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Risk stratification in primary sclerosing cholangitis: its time to move on from replicating imperfection and break the glass ceiling

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Primary sclerosing cholangitis (PSC) represents the greatest unmet need in modern hepatology, given its ill-defined aetiology, critical absence of medical therapy, and the fact that liver transplantation remains the only life-saving intervention for patients. Although rare, PSC now accounts for 10-15% of all liver transplant activity in European liver transplant programmes, and is now the lead indication for transplantation in Nordic countries [1,2]. However, rates of progression vary, and accurately predicting the disease course is of relevance to clinical practice and interventional trial design [3]. Patient expectations are also rising, with a feeling that doctors must be able to tell them if they are at risk, if so in what way, and with a reasonable degree of confidence [4].

To this effect, several attempts to construct 'the ideal' prognostic model have been made, each attributing different weights to clinical, laboratory, cholangiographic or histological variables [3]. Historic algorithms such as the Mayo PSC risk score (MRS) [5,6], derive mostly from tertiary referral centres, and predominantly liver transplant units. Although widely applied, these scores lose predictive accuracy beyond 4-5 years from the point of application. Moreover, the era in which they were conceived antedates the modern management of variceal bleeding. In a similar vein, cholangiography-based systems rely on biliary imaging by ERCP, which is not standard of care for monitoring in PSC [7,8].

More recently, intensive efforts have been conducted at a multi-centre level, to model the natural history using contemporary patient cohort data [9–11]. Akin to older prognostic scores before it, the Amsterdam Oxford model (AOM) is composed of mainly laboratory parameters, each demonstrating stratification properties in their

own right. Of note, only seven variables were chosen during derivation of the AOM (out of a total 13 which showed predictive utility). In the original study, the authors state that this was to limit the number of covariates present in the model, so as to ease use in clinical practice, whilst yielding an overall model C-statistic that was no more than 10% below the optimal reading possible. In turn, the way in which covariates were selected for the model was based on the rank of their individual C-statistic values. This approach is somewhat questionable, and less sensitive than selecting covariates based on likelihood, risk, or indeed their individual calibration accuracy [12].

Within the final AOM, the chosen covariates were disease phenotype (large duct versus small duct PSC), serum transaminases and alkaline phosphatase (ALP), together with biomarkers of more advanced liver disease such as bilirubin, albumin and total platelet count [10]. The landmark study from which the model derives, presents up to 30 years of patient follow-up data. Predicted event rates according to the AOM closely mirrored actuarial survival estimated by the Kaplan-Meier method (calibration accuracy). However, the chosen endpoint of PSC-related death included colorectal cancer mortality (in addition to liver transplantation), which is contentious given that all covariates in the model relate to hepatobiliary disease. Discriminant utility of the AOM was fair, as evidenced by a concordance (C)-statistic of 0.68 and accompanying wide confidence intervals (95% CI 0.51-0.85). C-statistics were similar when the model was applied at diagnosis, and annually up to three years thereafter. No sub-stratification according to disease stage, or variant clinical phenotypes was conducted.

In the current issue of *Journal of Hepatology*, Goet *et al.* present results of a very impressive prediction model study, using external patient data to validate findings of the AOM [13]. The studied cohort comprised 534 patients, the vast majority having classical large duct disease (87%) and receiving ursodeoxycholic acid therapy (92%). Notable differences to the original AOM study, were the fact that patients were all diagnosed at one of three liver transplant units (as opposed to a predominant population-based cohort), with the selected endpoint being liver transplantation and all-cause mortality [10,13].

The paper replicates several key findings, but most importantly, provides transparency surrounding utility and limitations of the model. Firstly, discriminant performance was near identical in this validation exercise as in the original AOM study (C-statistic: 0.67 at baseline; 95% CI 0.64-0.70), but seen to improve when applied at 5 years following diagnosis (0.75; 95% CI 0.71-0.78). The authors then go on to show good calibration accuracy of the model, and actually quantify differences between observed versus expected clinical events for the overall cohort. However, **Supplementary Figure 1** provides a major take-home message [13]. When testing the model over different time points, calibration accuracy was greatest for patients in the lower percentile risk groups ($<20^{th}$); whereas, the incidence of clinical events was underestimated in mid- and high-percentile scorers, particularly when applying the AOM at 3- and 5-years following the date of PSC diagnosis. A direct comparison of the AOM versus MRS was also provided, something that was lacking in the original AOM study. The MRS exhibited greater discriminatory value (C-statistic: 0.73, 95% CI: 0.73-0.76 at baseline; 0.79, 95% CI: 0.76-0.82 at 5 years), but overestimated the risk of future clinical events long-term. This trade-off between discrimination versus

calibration accuracy is recognised in prognostic modelling, particularly if one 'assumes' that distribution of disease risk is uniform across patient populations, when it may not be [12]. Nevertheless, in the related cholestatic disorder primary biliary cholangitis (PBC), prognostic models demonstrate both high-level discrimination as well as calibration accuracy [14–17]. This difference may relate to the fact serum ALP exhibits wider intra-individual variability between time-points in PSC, which is likely to impact the performance of any ALP-based stratification system such as the AMS [18]. Notably, the current publication points toward significant limitations to serum ALP as a biomarker, as well as raising questions surrounding its utility as a surrogate endpoint in PSC clinical trials. Firstly, the discriminant value of ALP was marginal at best (C-statistic ranging 0.52-0.63 during the first five years following diagnosis). Furthermore, assessment of ALP calibration revealed very large differences between observed and predicted survival rates.

