**Title: Multicentre validation of a clinical prognostic score integrating the systemic inflammatory response to the host for patients treated with curative-intent for colorectal liver metastases**

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**Abstract**

Introduction: Liver surgery is the only potentially curative treatment for colorectal liver metastases (CRM) but the outcome is very variable being dependent on multiple clinical features. Previous models or ‘scores’ that attempt to predict survival have limited utility and have not been externally validated or have not included variables of current interest such as neutrophil-to-lymphocyte ratio (NLR), considered to be an index of the systemic inflammatory response.

Methods: We identified independent prognostic factors in patients who underwent liver surgery for CLM in a tertiary centre in the United Kingdom (UK) between 2010 and 2015. A pre- and a postoperative score were created by combining these factors to stratify patients into different risk groups. These new scores were validated in an international cohort of 219 patients from China and France.

Results: Multivariate Cox regression analysis of the 364 patients in the UK cohort identified 6 preoperative and one additional postoperative prognostic factor for overall survival (OS): American Society of Anaesthesiologists (ASA) score, location and node status of the primary tumour, number and size of CLM, neutrophil-to-lymphocyte ratio (NLR) and resection margin. Both pre- and postoperative scores can be readily calculated with a smartphone application which we have developed and present here. The new scores outperformed previously published scoring systems.

Conclusion: We have developed a new prognostic score based on clinicopathological characteristics and on measurement of the systemic inflammatory response which could help to tailor patients’ management.

**Introduction**

Liver surgery remains the only potentially curative treatment for colorectal liver metastases (CLM), with 5- and 10-year overall survival (OS) rates of up to 51% and 16% respectively [[1](#_ENREF_1),[2](#_ENREF_2)]. However, survival rates are very disparate so that scoring systems have been developed with the aim of stratifying patients considered for liver resection into different risk groups. Theoretically, patients’ stratification could help tailoring patients’ management, such as considering peri-operative chemotherapy or ablation rather than resection, or contraindicating extreme liver resection. Despite several clinical scoring systems having been published, most of them were based on a single institution cohort of patients and before the era of modern chemotherapy and targeted therapy. Moreover, few have been validated in other institutions [[3-7](#_ENREF_3)]. These scores were built on clinicopathological variables, which makes them easy to use but potentially underpowered to monitor the tumour biology. Recently, cancer-related inflammation has gained attention in the understanding of carcinogenesis. The systemic inflammatory response of the host to the tumour is associated with survival in advanced and localized cancers and it can be monitored by inflammatory scores, such as the modified Glasgow prognostic score (mGPS) and/or the neutrophil-to-lymphocytes ratio (NLR) [[8](#_ENREF_8),[9](#_ENREF_9)].

The aim of our study was to create a new prognostic score integrating the systemic inflammatory response to predict survival in patients treated with curative intent for CLM.

**Patients and Methods**

*Patient selection*

We retrospectively analysed data from a prospectively accrued database of all patients who underwent curative-intent treatment with an open approach for CLM at a large tertiary hepatobiliary unit, Liverpool, UK between June 2010 and August 2015 (Table 1). All patients were identified during routine follow up as having recurrence, and subsequently were discussed at a specialist hepatobiliary multidisciplinary team (MDT), where ablation was considered as a curative-intent treatment. All patients with recurrence had a triple phase CT chest, abdomen and pelvis, a diffusion-weighted liver MRI and a PET-CT scan, unless absolute contra-indications existed. Patients were excluded from analysis if they had unresectable extra hepatic disease (EHD) and/or if they underwent a two-stage hepatectomy.

*Peri-operative management*

All patients had a baseline blood test performed within one week of surgery as part of routine preoperative workup. Preoperative NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. All liver resections and intraoperative ablations were performed through a reverse L-shaped laparotomy. Intraoperative ultrasound was routinely performed for staging and to guide surgical resection or ablation. A parenchymal preserving approach was performed whenever possible and use of intermittent Pringle manoeuvre was at the discretion of the operating surgeon. Liver parenchyma was transected with the Cavitron ultrasonic surgical aspirator (Valleylab, Boulder, CO). Intraoperative ablation technique was always microwave ablation (MWA) with standard energy deliverance of 100 watts for 90 seconds per lesion.

