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Preoperative Leucocyte-Based Inflammatory Scores in Patients with Colorectal Liver Metastases: Can We Count on Them?

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Abstract

Background Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) have been identified as potential prognostic factors for overall survival (OS) in primary colorectal cancer, and there is a growing interest in their use in colorectal liver metastases (CLMs). However, optimal cut-off values for these ratios have not been defined by making comparison between series difficult. This study aimed to confirm the prognostic value of inflammatory scores in patients undergoing resection for CLM.

Methods We retrospectively analysed data from 376 consecutive patients who underwent liver surgery for CLM between June 2010 and August 2015. We assessed the reproducibility of previously published ratios and determined new cut-off values using the Cut-off Finder web-based tool. Relations between cut-off values and OS were analysed with Kaplan–Meier log-rank survival analysis and multivariate Cox models.

Results Three hundred and forty-three patients had full preoperative blood tests for calculation of NLR, PLR and LMR. The number of cut-off values which showed a significant discrimination for OS was 49/249 (19.7%) for NLR, 28/316 (8.9%) for PLR and 22/214 (10.3%) for LMR, all with a scattered nonlinear distribution.

Conclusions This study showed that inflammatory scores expressed as ratios do not seem to be consistently reliable prognostic markers in patients with resectable CLM.

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Introduction

Liver resection remains the only potentially curative treatment for colorectal liver metastases (CLMs). Five-year overall survival (OS) rates of 37% were reported by Fong et al. [1] over 20 years ago. The development of multi-modal therapies and more advanced surgical techniques have led to reports of 5-year OS rates over 50% [2].

The wide range of clinical presentations, tumour characteristics and therapeutic strategies is associated with significant survival heterogeneity among patients with CLM. Several preoperative clinical scoring systems have been developed with the aim of providing better prognostication prior to liver surgery [1, 3–5]. 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 [6, 7]. The hallmarks of cancer-related inflammation include modulation of inflammatory cells and mediators such as cytokines and chemokines, which play a key role in neoangiogenesis and remodelling of the extra-cellular matrix which is necessary for stromal invasion and metastatic spread. Systemic levels of cytokines and chemokines are not routinely measured, limiting the clinical utility of such measures. However, these inflammatory mediators trigger direct changes in routinely assayed immune and hematopoietic cell populations, providing a direct surrogate marker of expression. Several prognostic scores based on shifts in these cellular populations have been proposed, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR). Several studies have suggested that these scores are predictive of OS and progression-free survival (PFS) in multivariate analysis. However, numerous cut-off values have been identified according to the receiver operating characteristic (ROC) curve analysis on each series of patients. The lack of standardization between series makes comparison difficult.

The aim of our study was therefore to validate these inflammatory scores for patients operated on for CLM and to define universal cut-off values which will allow comparison between different series.

Methods

Patient selection and follow-up

We analysed data from a prospectively maintained database of all patients undergoing liver surgery for CLM at a large tertiary hepatobiliary unit between June 2010 and August 2015. Patients who underwent curative-intent intraoperative microwave ablation combined with resection were included. Exclusion criteria included previous curative-intent treatment for CLM, two-stage hepatectomy and clinical evidence of preoperative infection.

All patients were discussed at a specialist hepatobiliary multidisciplinary team (MDT) meeting attended by surgeons, oncologists and interventional radiologists. Decision for preoperative chemotherapy was made by the MDT using a qualitative assessment of a number of prognostic factors related to the CLM and the primary tumour, and included number and size of lesions, synchronicity, grade of tumour and stage of primary disease. All specimens were inked, and positive margin (R1 resection) was defined as clearance <1 mm from the resection margin. There was no differentiation between R1 resections where the margin

was limited by a blood vessel (so called vascular R1 resection) or within the substance of the parenchyma.

Follow-up included regular outpatient visits every 3 months for the first year and every 6 months thereafter. All follow-up visits included physical examination, carcino-embryonic antigen (CEA) measurements and contrast CT scans of chest, abdomen and pelvis. This study had full ethical approval from the UK NHS North West Research Ethics Committee (10/H1010/51).

Inflammation scores

All patients had a baseline blood test performed within 1 week of surgery as part of routine preoperative workup. Preoperative NLR and PLR were calculated as the absolute neutrophil count or platelets, respectively, divided by the absolute lymphocyte count, whilst LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count.

