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Host phenotype is associated with reduced survival independent of tumour biology in patients with colorectal liver metastases

David P.J. van Dijk[1,2], Matthew Krill[3], Farshad Farshidfar[4], Ting Li[3], Sander S. Rensen[1,2], Steven W.M. Olde Damink[1,2,5,6], Elijah Dixon[3], Francis R. Sutherland[3], Chad G. Ball[3], Vera C. Mazurak[7], Vickie E. Baracos[8] & Oliver F. Bathe[3,4]*

[1]*Department of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands,* [2]*NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands,* [3]*Department of Surgery and Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Canada,* [4]*Arnie Charbonneau Cancer Institute, Calgary, Canada,* [5]*Department of General, Visceral and Transplantation Surgery, RWTH University Hospital Aachen, Aachen, Germany,* [6]*Institute for Liver and Digestive Health, University College London, London, UK,* [7]*Division of Human Nutrition, Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Canada,* [8]*Department of Oncology, University of Alberta, Edmonton, Canada*

Abstract

Background Most prognostic scoring systems for colorectal liver metastases (CRLMs) account for factors related to tumour biology. Little is known about the effects of the host phenotype to the tumour. Our objective was to delineate the relationship of systemic inflammation and body composition features [i.e. low skeletal muscle mass (sarcopenia) and low visceral adipose tissue (VAT)], two well-described host phenotypes in cancer.

Methods Clinical data and pre-operative blood samples were collected from 99 patients who underwent resection of CRLM. Pre-operative computed tomography scans were available for 97 patients; body composition was analysed at the L3 level, stratified for sex and age. Clinicopathological variables, serum C-reactive protein (CRP), and various body composition variables were evaluated. Overall survival was evaluated as a function of these same variables in multivariate Cox regression analysis.

Results Skeletal muscle was significantly correlated with VAT ($r = 0.46$, $P < 0.001$). Of patients with sarcopenia, 35 (65%) also had low VAT. C-reactive protein was elevated (≥5 mg/mL) in 42 patients (43.3%). Elevated CRP was more common in patients with sarcopenia (73.8% vs. 51.1%, $P = 0.029$). The most significant prognostic factors were the coincidence of elevated CRP and adverse body composition features (sarcopenia and/or low VAT; hazard ratio 4.3, 95% confidence interval 1.5–13.0, $P = 0.008$), as well as Fong clinical prognostic score (hazard ratio 2.9, 95% confidence interval 1.5–5.5, $P = 0.002$).

Conclusions Body composition in patients with CRLM is not directly linked to the presence of systemic inflammation. However, when systemic inflammation coincides with sarcopenia and/or low VAT, prognosis is adversely affected, independent of the Fong clinical prognostic score.

Keywords Colorectal cancer; Liver metastases; Inflammation; Sarcopenia

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**Correspondence to: Oliver F. Bathe, Division of Surgical Oncology, Tom Baker Cancer Centre, University of Calgary, 1331-29th St. NW, Calgary, AB T2N 4N2, Canada. Fax: 403-944-3926, Email: bathe@ucalgary.ca*

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western world.[1] Approximately 25% of CRC patients will develop liver metastases. The only curative treatment for colorectal liver metastases (CRLMs) is surgical resection, which has a median post-operative survival rate of 36–43 months and a 5 year survival rate of 36–47%.[2–4] Changes attributable to the host response to tumour may have clinically relevant consequences. For example, high pre-operative C-reactive protein (CRP) levels are associated with a poor prognosis in surgical patients with CRLM.[5–9] We

have confirmed that high CRP is associated with a proinflammatory cytokine profile in blood, including elevated interleukins IL-1β, IL-6, IL-12, and IL-15.[5] In addition, high mobility group box 1 (HMGB1), an inflammatory mediator, is elevated in serum of some patients with CRC[10] and could represent a driver of the acute phase response. Body composition features may also represent manifestations of the host response. Some of these features—such as sarcopenia, myosteatosis, and low adipose tissue mass—have been linked to drug toxicity[11] and poor prognosis.[12,13] In patients with CRLM, the effects of body composition on survival are inconsistent.[14–16] This may be because studies on the effects of body composition do not account for inflammatory changes. While inflammation and body composition are known to be associated in some instances such as cancer cachexia[17,18] and obesity,[19] it is possible that these processes are not always linked.