Patient follow-up included regular outpatient visits with the first visit scheduled at one month (with a contrast enhanced CT-scan for patients treated with ablation), and then three monthly for the first year, and every six months thereafter. All follow up visits included physical examination, carcino-embryonic antigen (CEA) measurements and contrast CT scans of chest, abdomen and pelvis.

*International multicentre validation cohort*

A multicentre cohort of 219 patients with the same inclusion criteria was used to validate the new score, and included measurement of the NLR. The cohort included 155 patients from Hong Kong, China and 64 patients from Lyon, France.

*Statistical Analysis*

All analysis was carried out using Stata/SE 14.2 (StataCorp, Texas, USA) and R version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria).Continuous variables were expressed as median and interquartile range. Categorical variables were presented as percentages. Highly skewed variables were log10 transformed. Overall survival (OS) was calculated from the date of liver surgery to the date of death from any cause or date of the last follow-up (censored observation). Survival estimates were calculated using the Kaplan–Meier estimator. Differences in survival between groups were assessed by log-rank test. Median follow-up was calculated using a reverse Kaplan–Meier estimator. The Liverpool, UK cohort was used as a training set on which the model was built and the external cohort comprising Chinese and French patients was used as a validation set. Univariable Cox regression analysis was undertaken to identify the prognostic variables. The new model was built using multivariable Cox regression with stepwise forward selection (similar results were obtained using backward selection) of variables significant at the 5% level. The proportional hazard assumption was tested by examining Schoenfeld residuals over time with zero slope indicating that assumption is not violated. In order to create the new risk score, the formula for the linear predictor was generated using the coefficients of the final model. A low and high risk group was identified by applying cut-offs to the linear predictor at the 50th centile (representing patients in the top 50% risk). The new model was then validated on an independent external cohort comprising of China and France.

The score described above is referred to hence forth as the ‘pre-operative’ score since all the requisite variables can be assessed preoperatively. This score was subsequently refined by adding the further variable of the ‘resection margin’ which was only available after the resected specimen had been examined pathologically, ‘the post-operative score’.

The new score was compared to previously published clinical prognostic scores using the following methods: (1) homogeneity within classification (differences in survival time among patients classified in the same group); (2) discriminatory ability (greater differences in survival time among patients in different groups); and (3) monotonicity of gradients (mean survival time in a more favourable group is longer than in a less favourable group). The likelihood ratio test was applied to evaluate the homogeneity. The linear trend chi-square test was used to quantify both the monotonicity and discriminatory ability. The Harrell’s concordance index (c-index) and Akaike information criterion (AIC) were employed to estimate the discriminatory ability.

A larger value of the likelihood ratio chi-square test indicates a system with better homogeneity and monotonicity; a larger value of the linear trend chi-square test implies a system with better discriminatory ability, and a larger value of the c-index and a smaller value of AICs signify a system with higher discriminatory ability.

Accuracy of the new score was assessed by comparison with previously published prognostic scores. Fong’s score includes 5 risk factors and stratifies patients into 2 groups (low and high risk) [[3](#_ENREF_3)]. Nordlinger’s score includes 7 risk factors within which clearance is not considered, as it cannot be measured preoperatively, and stratifies patients into 3 risk groups (low, intermediate and high risk) [[6](#_ENREF_6)]. Nagashima’s score includes 5 risk factors and stratifies patients into 3 risk groups [[5](#_ENREF_5)]. Konopke’s score includes 3 risk factors and stratifies patients into 3 risk groups [[4](#_ENREF_4)].

**Results**

Of 376 patients who underwent liver surgery for CLM between June 2010 and August 2015, 364 were eligible for the study. Clinico-pathological characteristics and peri-operative data of the training cohort are shown in Table 1. Overall survival according to each cohort is shown in Figure 1. Univariable analysis is presented in Table 2. Multivariable analysis of preoperative characteristics identified 6 significant prognostic factors for OS: American Society of Anaesthesiologists (ASA) score, location and node status of the primary tumour, number and size of CLM, and NLR (Table 3).When considering post-operative variables, the same 6 prognostic factors were identified, as well as resection margin (Table 3). We were therefore able to create a pre- and a post-operative score. Data about these prognostic factors in the 3 cohorts are detailed in Table 1.