Based on previous published studies, cut-off levels assessed for NLR were: 2.2, 2.5, 3, 3.5, 4 and 5 [8]. Those for PLR were: 150, 250, 254, 300 and 150/150–300/300 [9]. Those for LMR were: 2.14, 2.35, 2.83, 3, 3.11, 3.38 and 3.78 [10]. We also determined the optimal cut-off value for NLR, PLR and LMR in our study population.

Statistical analysis

Optimal cut-off values for NLR, PLR and LMR were determined by using the web application Cut-off Finder on OS [11]. We used the significance of correlation with survival variable method, which fitted Cox proportional hazard models to the dichotomized variable and the survival variable. The optimal cut-off was defined as the point with the most significant (log-rank test) split. 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). Progression-free survival (PFS) was measured from the date of liver surgery to the time of disease progression or death, or was censored at the last follow-up. Survival estimates were calculated using the Kaplan–Meier method. Differences in survival between groups were assessed by log-rank test. Median follow-up was calculated using a reverse Kaplan–Meier estimate. All variables associated with PFS or OS on univariate analysis with p value <0.10 were included in a multivariate Cox proportional hazard model. A p value ≤0.05 was considered statistically significant. All analyses were performed with EZR software [12].

Fig. 1 Flow chart
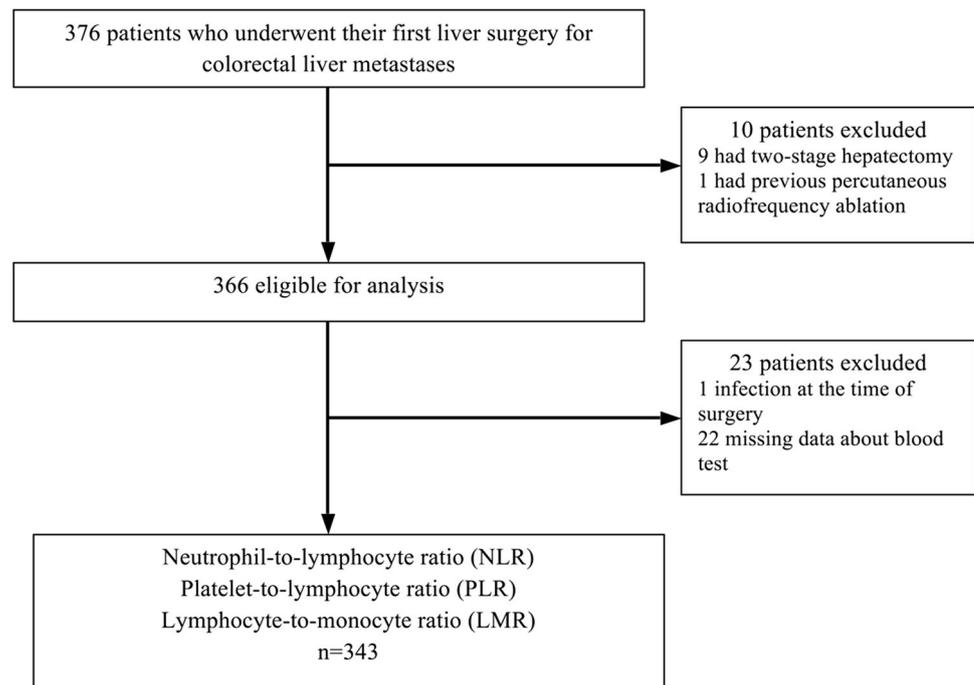
Results

Study population

Of 376 patients who underwent liver surgery for CLM between June 2010 and August 2015, 343 had adequate preoperative blood tests available for analysis. A detailed flowchart is shown in Fig. 1. Clinicopathological characteristics and perioperative data of the 343 patients are detailed in Table 1. Four patients had a preoperative portal embolization. Median follow-up was 49 (95% CI 46.3–53.6) months.

Validation of previously published inflammatory scores

We applied previously identified cut-off values for NLR, PLR and LMR to our patient cohort (Table 2). For NLR, the cut-off value of 2.5 was discriminant for both OS and PFS, and the cut-off value of 3 was discriminant for PFS only. For PLR, the cut-off values of 250 and 254 were discriminant for OS only and none for PFS. For LMR, the cut-off value of 2.14 was discriminant for OS only and none for PFS.