In patients with CRLM, the effect of tumour biology on prognosis is well known.[20] In addition, treatment factors such co-administration of chemotherapy may affect survival.[21] The contribution of the host phenotype to survival outcomes is less clear. This may be because there is some diversity in the host response to tumour, which may consist of variable body composition and inflammation. The objective of this study was to understand the effect of systemic inflammation and body composition on outcomes in patients with CRLM undergoing liver resection. Moreover, we sought to better define the association of these two features, clinically and biologically.

Materials and methods

Patients and clinical data

Consecutive patients undergoing liver resection for CRLM at the Foothills Medical Centre (Calgary, Canada) were prospectively recruited and consented. Patients without an available computed tomography (CT) scan were excluded from analysis. This study was approved by the Health Research Ethics Board of Alberta Cancer Committee (Study HREBA.CC-16-0769 and HREBA.CC-16-0770 and HREBA.CC-16-0760). Clinical data (demographic factors, clinicopathological factors, and oncological outcomes) and sera were collected by the University of Calgary GI/HPB Tumor Bank. Clinical prognostic score was calculated as described by Fong *et al*.[20]

Analysis of the inflammatory state

Serum samples were collected before surgery in gold top BD vacutainers and were analysed for CRP as described.[5] High mobility group box 1 was measured by ELISA. Briefly, sample and antigen prepared in 1× phosphate-buffered saline were added to a 96-well plate in duplicate and incubated at 4°C overnight. The primary antibody (SAB1403925; Sigma-Aldrich Canada, Oakville, Canada) was added based on manufacturer's instructions at 3 mg/mL and incubated for 1 h at 37°C. The plate was washed and incubated for 30 min at 37°C with a 1:10 000 dilution of horseradish peroxidase-conjugated secondary antibody. The plate was washed a final time in the chromogen 3,3′,5,5′-tetramethylbenzidine (Abcam Inc., Toronto, Canada). Absorbance was read at 450 nm.

Body composition analysis

Pre-operative abdominal CT scans were analysed by a single-blinded researcher trained in body composition analysis. First, a single slice at the level of the third lumbar vertebra (L3) was selected for analysis. Scans were analysed using SliceOmatic 5.0® (TomoVision, Magog, Canada). Using predefined Hounsfield unit (HU) ranges, the cross-sectional area of skeletal muscle (SM, −29 to 150 HU), visceral adipose tissue (VAT, −150 to −50 HU), and subcutaneous adipose tissue (SAT, −190 to −30 HU) was determined. Cross-sectional area of SM, VAT, and SAT at L3 is strongly correlated with total body SM mass and adipose tissue mass.[22] Values were corrected for patient height [i.e. L3 index (cm^2/m^2)]. In addition, the mean radiation attenuation value was recorded for all tissues. As body composition greatly varies between sexes and also changes with age, SM, VAT, SAT, and skeletal muscle radiation attenuation (SM-RA) were expressed as Z-scores using the CT values of a larger cohort of patients with metastatic CRC (derived from Martin *et al*.[12]; *table* S1). The Z-score is defined as the number of standard deviations each patient differs from the mean value of patients belonging to the same sex and age group. The use of Z-scores facilitates comparison of the effects of body composition in heterogeneous patient cohorts, correcting for the effects of sex and age.

