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Editorial

Portal hypertension and development of hepatocellular carcinoma: Factors influencing significance in prognostic models ☆

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In this issue of the Journal, Ripoll et al. report interesting results about the prognostic association of the hepatic venous pressure gradient (HVPG) with the risk of developing hepatocellular carcinoma (HCC) in early cirrhosis [1]. They have developed three different Cox proportional hazards models, all of which include HVPG as the most significant predictor of HCC. Although these new interesting results are entirely valid in the patients used for their derivation, they are to some extent unexpected, since well recognised prognostic variables in cirrhosis like age, Child-Pugh score, MELD, serum bilirubin and INR (prothrombin time) had no significant independent prognostic influence in the models. Several factors may have influenced this particular outcome.

Selection criteria. The study is retrospective and based on data from a randomized controlled trial designed to evaluate the efficacy of the non selective beta-blocker timodol in preventing gastroesophageal varices [2]. Patients were followed until development of varices or variceal bleeding, which was the primary end point. The admission criteria included cirrhosis and portal hypertension. HVPG should be at least 6 mm Hg. Among the included patients the median HVPG was 11 mm Hg (range 6–25) and 63% had HVPG $\geqslant$10 mm Hg [1]. However, patients with gastroesophageal varices were excluded, and this criterion alone excluded 37% of the patients screened for varices [2]. Patients with ascites requiring diuretics were also excluded. Thus the patients, which were actually included in the study, were rather special: they had portal hypertension, but had neither gastroesophageal varices nor ascites. Of the included 213 patients, 89% belonged to Child-Pugh class A and none to class C. The mean Child Pugh score was 5.4 (median 5, range 5–8), mean bilirubin was 1.16 mg/dl (median 0.9, range 0.2–5.9), mean albumin was 3.9 g/dl (median 4.0, range 2.1–5.4), mean INR (prothrombin time) was 1.34 (median 1.1, range 1–2) and mean creatinine was 0.9 mg/dl (median 0.9, range 0.2–1.9) [1,2]. Thus the patients seem to belong to a somewhat special group of cirrhosis with quite divergent variables: relatively more structural fibrotic and vascular abnormality [3,4] leading to elevated HVPG but relatively little decompensation or metabolic abnormality with little effect on liver and kidney function. Thus in the included patients the usual biochemical prognostic variables in cirrhosis did not vary as much as HVPG, which was allowed an unrestricted degree of abnormality. This could relatively favour HVPG in the analysis and explain to some degree why this variable achieved its prognostic influence.

Variables analysed. The variables recorded and available for analysis vary between prognostic studies [5]. Most frequently the easily obtainable variables like symptoms, signs and simple laboratory tests are recorded. Therefore these have a greater chance of being analysed and included in prognostic models than more special invasive investigations like measurement of

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HVPG, even if this variable is of key interest in evaluating the hazard of the patient. Therefore the demonstration of the paramount prognostic importance of HVPG in the paper by Ripoll et al. [1] underlines the great importance of the structural hepatic vascular anomalies [3,4] in regard to prognosis. However, not all variables recorded may be selected for analysis and for potential inclusion into a prognostic model. Serum creatinine has been reported to be a prognostic variable in cirrhosis in many studies [5]. Although this variable was recorded, it was not selected for analysis [1], probably because of its limited variation in the included patients (see above).

The endpoint. In the paper by Ripoll et al. [1] this was the development of HCC according to histological confirmation, typical image suggested by two radiological techniques or only in one imaging technique with an alpha-fetoprotein (AFP) greater than 400 ng/ml. Although HCC is associated with cirrhosis, development of HCC cannot be expected to have the same prognostic indicators as cirrhosis. A recent review shows that in HCC prognostic indicators comprise both tumour- and liver-related variables including the Child-Pugh class [6]. The demonstrated association between HVPG and the development of HCC by Ripoll et al. [1] is interesting since the study was not primarily designed to predict the development of HCC, and baseline alpha-fetoprotein (AFP) was only recorded retrospectively as a binary variable [1] after termination of the original study [2].

Scoring of variables. In a prognostic model the scoring of the included variables will markedly affect their influence in the model [7,8]. Normally quantitative variables should be kept as such and not dichotomized, since this will lead to loss of information. However, for regression models like the Cox model the assumption of proportional hazards or linearity must be fulfilled. This may necessitate a particular scoring of the included variables. For example variables like bilirubin, INR (prothrombin time), AST, ALT and creatinine most often need to be included as the logarithm of the value for the assumption of proportional hazards to be fulfilled. In the study by Ripoll et al. [1] bilirubin, AST, ALT and INR was studied without logarithmic transformation, and reportedly they could not find model assumptions to be violated. However, this could be due to the relatively small variation of these variables among the patients (see above). Alpha-fetoprotein (AFP) did not achieve significance in the final Cox model, possibly because it could only be scored as a binary variable [1].

Variable selection method. To reduce overfitting, variables should normally be included in the analysis in accordance with their *a priori* probability of prognostic influence. Ripoll et al. [1] used the stepwise backward elimination method [8] in their Cox regression analyses. As demonstrated in their Table 3 [1] starting with different sets of variables led to three different final Cox models as might be expected [8]. In addition, the influence of first order interactions between HVPG and the other variables was studied, but none were significant. Thus the analyses had an explorative element, and this may have given rise to slight overfitting. However, the authors consider their models only explicative and do not think they should be used for prediction purposes in new patients [1] before they have been verified in independent patients.

In summary, Ripoll et al. have provided new interesting results on the association between HVPG and development of HCC [1]. However, given the retrospective nature of the study, the rather special selection criteria and some particulars in the analysis, it would be important to validate the results in independent patients. If verified in new patients the results would provide an important lead, both with regard to the pathogenesis [9] and the screening strategy for HCC [10].

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