Correlation of inflammatory scores with clinical data

Univariate analysis was performed on previously reported clinicopathological characteristics to determine their association with OS (supplementary Table 1). Node-positive primary tumour, right-sided primary tumour, delay from primary tumour less than 1 year, higher number and higher size of liver metastases, presence of resectable extra-hepatic disease (EHD), intra-operative ablation, higher blood loss, blood transfusion, positive margin and post-operative morbidity were significantly associated with reduced OS in univariate analysis. Seven multivariate analyses with all these variables were conducted, adding one of the cut-off values found to be significant to each iteration of the analysis (i.e. 2.5 and 7.26 for NLR; 250, 254 and 380 for PLR; 2.14 and 2.25 for LMR). On multivariate analysis, node-positive primary tumour (HR between 1.810 and 1.986, $p<0.002$), right-sided primary tumour (HR between 2.102 and 2.304, $p < 0.001$), metastasis larger than 50 mm (HR between 1.855 and 1.961, $p < 0.001$), presence of resectable EHD (HR between 1.689 and 1.981, $p<0.04$) and positive margin hepatectomy (HR between 2.192 and 2.415, $p < 0.001$) were associated with poorer OS. Post-operative morbidity was associated with poorer OS (HR between 1.494 and 1.599, $p < 0.05$), except when 7.26 ($p = 0.06$) and 380 ($p = 0.06$) were used as cut-off values for NLR and PLR, respectively. High NLR (HR between 1.854 and 2.721, $p < 0.002$), high PLR (HR between 1.869

Table 1 Clinicopathological characteristics of patients and perioperative data

Characteristics	Total ($n = 343$)
Age (years)	65.8 ± 10.9
Sex ratio (F/M)	107 / 236
BMI (kg/cm^2)	27.8 ± 4.7
Number of lesions	2.8 ± 2.8
Size of largest metastasis (mm)	39.8 ± 27
Resectable EHD	36 (10.5%)
Preoperative chemotherapy	198 (57.7%)
Primary tumour	
Synchronous presentation (<6 months)	169 (49.3%)
Right colon	73 (21.3%)
Left colon	126 (36.7%)
Rectum	142 (41.4%)
Multiple	2 (0.6%)
N+	206 (60.1%)
≥T3	288 (84%)
RAS mutation[a]	42 (31.8%)
Preoperative NLR	2.92 (0.85–25.5)
Preoperative PLR	158 (30–774)
Preoperative LMR	2.69 (0.63–9.94)
Type of liver surgery	
Anatomical resection	92 (26.8%)
Non-anatomical resection	173 (50.4%)
Anatomical and non-anatomical resections	57 (16.6%)
Microwave ablation with resection	66 (19.2%)
Microwave ablation without resection	21 (6.1%)
Pringle manoeuvre	244 (71.1%)
Blood loss	590 ± 765
Intra- and post-operative red blood cells transfusion	20 (5.8%)
R1 resection	161 (46.9%)

Variables are expressed as mean±standard deviation or as median (range) or as frequency (percentage)

[a] RAS status not available in 211 patients

BMI body mass index, *EHD* extra-hepatic disease, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio

and 2.949, $p < 0.006$) and low LMR (HR 1.920 and 2.049, $p < 0.001$) were significantly associated with poorer OS for all the 7 cut-off values tested (supplementary Table 2).

Identification of significant cut-off values

The optimal cut-off values (i.e. which provided the greatest discrimination for OS) in our series for NLR, PLR and LMR were 7.26, 380 and 2.25, respectively. These all reflected a significant difference in OS (Table 2).

Plotting of the hazard ratios (HR) obtained with the Cox proportional models showed that a wide range of cut-off values could be employed to find a significant difference (Figs. 2, 3, 4). Indeed, 49 out of the 249 (19.7%) cut-off values tested could be used for NLR (Fig. 2). For PLR, 28 out of 316 (8.9%) cut-off values tested could be used. For LMR, 22 out of 214 (10.3%) cut-off values tested could be used (Fig. 4).

A key observation was that these significant cut-off values were distributed throughout the whole range of ratios, without any linear correlation. That is, there was no ratio beyond which all values were predictive of long-term survival.

