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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: The Liverpool score

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ABSTRACT

Background: This study aimed to create a new prognostic score integrating the systemic inflammatory response to predict survival in patients treated with curative intent for colorectal liver metastases (CLM).
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 (Liverpool 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 of the UK cohort identified 6 preoperative and 1 postoperative prognostic factors 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 calculated with an online calculator at https://jscalc.io/calc/PXatrmjfrEFpYy2t. Using the pre-operative model on the UK cohort, 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 ($n = 162$, $p < 0.0001$). The same difference was observed in the validation cohort. The Liverpool score outperformed previously published scoring system with a c-index of 0.619 pre-operatively and of 0.637 post-operatively.
Conclusion: We developed a new prognostic score based on clinicopathologic characteristics including the site of the primary tumour location 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 [1,2]. However, survival rates are very disparate among patients, so that scoring systems have been developed since the nineties 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

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have 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]. These scores were built on clinicopathological variables, which makes them easy to use but potentially underpowered to monitor the tumour biology. Recently, the site of the primary tumour location is seen as increasingly of importance for the prognosis and treatment outcome of metastatic colorectal cancer [8]. Likewise, cancer-related inflammation has gained interest 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) [9,10].

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

Patients and methods

Patient selection

We retrospectively analysed data from a prospective database of all patients who underwent their first curative-intent treatment with an open or a laparoscopic approach for CLM at a large tertiary hepatobiliary unit between June 2010 and August 2015. All patients were discussed at a specialist hepato-biliary multidisciplinary team (MDT), where intra-operative 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 and/or multiple primary colorectal cancer. The study had full ethical approval from the UK NHS Research Ethics Committee and from the Chinese University of Hong Kong Clinical Research Ethics Committee. According to French law, no formal ethics approval was required for this type of study.

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. Intraoperative ultrasound was routinely performed for staging and to guide surgical resection or ablation. A parenchymal preserving approach, including ablation, was performed whenever possible and use of intermittent Pringle manoeuvre and the method of liver transection were at the discretion of the operating surgeon. Intraoperative ablation technique used microwave ablation (MWA), with a standard energy delivery of 100 W for 90 s per lesion. Intra-operative MWA was considered as a parenchymal-sparing policy, for tumours distant from major vessels and measuring less than 3 cm.

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), followed by every three months 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, which includes measurement of the systemic inflammatory response. 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 $\log_{10}$ 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 to build the model 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 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 50^{th} 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 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) [11]. 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.

Comparison with previously published clinical prognostic scores

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]. 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]. Nagashima's score includes 5 risk factors and stratifies patients into 3 risk groups [5]. Konopke's score includes 3 risk factors and stratifies patients into 3 risk groups [4]. Parameters of those prognostic scores are detailed in Supplementary Table 1.

Results

Of 376 patients who underwent a liver surgery for CLM between

Table 1
Clinicopathologic characteristics of the 3 cohorts.

Variables	Aintree, Liverpool, UK (n = 364)	Hong Kong (n = 155)	Lyon, France (n = 64)
Male, n (%)	250 (68.7), n = 364	86 (55.5), n = 155	NA
Age (years)	66 (60, 74), n = 364	61 (54, 69), n = 155	63 (55, 69), n = 64
Size of largest metastasis (cm)	3.3 (2.2, 5), n = 363	3.5 (2.5, 5.5), n = 155	2 (1.5, 3.1), n = 64
NLR	2.92 (2.04, 3.99), n = 341	2.69 (2, 3.53), n = 141	2.17 (1.62, 2.92), n = 64
With ASA 3/4, n (%)	82 (23.3), n = 352	16 (10.3), n = 155	1 (1.6), n = 64
Had blood loss ≥1000 ml, n (%)	56 (18.0), n = 312	NA	NA
<12 months interval from primary to liver metastasis, n (%)	257 (70.6), n = 364	NA	NA
With EHD, n (%)	38 (10.4), n = 364	NA	NA
With solitary liver metastasis, n (%)	169 (46.4), n = 364	89 (57.4), n = 155	28 (43.8), n = 64
With positive margin, n (%)	169 (49.6), n = 341	10 (6.5), n = 155	1 (1.6), n = 64
With stage T3/T4 of primary liver, n (%)	302 (84.1), n = 359	NA	NA
Node positive primary tumour, n (%)	216 (60.3), n = 358	110 (71.0), n = 155	33 (51.6), n = 64
Right location of primary tumour, n (%)	74 (20.3), n = 364	28 (18.1), n = 155	11 (17.2), n = 64
Death, n (%)	195 (53.6), n = 364	94 (60.7), n = 155	16 (25.0), n = 64
Median OS (95% CI), months	41.8 (36.2, 47.2), n = 364	59.74 (39.41, 73.65), n = 155	130.46 (75.30), n = 64
Median follow up (95% CI), months	50.5 (47.5, 54.7), n = 364	93.42 (76.09, 112.17), n = 155	51.22 (45.53, 55.82), n = 64

