Editorial

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Towards a personalized approach to hepatic resection in cirrhotic patients

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See Article, pages 920–929

In this issue of the *Journal*, a multicentre study from several experienced French hepatobiliary units provides relevant information regarding the prediction of outcome of liver resection in cirrhotic patients.[1]

Hepatic resection (HR) is theoretically the best non-transplant treatment for patients with primary liver cancer, since it allows radical removal of the tumour, as well as providing prognostic information from the histological examination of the specimen.

Evaluating whether HR is the appropriate treatment for patients with a cirrhotic liver is extremely complex. In assessing the option of HR, the team needs to weigh up the risk of post-hepatectomy liver failure (PHLF),[2,3] the risk of recurrence of the disease, the efficacy of alternative treatments, and the probability of dying of liver-related and other diseases in the long run. The study by Proudeau *et al.* concentrates on the issue of postoperative liver failure, a strong determinant of early mortality and resource use. It identifies that the main preoperative factors that predict postoperative liver failure are platelet count, percentage of residual liver, and intended laparoscopy, all of which are easily available. The postoperative factors that complete the model are whether conversion to laparoscopy is needed and blood loss.

Seen from a broader perspective, recent guidelines from the European Association for the Study of the Liver (EASL) have endorsed the transition from a mono-parametric to a multi-parametric algorithm to select surgical candidates with hepatocellular carcinoma (HCC) on a cirrhotic liver.[4]

The mono-parametric model (with single decision knots directing the patient one way or the other) was proposed by the Barcelona Clinic Liver Cancer (BCLC) group[5] and ended up in a series of single criteria as indications to HR (*i.e.* solitary tumours and very well-preserved liver function, hepatic vein to portal system gradient ≤10 mmHg or bilirubin ≤17 μMol/L).[6] The mono-parametric model, therefore, could be (and was) interpreted as allocating only "ideal candidates" to HR. Such a critique missed the point that the outcome on which the algorithm was constructed was long-term survival (5-year), and not surgical morbidity or mortality, which were very low in the original study. A negative parameter was not meant to establish an absolute contraindication, implying that resection should be decided in comparison with other treatments in terms of advantages, complications, and overall results. It is however clear that nowadays the limits for safe liver resection can no longer be decided only on the BCLC criteria, that does not include information such as the position of the tumour (central or peripheral), the proportion of functional liver resected, and the use of less invasive techniques such as laparoscopy.

A recent prospective study from Cucchetti *et al.* noted that HR could be performed in patients with mildly elevated portal hypertension with a low risk of PHLF and 0% postoperative mortality.[7] Similarly, a large multicentre study has shown that patients exceeding one or more of the described mono-parametric criteria had an optimal post-HR outcome in experienced centres.[8]

Optimal surgical candidacy is based on a multi-parametric evaluation including compensated Child-Pugh class A liver function with a model for end-stage liver disease (MELD) score <10, to be matched with the grade of portal hypertension, acceptable volume of remaining parenchyma and the possibility to adopt a laparoscopic/minimally invasive approach.[4]

In line with this multi-parametric concept, some algorithms to select optimal candidates for HR on a cirrhotic liver have been proposed.[9,10] For example, the algorithm from Citterio *et al.*[10] was endorsed in recent EASL guidelines.[4] In this algorithm, the authors weighted the prognostic impact of portal hypertension, MELD score, and the extent of HR in determining PHLF and evaluated the hierarchic interaction between these variables. Based on their results, the authors proposed a simple algorithm to stratify the risk of PHLF with the potential to individualise the decision to resect or not resect individual patients with HCC based on the availability and prognostic profile of alternative therapeutic solutions. The main limitation of the study by Citterio *et al.*[10] was that the investigators did not measure the prognostic weight of the minimally invasive surgical approach.