Discussion

Precision medicine is of increasing importance when considering liver resection for CLM, where palliative chemotherapy can prolong the survival with reported median OS of up to 30 months [13]—comparable to that seen for many patients undergoing resection. Liver resection remains the standard of care for resectable disease, and many efforts have been made over the years to identify patients who would benefit from surgery. Several scoring systems have been proposed to stratify patients based on likely prognosis. Historically, scoring systems were based on clinicopathological data [1, 3]. Advances in laboratory technologies and understanding of cancer biology have seen the identification of numerous other potential markers [14]. Some of them, such as circulating tumour cells or liquid biopsies, are some way from clinical practice. RAS mutations are associated with worse outcomes, but RAS mutation testing is still not widely performed as part of routine care.

There is a growing interest in scoring systems based on hematopoietic cells, because they reflect the inflammatory response of the host to the tumour. Inflammatory ratios remain a biologically plausible biomarker, with several hypotheses raised to explain the underlying mechanism of NLR, PLR and LMR. Briefly, lymphocytes have an anti-tumour effect and mediate the response of the host to the tumour [15], whereas neutrophils might promote tumour growth and metastasis [16], as well as platelets through pro-inflammatory factors and neoangiogenesis [17]. Monocytes might promote tumour growth and have an immunosuppressive effect, either directly or through tumour-associated macrophages or through monocytic myeloid-derived suppressor cells [18].

Several studies have shown that NLR, PLR and LMR were independent prognostic factors for OS after surgery for colorectal cancer, including surgery for CLM [8]. However, although many cut-off values have been

Table 2 Patient distribution and survival data according to different prognostic scoring systems

Prognostic scoring system	Cut-off value	Number of patients under/above cut-off value ($n = 343$)	OS	p value	PFS	p value
NLR	2.2	103/240	47.5 versus 39.7	0.170	11 versus 9.8	0.194
	2.5	134/209	50.3 versus 38.4	0.037	11.6 versus 9.7	0.017
	2.6[a]	140/203	50.3 versus 37.9	0.028	11.3 versus 9.7	0.021
	3	182/161	47.5 versus 37.9	0.103	10.9 versus 9.4	0.026
	3.5	222/121	45.3 versus 39.2	0.417	10.4 versus 9.7	0.145
	4	259/84	44.6 versus 39.2	0.346	10.8 versus 9.2	0.401
	5	292/51	44.8 versus 37.6	0.085	11 versus 6.5	0.051
	7.26[b]	323/20	44.8 versus 25.4	0.014	10.3 versus 6.3	0.109
PLR	136[a]	128/215	39.2 versus 44.8	0.537	9.9 versus 10.1	0.825
	150	153/190	43 versus 43.9	0.942	9.9 versus 10.2	0.991
	250	281/62	45.8 versus 30.3	0.034	10.8 versus 7.2	0.143
	254	284/59	45.8 versus 29.9	0.021	10.8 versus 7.3	0.173
	300	301/42	44.6 versus 37.6	0.405	10.1 versus 8.4	0.945
	380[b]	328/15	44.6 versus 21.6	0.006	10.7 versus 4.2	0.044
	150–300	153/(148)/42	39.2 versus 44.8	0.670	9.9 versus 10.8	0.974
	150/150–300/300	153/148/42	43 versus 44.8 versus 37.6	0.695	9.9 versus 9.9 versus 8.4	0.998
LMR	2.14	111/232	35.9 versus 47.2	0.035	9.7 versus 10.7	0.102
	2.25[b]	124/219	34.3 versus 47.3	0.013	9.6 versus 10.8	0.097
	2.35	136/207	36.2 versus 47.2	0.062	9.9 versus 10.6	0.297
	2.4[a]	143/200	36.2 versus 47.3	0.050	10.1 versus 10.3	0.312
	2.83	196/147	38.4 versus 47.1	0.195	10.2 versus 9.9	0.485
	3	210/133	39.2 versus 47.3	0.272	10.2 versus 9.9	0.639
	3.11	225/118	38.4 versus 51.3	0.192	10.1 versus 10.4	0.313
	3.38	251/92	43 versus 45.3	0.425	10 versus 11.3	0.363
	3.78	278/65	43.1 versus 45.3	0.484	9.8 versus 12.1	0.423

[a]Determined by Cox hazard proportional hazard ratio on our series

[b]Determined by ROC curve analysis on our series

OS overall survival, *PFS* progression-free survival, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *ROC* receiver operating characteristic

successfully identified for these ratios, most of them are based on small single-centre cohorts and have not been validated in different populations. It therefore seems likely that there is a relationship between these inflammatory scores and survival, but cut-offs are population specific [19, 20]. In order to integrate a potential prognostic marker in patient care, an optimal and universally applicable cut-off value for use in further validation studies is necessary.