June 2010 and August 2015, 364 were eligible for the study. Clinicopathological characteristics and peri-operative data of the training cohort are shown in Table 1. Overall survival according to each cohort is shown in Fig. 1. Univariable analysis is presented in Supplementary 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 2). When considering post-operative variables, the same 6 prognostic factors were identified, as well as resection margin (Table 2). 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

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) (Fig. 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) (Fig. 2B).

Postoperative model

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) (Fig. 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) (Fig. 2D).

Summary of the median OS and the corresponding hazard ratios for the risk groups in the two models is presented in Table 3. Both pre- and postoperative scores can be calculated with an online calculator at https://jscalc.io/calc/PXatrmjfrEFpYy2t. The formula employed for calculation is shown in Supplementary Table 3.

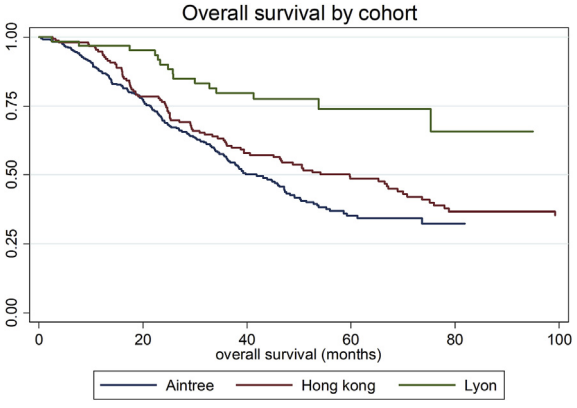

Fig. 1. Kaplan-Meier graphs showing survival according to each cohort.

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 (Fig. 3). For direct comparison, we converted three-strata scores into two-strata scores (Nordlinger, Nagashima, Konopke). Both pre- and post-operative new scores were more discriminant than the four previously published scores tested with a c-index of 0.619 pre-operatively and of 0.637 post-operatively (Supplementary Table 4).

Discussion

This study describes the development of a new prognostic score for patients managed with curative-intent for CLM, and its international validation. This score is based on easily available preoperative characteristics. Some of them have been recognized as prognostic factors for decades such as the tumour burden (number and size of metastases, nodal involvement of the primary tumour). Others prognostic factors, such as the location of the primary tumour and the systemic inflammatory response of the host to the tumour, have been identified only recently and are still under investigation [9,12,13]. It is the first clinical risk score integrating the measurement of the systemic inflammatory response through the NLR. Its strength lies in the international validation, as the limitations of scoring systems are their lack of reproducibility when applied in other institutions [14]. 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]. We also developed a post-operative model which add the resection margin to the preoperative characteristics. We observed a better OS in the Lyon cohort, probably due to a sampling bias. The number of deaths in the Lyon cohort was too small for that cohort to be used

Table 2
Multivariable cox regression analysis of clinicopathologic characteristics and peri-operative data in relation to overall survival in the UK cohort.

Variables	Pre-operative model		Post-operative model	
	Hazard ration (95% CI)	P-value	Hazard ration (95% CI)	P-value
Size of metastatic tumour (cm)	1.139 (1.087, 1.193)	<0.0001	1.142 (1.087, 1.200)	<0.0001
Positive margin				
No	–	–	1	
Yes	–	–	2.129 (1.515, 2.992)	<0.0001
Right location of primary tumour				
No	1		1	
Yes	1.743 (1.209, 2.513)	0.003	2.214 (1.494, 3.281)	<0.0001
Node positive primary tumour				
No	1		1	
Yes	1.660 (1.202, 2.293)	0.002	1.890 (1.342, 2.663)	<0.0001
ASA				
1 & 2	1		1	
3 & 4	1.567 (1.119, 2.196)	0.009	1.467 (1.025, 2.100)	0.036
Log10 (NLR)	2.366 (1.242, 4.509)	0.009	2.666 (1.377, 5.163)	0.004
Number of liver metastasis				
Solitary	1		1	
Multiple	1.685 (1.224, 2.318)	0.001	1.436 (1.027, 2.008)	0.034

ASA: American society of anaesthesiologists, NLR: neutrophil-to-lymphocytes ratio.
*Size and NLR were analysed as continuous variables.