Statistical analysis

Data were analysed using IBM SPSS statistics 23 for Microsoft Windows. Descriptive statistics were used to characterize the study cohort. Continuous data were compared using *t*-test or Mann–Whitney *U* test for non-parametric data. χ^2 test was used for comparison of categorical variables. Spearman's correlation coefficients (r_s) were used to test for relationships between variables. A correlation matrix was used to visualize these correlations using R 3.4.1 for Microsoft Windows. Venn diagrams were prepared using eulerAPE (University of Kent, Canterbury, UK).[23] Follow-up was determined using the Kaplan–Meier estimates. Survival was calculated from date of surgery to date of first appearance of recurrence (for disease-free survival) or to date of death (for overall survival). Survival curves were estimated using the Kaplan–Meier method and then compared using the log-rank test. The

effects of selected clinical factors on prognosis were analysed using the Cox proportional hazards model. All variables with a *P*-value < 0.1 on univariate analysis were included in a multivariate analysis. Age and sex were always included in multivariate analyses. A *P*-value < 0.05 was considered significant.

Results

Patient characteristics

Of the 99 patients comprising the prospective cohort, 97 were included for analysis. Two patients were excluded because there was no abdominal CT scan available. Median follow-up was 73.6 months (interquartile range: 61.0–88.4 months). Patient characteristics including distribution among body composition features and CRP are summarized in *Table* 1.

In general, men had larger musculature (SM, $P < 0.001$), more visceral fat (VAT, $P = 0.010$), and less subcutaneous fat (SAT, $P = <0.001$) than women (*Figure* 1). Skeletal muscle radiation attenuation was also higher in men ($P = 0.035$), which is indicative of a lower fat content in muscle. However, only one of the patients (1.0%) had muscle radiodensity ≤30 HU, and three patients (3.1%) had muscle density in range of 31–40 HU. Therefore, myosteatosis *per se* was uncommon in this cohort. Sarcopenia (low SM) was more common in older patients. Patients with low SM (Z-score < 0) were significantly older than patients with high SM: 63.0 ± 10.7 vs. 58.3 ± 10.2 years, respectively ($P = 0.035$).

Eighty-seven patients had serum available for CRP measurements. The relationship of elevated CRP with various patient characteristics is summarized in *Table* 1. No demographic or clinical features correlated with systemic inflammation (CRP ≥ 5 mg/L). None of the clinical factors that comprised the clinical prognostic index was significantly associated with any of the body composition variables or features of systemic inflammation.

Relationship between body composition features and systemic inflammation

In sarcopenic patients, the mean SM-RA was lower than in patients with normal muscle mass (36.2 ± 8.9 vs. 40.2 ± 8.8 HU, respectively; $P = 0.032$), although no patients had criteria for myosteatosis. *Figure* 2A shows a correlation matrix that illustrates the co-relationship of various body composition parameters and inflammatory changes. Skeletal muscle is significantly correlated with VAT: patients with a low muscle mass tend to have lower amounts of visceral fat

Table 1. Patient characteristics according to body composition and systemic inflammation

		SM (Z-score)			VAT (Z-score)			SAT (Z-score)			C-reactive protein (mg/L)		
Patient characteristics	Overall	<0	≥0	*P*	<0	≥0	*P*	<0	≥0	*P*	<5	≥5	*P*
Age (years)	61.2 ± 10.7	63.0 ± 10.7	58.3 ± 10.2	0.04	60.4 ± 11.4	61.9 ± 10.1	0.51	60.3 ± 12.6	61.7 ± 9.3	0.56	60.4 ± 10.4	61.3 ± 11.3	0.70
Sex (*N* (%))				0.27			0.10			1.00			1.00
Male	67 (69%)	39 (65%)	28 (76%)		28 (61%)	39 (77%)		27 (69%)	40 (69%)		30 (67%)	28 (67%)	
Female	30 (31%)	21 (35%)	9 (24%)		18 (39%)	12 (23%)		12 (31%)	18 (31%)		15 (33%)	14 (33%)	
Fong score (*N* (%))				0.71			0.08			0.51			0.92
≤1	41 (42%)	26 (43%)	15 (41%)		14 (30%)	27 (53%)		14 (36%)	27 (46%)		18 (40%)	18 (43%)	
2	40 (41%)	23 (38%)	17 (46%)		23 (50%)	17 (33%)		17 (44%)	23 (40%)		18 (40%)	17 (40%)	
≥3	16 (17%)	11 (18%)	5 (13%)		9 (20%)	7 (14%)		8 (20%)	8 (14%)		9 (20%)	7 (17%)	
Synchronous metastasis (*N* (%))	56 (58%)	36 (60%)	20 (54%)	0.57	28 (61%)	28 (55%)	0.55	27 (69%)	29 (50%)	0.06	27 (60%)	24 (57%)	0.79
Node positive primary (*N* (%))[a]	63 (66%)	38 (64%)	25 (68%)	0.75	32 (70%)	31 (62%)	0.44	27 (69%)	36 (63%)	0.54	32 (71%)	27 (66%)	0.60
Largest metastasis (≥5 cm)	15 (16%)	7 (12%)	8 (22%)	0.19	7 (15)	8 (16%)	0.95	5 (13%)	10 (17%)	0.56	6 (13%)	7 (17%)	0.66
CEA (ng/mL)[a]	21.3 ± 40	23.9 ± 46.3	16.9 ± 26.5	0.41	24.0 ± 34.9	18.8 ± 44.0	0.53	26.5 ± 53.8	17.6 ± 26.3	0.34	16.8 ± 25.1	26.6 ± 53.0	0.28
Chemotherapy (*N* (%))													
Pre-operative	46 (47%)	27 (45%)	19 (51%)	0.54	25 (54%)	21 (41%)	0.20	21 (54%)	25 (43%)	0.30	21 (47%)	20 (48%)	0.93
Post-operative	68 (70%)	45 (75%)	23 (62%)	0.18	35 (76%)	33 (65%)	0.22	28 (72%)	40 (69%)	0.77	30 (67%)	32 (76%)	0.33