The aim of our study was therefore to assess the reliability of inflammatory scores in a modern series of consecutive patients operated on for CLM, using cut-off values that have been published by other groups. Among the cut-off values previously published, only an NLR of 2.5 was an independent prognostic factor for OS and PFS in our cohort. Only one previous study showed that NLR >2.5

was associated with decreased OS (but not with PFS), in 169 patients operated on for CLM [21]. Based on 140 patients from the same data set, the same authors showed that PLR >150 and LMR <3 were associated with decreased OS [22, 23]. Both of these cut-off values were not found to be relevant in our cohort. Neal et al. found that NLR <5 was the only inflammatory score having an independent association with OS in resectable CLM, compared to PLR and LMR [24]. Although data about inflammatory scores, especially for PLR and LMR, are limited in resectable stage IV colorectal cancer, numerous studies have demonstrated the independent prognostic role of inflammatory scores in primary colorectal cancer [8, 19, 20, 25]. However, heterogeneity of these studies prevents a proper meta-analysis, mainly because of the

Fig. 2 Plots of the differences in hazard ratio for overall survival (OS) for each cut-off value of NLR. Vertical lines designate the cut-off value showing the most significant difference in OS. Dashed lines represent the 95% confidence interval. The distribution of cut-off values in the 343 patients is shown as a rug plot at the bottom of the figures. Arrows show the area of interest, i.e. where the difference is significant
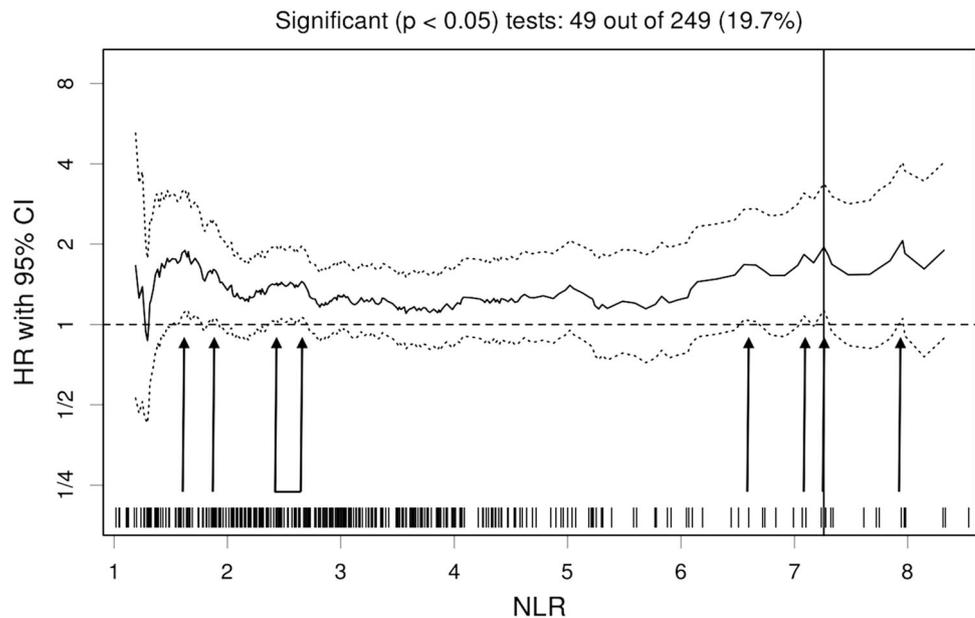