Preoperative model

The new preoperative score was obtained by the formula:

*0.130 x metastatic tumour size (cm) +*

*0.556 x right location (no=0, yes=1) +*

*0.507 x node positive primary tumour (no=0, yes=1) +*

*0.861 x log10 (NLR) +*

*0.521 x multiple liver metastasis (no=0, yes=1) +*

*0.449 x ASA 3 or 4 (no=0, yes=1).*

In a two-level stratification at the 50th percentile (1.670), median OS was 61.22 (50.23,not reached) months in the low-risk group (n=162) and 30.36 (23.68, 35.95) months in the high-risk group (n=162, p<0.0001) (Figure 2A). The same difference was observed in the validation cohort with median OS of 99.28 (66.45, not reached) months in the low-risk group (n=122) and 41.25 (29.08, 73.65) months in the high-risk group (n=83, p=0.0023) (Figure 2B).

Postoperative model

The new post-operative score was obtained by the formula:

*0.133 x metastatic tumour size (cm) +*

*0.756 x positive margin (no=0, yes=1) +*

*0.795 x right location (no=0, yes=1) +*

*0.637 x node positive primary tumour (no=0, yes=1) +*

*0.981 x log10 (NLR) +*

*0.362 x multiple liver metastasis (no=0, yes=1) +*

*0.383 x ASA 3 or 4 (no=0, yes=1)*

In a two-level stratification at the 50th percentile (2.186), median OS was not reached in the low-risk group (n=152) and 30.36 (23.32, 34.67) months in the high-risk group (n=152, p<0.0001) (Figure 2C). The same difference was observed in the validation cohort with median OS of 75.30 (66.45,116.12) months in the low-risk group (n=160) and 29.08 (22.99 – 53.78) months in the high-risk group (n=45, p=0.0003) (Figure 2D).

 A summary of the median OS and the corresponding hazard ratios for the risk groups in the two models is presented in Table 4.

Comparison with existing prognostic scores

When previously published scoring systems (Fong, Nordlinger, Nagashima, Konopke) were used in patients from the UK cohort, we observed a significant difference in OS between patients in the low-risk group and those in the high-risk group (Figure 3). For direct comparison, we converted three-strata scores into two-strata scores (Nordlinger, Nagashima, Konopke). Both pre- and postoperative new scores were more discriminant than the four previously published scores tested (Table 5).

**Discussion**

This study describes the development of two new prognostic scores for patients managed with curative-intent for CLM, and their international validation. One score is based on easily available preoperative characteristics. Some of them have utilised long-recognized prognostic factors (such as the tumour burden, number and size of metastases, nodal involvement of the primary tumour). In contrast, the location of the primary tumour and the systemic inflammatory response of the host to the tumour have only been more recently recognised and are still under investigation [[8](#_ENREF_8),[10](#_ENREF_10),[11](#_ENREF_11)].\*\*\* Ours are the first clinical risk scores integrating the measurement of the systemic inflammatory response through the NLR with international validation. Such validation is crucial as one of the major limitations of current risk scoring systems is their lack of reproducibility when applied in other institutions [[12](#_ENREF_12)]. We calculated the scores at the time of the surgery, as scoring systems seem to have higher predictive capacity if calculated after neoadjuvant therapy [[17](#_ENREF_17)]. We also developed a post-operative score which added the resection margin, an important variable only assessible after the resection specimen has benn evaluated.

Even though liver resection remains the standard of care for patients with CLM, recent progress in chemotherapy and targeted therapy could challenge this paradigm. Indeed, median survival of 30 months has been reported with palliative chemotherapy for stage IV colorectal cancer [[13](#_ENREF_13)]. When considering the two-level stratification at the 85th percentile with our model, median OS of the high-risk group was 19.38 (14.08 – 24.24) months.

