how 10-year risk is distributed in the population. The number of people who develop a liver event within a given risk group depends not just on the 10-year risk, but also on the number of people who fall into that risk group. Note that low risk is not zero risk; thus, if the number of low-risk individuals is sufficiently high, there will naturally be scope for many events to occur. Vice versa, if the number of high-risk patients is relatively small, then it is not surprising if the number of events occurring in this group is also small. However, this does not take away from the fact that high risk individuals are de-facto more likely to develop the outcome event than low-risk individuals. Thus, the occurrence of events in low-risk

patients does not undermine our conclusion regarding the ability of FIB4/APRI to predict 10-year risk.

From a broader perspective, the phenomenon Schneider et al describe – i.e. cases from low risk groups exceeding those from high risk groups – is a corollary of the prevention paradox, which applies widely to many risk factors and scores. [6] For example, older maternal age is strongly associated with a higher likelihood of giving birth to a Child with Down's syndrome. Despite this, most children with Down's syndrome are born to younger mothers. [6] Does this mean therefore that maternal age is not a "useful" predictor of giving birth to a child with Down's syndrome?

Schneider et al call for more research "to enable the detection of liver-sick patients". This may entail efforts to improve the discriminative ability and calibration of existing risk models – e.g. as we tried to do in our study by integrating genetic data – or even the development of new risk models entirely to estimate 10 year risk. We support this. However, we shouldn't expect that an improved risk model is going to suddenly present us with a different and more convenient risk distribution. In our view, the prevention paradox that Schneider et al highlight, is not a poor reflection on the risk score, but a reflection on the risk distribution which the risk score is simply describing. Nevertheless, Schneider et al are right to question how 10-year risk could be used in clinical practice. In our view, we need an open discussion between patients, clinicians and healthcare payers about the risk/trade-offs we are willing to tolerate. This will inform development of decision-rules, mapping risk to clinical action. These ideas are eloquently articulated by Rowe and D'Amico. [7] At the moment, the "cart is before the horse" – i.e. we arguably have the risk tools, but we have not built consensus around how to use them. Overall, we contend that considering ten-year risk and how it is distributed is vital. Understanding this will facilitate a more strategic and patient-centred approach to managing liver disease in the community.

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