Fig. 3 Plots of the differences in hazard ratio for overall survival (OS) for each cut-off value of PLR. Vertical lines designate the cut-off value showing the most significant difference in OS. Dashed lines represent the 95% confidence interval. The distribution of cut-off values in the 343 patients is shown as a rug plot at the bottom of the figures. Arrows show the area of interest, i.e. where the difference is significant
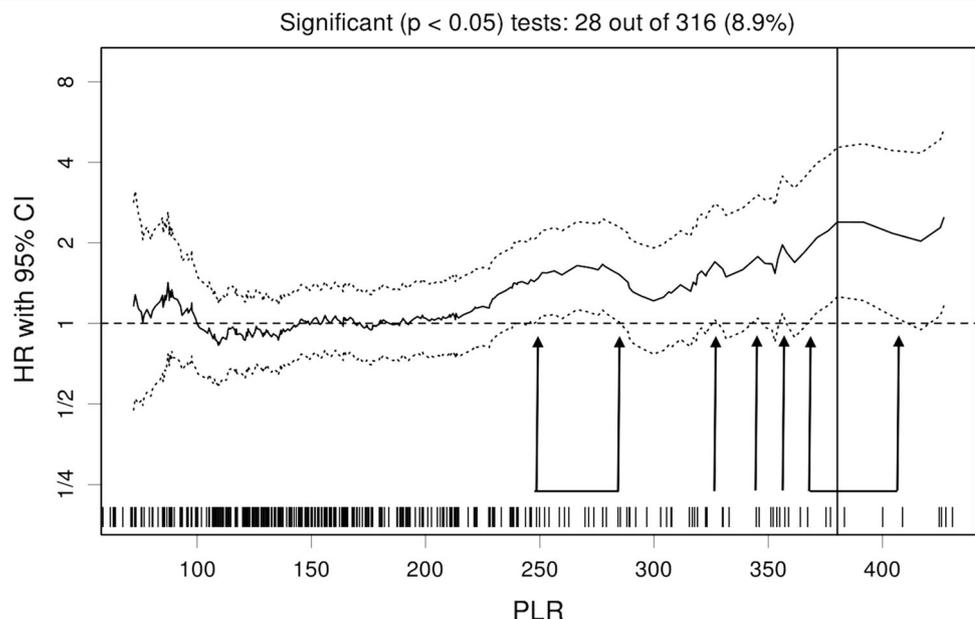
wide range of cut-off values used. In our study, we found several cut-off values for each inflammatory score with an association with OS. However, few previously published cut-off values were predictive of outcome in our cohort. Heterogeneity could be explained by several factors including the heterogeneity in chemotherapy administration, the retrospective nature of the studies, which is associated with several well-known biases, and the methods used to find the cut-off value. In previously published studies, methods employed to find the cut-off values are heterogeneous, often inaccurate and sometimes not

reported. For example, when the method is based on ROC curve analysis, a time-dependent ROC curve should be used rather than ROC curve analysis on median OS or 5-year OS, to include censored data [26]. Another method is to use web-based tools, such as Cut-off Finder [11], which uses several methods of cut-off optimization. One of them is based on the correlation of the dichotomization with survival, where the optimal point is defined by the largest significant difference in survival. We show in Figs. 2, 3 and 4 that by plotting hazard ratio with the confidence interval observed within each ratio,

Fig. 4 Plots of the differences in hazard ratio for overall survival (OS) for each cut-off value of LMR. Vertical lines designate the cut-off value showing the most significant difference in OS. Dashed lines represent the 95% confidence interval. The distribution of cut-off values in the 343 patients is shown as a rug plot at the bottom of the figures. Arrows show the area of interest, i.e. where the difference is significant
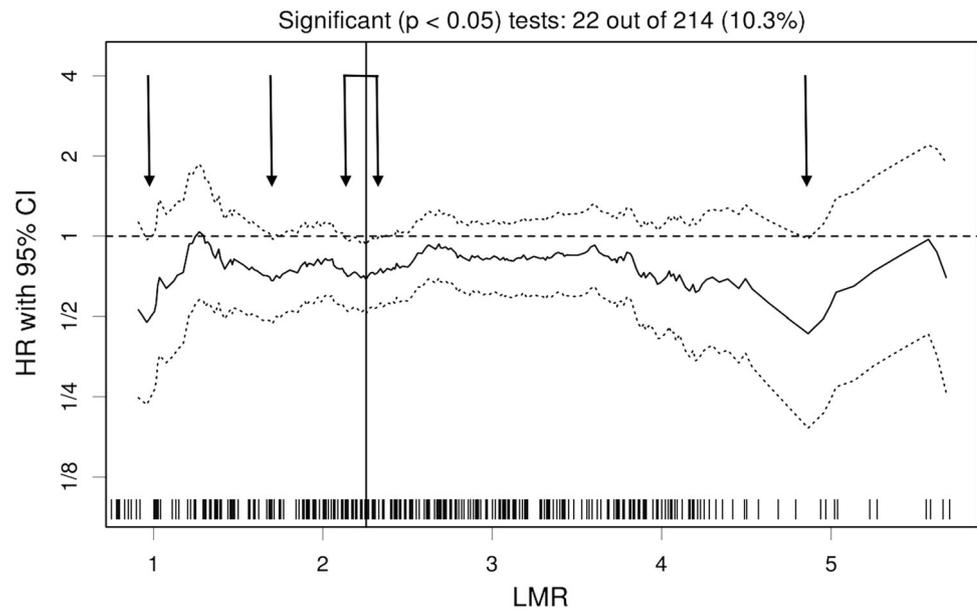
identification of significant cut-off values was easy. We observed that 49 out the 249 cut-off values of NLR could potentially be used to stratify patients. Critically, if ratios are plotted along the X-axis, we would expect to see a clear inflection point, with all ratios beyond this point also prognostic. However, we observed that these statistically significant ratios appeared to be randomly distributed throughout the whole range of values, rather than clustered. PLR and LMR did appear to show consistent tracking of the curves away from a HR of 1 at higher ratios, but a consistently significant difference was not observed. It may be that cut-offs beyond a certain ratio therefore do carry prognostic value, but this data set is not statistically stable enough to clarify this.