It could suggest that patients in the high-risk group would not benefit from liver surgery, compared to chemotherapy only. However, it seems difficult in daily practice to contraindicate patients to potentially curative surgery, solely based on this new score and, more generally, on prognostic scores. Scores could instead be used to tailor patient’s management in case of clinical equipoise. For example, ablation could be preferred to resection in patients in the high-risk group. Progress in surgical techniques and peri-operative management have also increased the number of candidates to liver surgery. The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure is an example of a recent and aggressive technique for patients with otherwise unresectable CLM [[14](#_ENREF_14)]. This technique is associated with a post-operative mortality rate of about 10% and it raised questions about the oncologic benefit. Even if patients with two-stage hepatectomy were excluded from this analysis, our score could be helpful to select patients for such aggressive strategies. Identifying high-risk patients, whether it is from an oncologic (early recurrence and/or short OS) or from a surgical point of view (high rates of morbidity and mortality), has been recently used as an inclusion criteria in randomized trials about liver surgery for CLM. In the LAVA trial [[15](#_ENREF_15)], comparing ablation versus resection, some of the criteria used to define high-risk patients are subjective (“poor prognosis due to tumour burden”), which could introduce a bias. On the contrary, in the CHARISMA trial [[16](#_ENREF_16)], which will assess the benefit of neoadjuvant chemotherapy, high-risk patients are objectively defined by a Fong score of 3 to 5 (i.e. high-risk group). The postoperative model could be used to tailor the administration of postoperative chemotherapy in daily clinical practice or in further clinical trials.

Scoring systems were developed more than two decades ago and so were based on clinicopathological data only [[3](#_ENREF_3),[6](#_ENREF_6)]. Numerous other potential prognostic markers reflecting tumour biology have been identified [[17](#_ENREF_17)]. Among them, RAS status is probably the most evaluated one. Recently, the Fong score has been enhanced by adding RAS or KRAS status in two multicentre retrospective studies [[18](#_ENREF_18),[19](#_ENREF_19)]. RAS status was not available in our cohort of patients, so that these two new scores could not be included. However, incomplete data about RAS status is not surprising, as RAS mutation testing is still not routinely performed for resectable CLM.

Compared to these two very new scores based on historical series of patients, the cohorts were homogeneous regarding access to modern chemotherapy regimens, targeted therapies and interventional radiology with loco-regional chemotherapy. Interestingly, this study provides external validation of four previously published scores, demonstrating that these scoring systems are still relevant in the era of modern chemotherapy and multidisciplinary management.

There is growing interest in the inflammatory response of the host to tumour as a prognostically important variable. Several studies have suggested that modulation of the inflammatory response is a key step in the establishment of a metastatic niche [[20](#_ENREF_20),[21](#_ENREF_21)]. The modified Glasgow prognostic score (mGPS) and the NLR seem to be the most reliable tools to measure the inflammatory response as they were found (as in the present study) to be independent prognostic factors for OS after surgery for colorectal cancer, including surgery for CLM [[22](#_ENREF_22)]. We integrated the NLR rather than the mGPS in our score, because c-reactive protein and/or albumin were not recorded in the majority of our patients. Although NLR is cheap and easily measurable, many different cut-off values have been identified so as to classify patients into low- or high-risk. Such dichotomisation is recognised to waste information contained in datasets; a more effective way to maximise information extraction is to utilise to use the data in a continuous manner This is the approach we have adopted for all non-categorical variables (including NLR) in this study and may be one reason for the success of our models.

Although the formula to calculate the score is complex, it can be applied at the bedside using a simple online calculator that can be accessed on a smartphone.

In conclusion, this new prognostic score, which integrates the measurement of the systemic inflammatory response, could be helpful to identify very high-risk patients with poor prognosis after liver surgery for CLM and to tailor the peri-operative management of these patients.

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**Figure legend**

Figure 1: Kaplan-Meier graphs showing survival according to each cohort.

Figure 2: Kaplan-Meier graphs showing survival according to each risk group as defined by the pre-operative and post-operative score in the (A/C) training set and (B/D) validation set.

Figure 3: Kaplan-Meier analysis of overall survival after liver resection obtained with Nordlinger, Fong, Nagashima and Konopke scores.

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