The authors also stratified patients according to high- versus low-risk groups, following a grid search to identify the most discriminatory AOM cut-point (<2.0 versus $\geq$2.0). In so doing, they identify that 8.4%, 13.9% and 25.4% of patients who were identified as being low-risk at diagnosis actually move into a high-risk category when the model is applied at 1-, 3- and 5-years, respectively, indicating the progressive nature of PSC as a disease and a big caveat if applying the model to counsel patients in clinic.

A head-to-head comparison between the AOM and other contemporaneous models, such as the UK-PSC score and the PREsTo index, has yet to be conducted [9,11]. For a fair evaluation, the performance of each would need to be tested simultaneously in

the same population. When assessing discriminant utility, factors such as censoring distribution and intra-predictor correlation also need to be considered, and study endpoints consistent to allow comparability. Of note, all existing models examine the cumulative incidence of events at specific time points; however, prognostic factors likely differ for endpoints developing in the first few years after diagnosis to those which manifest a decade later. Yet by current methodology, both early and late events are counted when calculating overall 10-year event-free survival. Perhaps a more precise method would be to identify predictors of clinical events occurring at specific intervals; for instance, from diagnosis up to 2 years, 2–5 years, and 5–10 year timeframes. A further drawback across all risk models, which has been identified by patient focus groups in the UK, is that they rely on the date of diagnosis being known and accurate. In reality, however, individuals may experience years from first presentation to the moment they are diagnosed. Therefore, patients request that dynamic biomarkers or prediction models be developed, which can be applied at any point and irrespective of the date they are told they have PSC [4].

In any event, the development and validation of new risk scores represent a major advance for risk stratification in PSC. The question that follows is: "how and when to use them?" To a patient, it is more meaningful to know what the probability of a clinical event occurring is over a given time period. In this case the AOM is placed well, given the validation in calibration accuracy across two high quality studies [10,13]. It is important however, to re-calculate the score and update patients about their risk profile over sequential clinic visits, given that 25% of patients classified as low risk become high risk over 5 years. In turn, when stratifying patients toward clinical trials, scores with greater discriminant utility may be more appropriate [9,11].

Efforts toward prognostic modelling continue to be refined, but there remains need to differentiate variables associated with early-yet-rapidly progressive disease from that which is already advanced. Discriminant utility and accuracy of existing tools appear to have reached a ceiling, so perhaps a hierarchical approach to risk stratification is now needed, rather than repeated permutations and combinations of routinely available laboratory parameters to heterogeneous groups of patients. It is plausible that different variables are relevant at distinct disease stages. For instance, measures of biliary disease involvement are likely to be more relevant early on in the disease process, and help to predict longer-term outcomes. Reciprocally, tools that measure the extent of parenchymal disease are more likely to predict clinical events that develop more immediately (**Figure 1**). The critical challenge in PSC lies in its heterogeneity, varying phenotypic presentations, and identifying the juncture at which early prognostic markers become redundant, and overridden by those directly linked to the burden of liver fibrosis [19,20].

Conflicts of interest

None to declare.

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Figure 1: Stratifying the stratifiers: a hypothetical approach to applying prognostic tools

In primary sclerosing cholangitis (PSC), several predictive tools, biomarkers and prognostic models have been created, for which a hierarchical ranking based on disease stage is proposed. Whilst non-modifiable patient factors (green), such as sex and inflammatory bowel disease phenotype are proven in large observational cohorts, their predictive utility is seemingly lost during the validation of biochemical risk stratifiers (yellow), such as that presented in the current study. In a similar vein, cholangiographic methods have the potential to track biliary disease progression more readily (orange). However, their prognostic utility is likely attenuated once liver fibrosis has reached a certain stage, which is evident by the underestimation of clinical event rates in high-risk groups. At a certain point, surrogate biomarkers of fibrosis such as the enhanced liver fibrosis score (ELF) and transient elastography, would become more meaningful (red). The critical challenge in PSC as a disease is identifying at what ELF score or elastography reading do earlier stratification tools become superseded? Regardless, the onset of advanced liver disease with features of hepatic decompensation, persistently elevated bilirubin, or hypoalbuminaemia, is more immediately linked to development of clinical events (black), following which the utility of any prognostic tool before it becomes moot. *Asterisks denote emerging stratification tools with potential, but that have not yet been proven in PSC specifically.

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