Whenever prognostic scoring systems are suggested in CLM, the question of clinical utility is often raised. Indeed, despite numerous publications about scoring systems over the years, it is unlikely that management of patients has been influenced in daily clinical practice based on risk stratification. The use of perioperative chemotherapy for resectable CLM is still debated, and so one application of scoring systems could be to tailor the use of neo- and/or adjuvant chemotherapy. Numerous studies have been published about leucocyte-based ratios as prognostic factors, and with the advances in immunotherapy, inflammation-based scoring systems are likely to be more employed, but NLR, PLR and LMR dichotomized by cut-off values are not reliable surrogate markers of the inflammatory response. However, evaluation of the systemic inflammatory response of the host to the tumour could add valuable information in the clinical decision-making process, notably to tailor perioperative chemotherapy. The modified

Glasgow prognostic score (mGPS), based on albumin and C-reactive protein, is a reliable and reproducible marker of the systemic inflammatory response [27]. Thus, the mGPS should be used instead of leucocyte-based ratios.

This study has several limits due to its retrospective nature. However, it represents one of the largest consecutive cohorts assessing inflammatory markers in which all patients had multimodality imaging for staging and follow-up, as well as access to modern multimodal treatment. RAS mutation status was performed in only 38.5% of the patients, and BRAF mutation status was not available. Thus, it was not possible to analyse the impact of these functionally important mutations on prognosis and any possible correlation between RAS mutation status and inflammatory scores. The R1 resection rates reported in this study are higher than those previously published. However, resection margins were inked, and all liver resections were made with the cavitational ultrasonic surgical aspirator. Both are known to overestimate positive margin, especially when a parenchymal-sparing policy is adopted [28]. In addition, vascular detachment (R1 vascular) was not distinguished from parenchymal R1 resection. Another point worthy of discussion is the use of perioperative chemotherapy in 57.7% of patients. Patients with multiple CLM, synchronous presentation, right primary tumour location and extra-hepatic disease were more likely to receive preoperative chemotherapy (data not shown). However, in univariate analysis, preoperative chemotherapy did not have any impact on overall survival. Data on ratios before and after systemic chemotherapy were not available, but could also offer some insight into the impact of cytotoxic therapy on host immunomodulation. Although

a gap of 6 weeks was given between chemotherapy and surgery, it is also possible that chemotherapy could affect blood results even this far after treatment. In addition, data about response to chemotherapy (i.e. stable or responder) were not available, limiting the ability to correlate inflammatory markers with response to chemotherapy. Another limitation is the missing data about medication that could interfere with blood tests, such as non-steroidal anti-inflammatory drugs or steroids. Other external factors can modify blood tests such as stress, smoking or geographical and ethnical differences. Finally, multivariate analysis was not performed for all cut-offs evaluated. This would have represented more than one hundred multivariate analyses, a level of analysis which the size of this cohort would have rendered statistically unstable.

In conclusion, single cut-off values of NLR, PLR and LMR do not seem to be reproducible between cohorts and so cannot currently be recommended as prognostic factors in patients with resectable CLM. However, the repeated identification of inflammatory ratios as prognostically relevant combined with a biologically plausible mechanism suggests a potentially useful and easily measurable biomarker. Further investigative work in large cohorts is required to better clarify their precise value.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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