CEA, carcinoembryonic antigen; SM, skeletal muscle; SAT, subcutaneous adipose tissue; VAT, visceral adipose.
Z-scores are the number of standard deviations from the sex-specific and age-specific mean.
[a]Missing data: HMGB1 $n = 8$; CEA $n = 2$; node positive primary $n = 1$.

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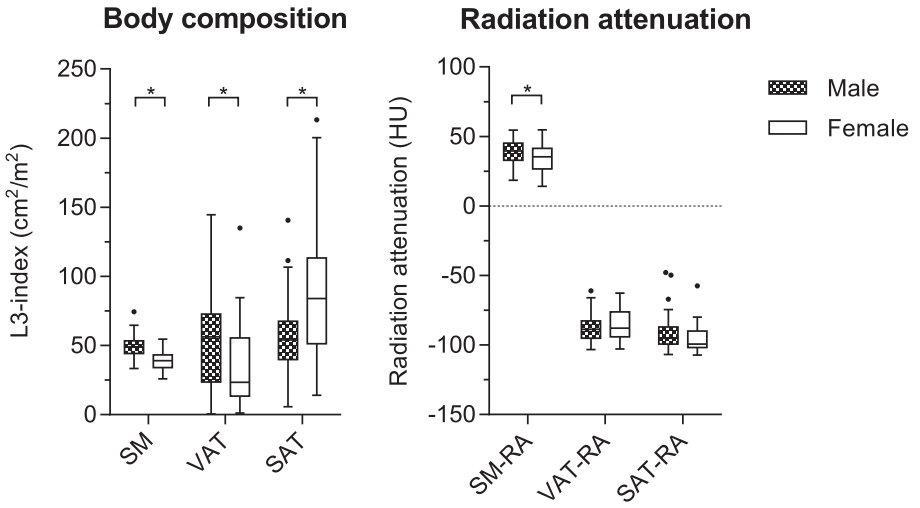
Figure 1 Sex-specific values for body composition variables assessed by computed tomography scan. Boxes represent median and interquartile range. Whiskers are set at either the 25th or 75th percentile +1.5 times the interquartile range (Tukey method). Dots represent outliers. $^{*}P < 0.05$. RA, radiation attenuation; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.



(r_s = 0.46, $P < 0.001$). Visceral adipose tissue is significantly correlated with SAT (r_s = 0.61, $P < 0.001$), although there are sex differences as described previously, where men tend to have more visceral fat and women tend to have more subcutaneous fat.