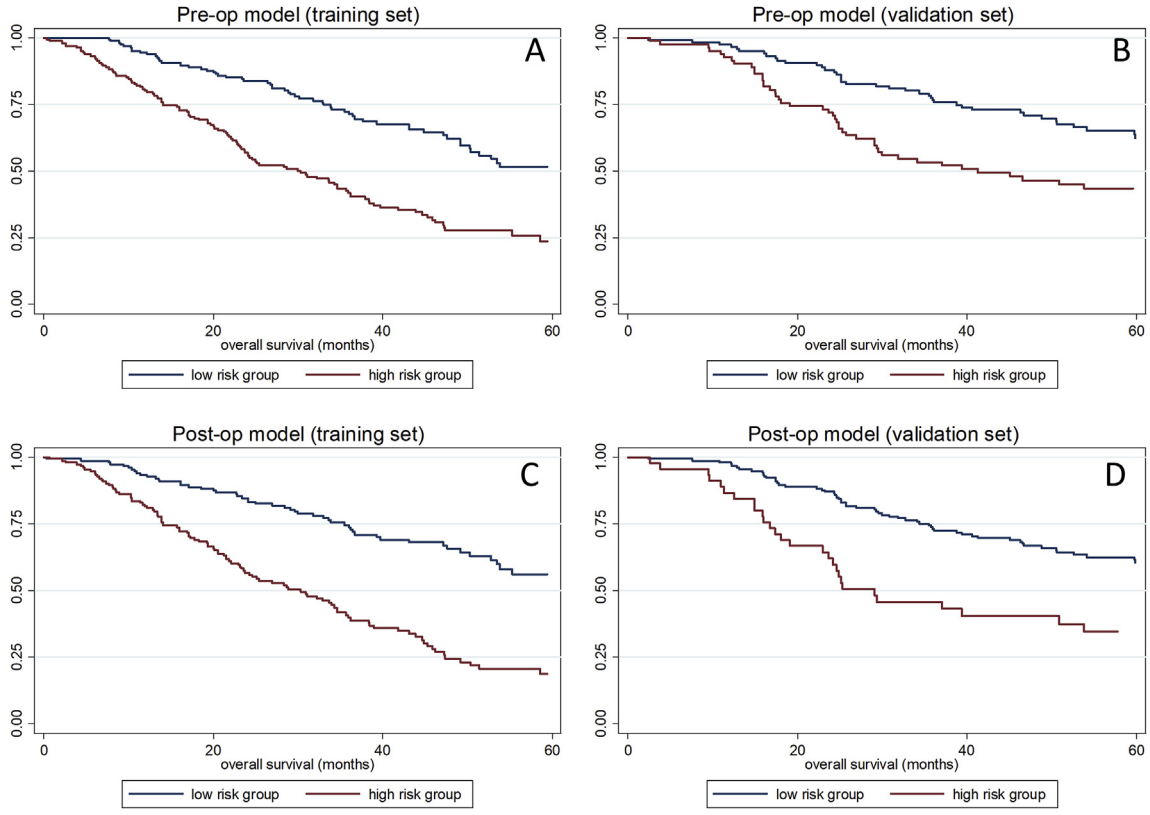

Fig. 2. Kaplan-Meier graphs showing survival according to each risk group as defined by the pre-operative and post-operative score in the (A/C) training set and (B/D) validation set.

on its own for validation. Hence, data from Hong-Kong and Lyon were combined. The Liverpool score maintains its validity when applied on Hong-Kong dataset.

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 [15]. When considering the two-level

Table 3
Median OS and hazard ratio by risk group.