There is growing evidence that laparoscopic or robotic HR can treat liver tumours on a cirrhotic liver with decreased postoperative morbidity and risk of PHLF, without compromising oncological outcomes compared to the conventional open approach.[11–13]

In the present study, Prodeau *et al.*[1] found that preoperative and postoperative models were able to efficiently predict the risk of PHLF in a cohort of 343 cirrhotic patients. The main

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finding of this study is that, for the first time, the laparoscopic approach has been included as an independent variable.

This result is particularly important because while platelet count, liver dysfunction, and the extent of HR are usually unchangeable variables inherent to the characteristics of the patient's disease, the possibility of adopting a laparoscopic approach is in the hands of the team, and has the potential to expand the indications of HR to patients with HCC and borderline liver function.

The prognostic benefit of laparoscopic HR in cirrhotic patients can be considered multi-factorial.[11–13] The lower invasiveness of laparoscopy is probably related to the decreased damage to the abdominal wall, avoiding interruption of collateral veins and to the lymphatic circulation.[14] Also, the decreased exposure of the abdominal viscera may reduce the incidence of ascites.[15] The CO_2 pneumoperitoneum, which has been demonstrated to reduce local immune responses against surgical stress,[15] could be another explanation. Other possible explanations include reduced mobilisation and manipulation of the liver, and less intraoperative fluid requirements, less blood loss and blood transfusion.[15] These can be explained by the haemostatic effect of pneumoperitoneum, better magnification, and application of newly developed devices for parenchymal transection. Other less demonstrable confounders may be the expertise of the surgeon and the team, and the more peripheral position of tumours associated with laparoscopic liver resections.

The model proposed by Prodeau *et al.*[1] also included platelet count and liver remnant volume ratio, in line with other models including portal hypertension and extent of hepatectomy.[9,10]

This study was the first to show a linear correlation between liver remnant volume ratio and PHLF. The limitations of this study are well discussed by the authors, such as the selection of patients submitted to reselection in very experienced centres: liver functional scores such as MELD or Child-Pugh were not significant in the multivariable analysis, and the prognostic performance of the models was acceptable (AUC between 0.73 and 0.81) but far from perfect. An additional limit, shared with all published predictive scores[1,9,10] for HR in cirrhotic patients, is the absence of strong external validation. Thus, none of the proposed models have undergone the evidence-based validation required for them to be routinely adopted in every day clinical practice.

Independently from the predictive accuracy and applicability of the model proposed by Prodeau *et al.*,[1] we think that the study is important because it introduces the idea of using continuous and not binary/cut-off scores. The online calculator is an interesting tool to obtain individualised predictions of the risk of developing PHLF grade A, B, or C on a continuous scale.

In fact, in clinical practice, it is very difficult to determine a cut-off of grade C PHLF probability beyond which the risk of PHLF would be considered as prohibitive and HR contraindicated. Similarly, the 3% mortality rate cut-off proposed by recent guidelines[4] is controversial as the final decision to adopt HR strongly depends on the available alternative therapies.

This is a very important point because the recent concepts of left-to-right or right-to-left treatment stage migration,[4] and the concept of "therapeutic hierarchy"[16] have increased decision-making flexibility compared to previous strict algorithms for patients with HCC, which provided only one treatment option for each stage or sub-stage. This flexibility enables the clinician to evaluate the feasibility of more treatment options for each tumour stage or sub-stage and to choose the option that will confer the highest survival benefit to the patient. The lack of information on long-term survival in the study, a crucial piece of information in the decision process, could be addressed in a future investigation, and we encourage the authors to conduct it in the future.

In conclusion, we think that this study introduces very interesting findings, mainly because it gives further support to the new multi-parametric decisional model for HR in patients with HCC introduced in recent guidelines. The inclusion of the laparoscopic approach as a variable is clinically relevant, since it depends to some extent on the surgeon and can expand the indications for HR.

Although we are still far from the perfect model to individualise the prediction of the PHLF risk, this study represents a good example of design and statistical methodology that should be implemented in larger validation cohorts.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Author names in bold designate shared co-first authorship

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