Systemic inflammation was significantly associated with sarcopenia and low SM-RA, representing muscle fat content (myosteatosis) (*Figure* 2A). C-reactive protein was negatively correlated with SM (r_s = −0.22, P = 0.042) and SM-RA (r_s = −0.33, P = 0.002) (*Figure* 2A), although these could be categorized as weak correlations. Accordingly, patients with a CRP ≥ 5 mg/L had a significantly lower SM-RA (35.7 ± 8.0 HU vs. 39.7 ± 9.2 HU; P = 0.035). While the same linear relationship was not present between CRP and SM, the proportion of patients with CRP ≥ 5 mg/L was higher in patients with sarcopenia compared with patients with no sarcopenia (73.8% vs. 51.1%; P = 0.029). Finally, CRP was positively correlated with serum HMGB1 levels (r_s = 0.327, P = 0.003; *Figure* 2A), and patients with CRP ≥ 5 mg/L had significantly higher HMGB1 levels than patients with lower CRP levels (243 ± 47 vs. 216 ± 48; P = 0.013).

Figure 2B illustrates the association of systemic inflammation and two adverse body composition features in the whole patient cohort. This provides a clearer picture of the coexistence of these features in individuals. Fourteen patients (16%) had normal CRP (CRP < 5), normal muscularity (SM Z-score > 0), and visceral adiposity (VAT Z-score > 0). None of the features were mutually exclusive. Systemic inflammation, sarcopenia, and low VAT coexisted in 31 patients (32.0%). While there was a correlation between SM and VAT (as described previously), sarcopenia and low VAT only coexisted in 35 patients (56% of patients with low SM).

Survival analysis

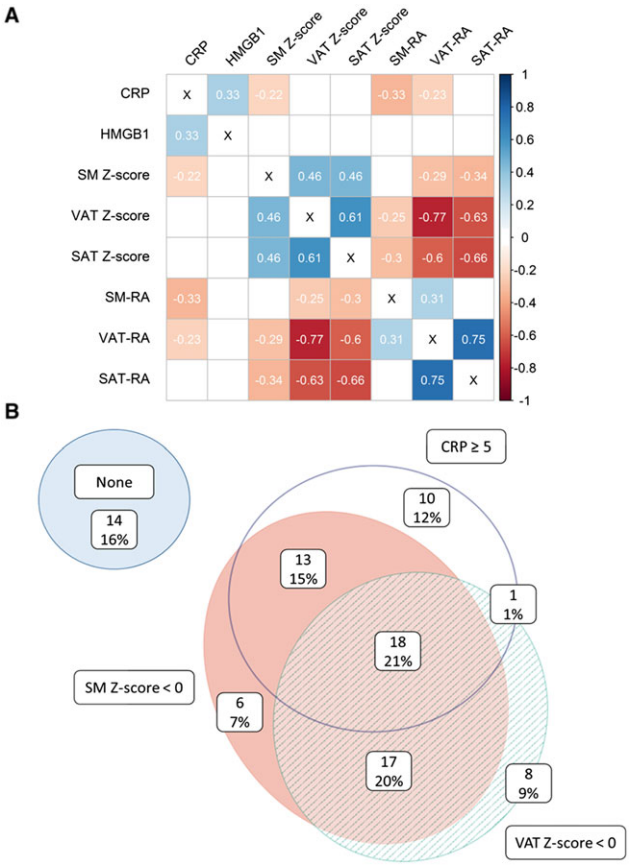
Univariate and multivariate Cox regression analyses are shown in *Figure* 3. On multivariate analysis, high CRP [hazard ratio (HR) 2.08, 95% confidence interval (CI) 1.13–3.83, P = 0.019] and high clinical prognostic score (Fong score-2) (HR 3.05, 95% CI 1.58–5.90, P = 0.001) were most significantly associated with a truncated overall survival. Older age was also associated with a poor prognosis (HR 1.03, 95% CI 1.00–1.06, P = 0.038). Women had a significantly better survival compared with men (HR 0.47, 95% CI 0.24–0.92, P = 0.027). Finally, there was a trend towards a protective effect associated with post-operative chemotherapy (HR 0.53, 95% CI 0.27–1.02, P = 0.057).