Model	Set	Risk group	N	Median overall survival, months (95% C.I.)	p-value (for median OS)	Hazard ratio (95% C.I.)	p-value (for HR)
Pre-operative model	Training	Low	162	61.22 (50.23)	<0.0001	1	<0.0001
		High	162	30.36 (23.68, 35.95)		2.44 (1.78, 3.35)	
	Validation	Low	122	99.28 (66.45)	0.0023	1	0.003
		High	83	41.25 (29.08, 73.65)		1.81 (1.23, 2.68)	
Post-operative model	Training	Low	152	Not reached	<0.0001	1	<0.0001
		High	152	30.36 (23.32, 34.67)		3.10 (2.21, 4.34)	
	Validation	Low	160	75.30 (66.45, 116.12)	0.0003	1	<0.0001
		High	45	29.08 (22.99, 53.78)		2.16 (1.41, 3.32)	

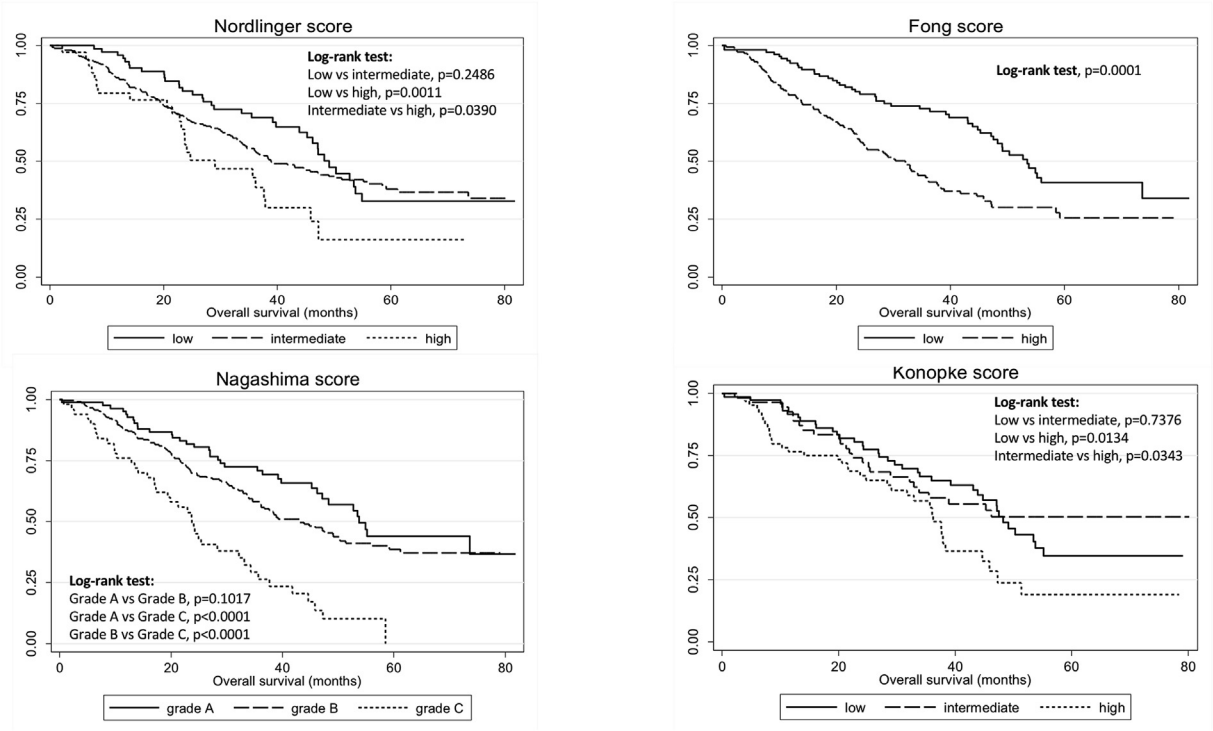

Fig. 3. Kaplan-Meier analysis of overall survival after liver resection obtained with Nordlinger, Fong, Nagashima and Konopke scores.

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 patients 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 [16]. 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 patient 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 criterion in randomized trials about liver surgery for CLM. In the LAVA trial [17], 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 [18], which will assess the benefit of neoadjuvant chemotherapy, high-risk patients are objectively defined by a Fong score of 3–5 (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 [3,6]. Numerous other potential prognostic markers reflecting tumour biology have been identified [19]. 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 [20,21]. RAS status was not available in our cohort of patients, so that these two new scores could not have been tested. 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 locoregional 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 now 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 [22,23]. 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 to be independent prognostic factors for OS after surgery for colorectal cancer, including surgery for CLM [24]. We integrated the NLR rather than the mGPS in our score, because c-reactive protein and/or albumin were available in about 30% of the patients only. 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 and location of the primary tumour, 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.022.

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