None of the individual body composition features (SM, VAT, SAT, or SM-RA) had a significant effect on survival when the clinical prognostic score was included in the model. However, it was considered that the effects of body composition on survival may be more subtle, and therefore, their effects were examined as continuous Z-scores after excluding the Fong clinical prognostic score, which dominated the model *in toto*. Indeed, following this exclusion, the most deleterious effects on survival were seen with lower SM-Z (HR 1.37, 95% CI 1.00–1.89, P = 0.052) and lower VAT-Z (HR 1.37, 95% CI 1.03–1.84, P = 0.029). SAT-Z and SM-RA-Z did not have any prognostic value.

Adverse host phenotypes

While individual body composition features (sarcopenia and low VAT) had only a small effect on prognosis (within the power limitations of the study cohort), their effects may be

Figure 2 Relationships between serum markers and body composition. (A) Correlation matrix for serum markers and body composition. Spearman's correlation coefficients are represented in colour according to the heat map. Blank squares indicate non-significant correlations ($P > 0.05$). (B) Venn diagram depicting the coexistence of systemic inflammation, sarcopenia, and low visceral adipose tissue in patients. CRP, C-reactive protein; HMGB1, high mobility group box 1; RA, radiation attenuation; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.



additive. Moreover, it is possible that their deleterious effects could be confounded by coexistent inflammation. To test this hypothesis, prognosis was evaluated as a function of CRP and low SM and/or low VAT (*Figure* 4A). In patients with inflammation and one of the adverse body composition features, median survival was 43.4 months (95% CI 28.9–57.9 months); patients with *either* inflammation or an adverse body composition feature had a median survival of 79.0 months (95% CI 48.8–109.2 months); and patients with neither of these adverse host factors had a median survival of 109.5 months (95% CI NA). The differences in survival were significant ($P = 0.010$; *Figure* 4B). On multivariate analysis, this composite host phenotype had a significant effect that was independent of the Fong clinical prognostic score. That is, the presence of inflammation and an adverse body composition feature was associated with an HR of 4.38 (95% CI 1.48–12.96, $P = 0.008$). The effect was almost double the effect of inflammation alone.

Discussion

Various clinical prognostic scoring systems for CRLM have been described by a number of groups including Fong *et al*.[20] and others.[24] In general, these prognostic scoring systems focus on factors mostly affected by tumour biology, such as stage of the primary tumour, presence of synchronous liver metastases, high carcinoembryonic antigen levels, and size and number of liver metastases.[20,24] The host response to tumour may also have an (independent) effect on prognosis. For example, systemic inflammation often accompanies CRC, and it has a potential effect on locoregional and metastatic disease.[25] Cancer also has effects on body composition. Perhaps the most extreme example is cachexia, which includes muscle wasting and loss of fat reserves. We have

Figure 3 Forest plot depicting the effect of clinical factors, body composition, and systemic inflammation on overall survival in patients with resectable colorectal liver metastases. Inflammation was defined as CRP ≥ 5 mg/L. Adverse body composition was defined as SM-Z < 0 and/or VAT-Z < 0. $^{*}P < 0.05$. CRP, C-reactive protein; RA, radiation attenuation; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

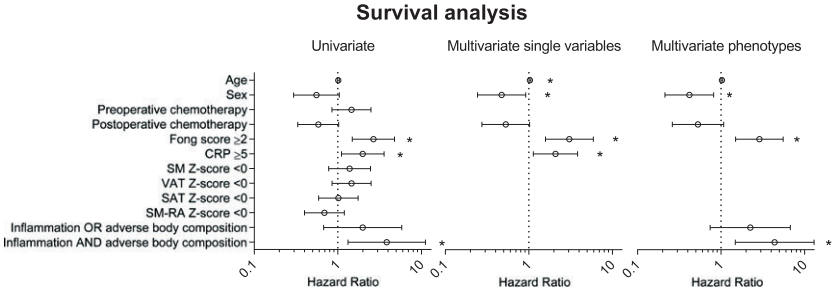


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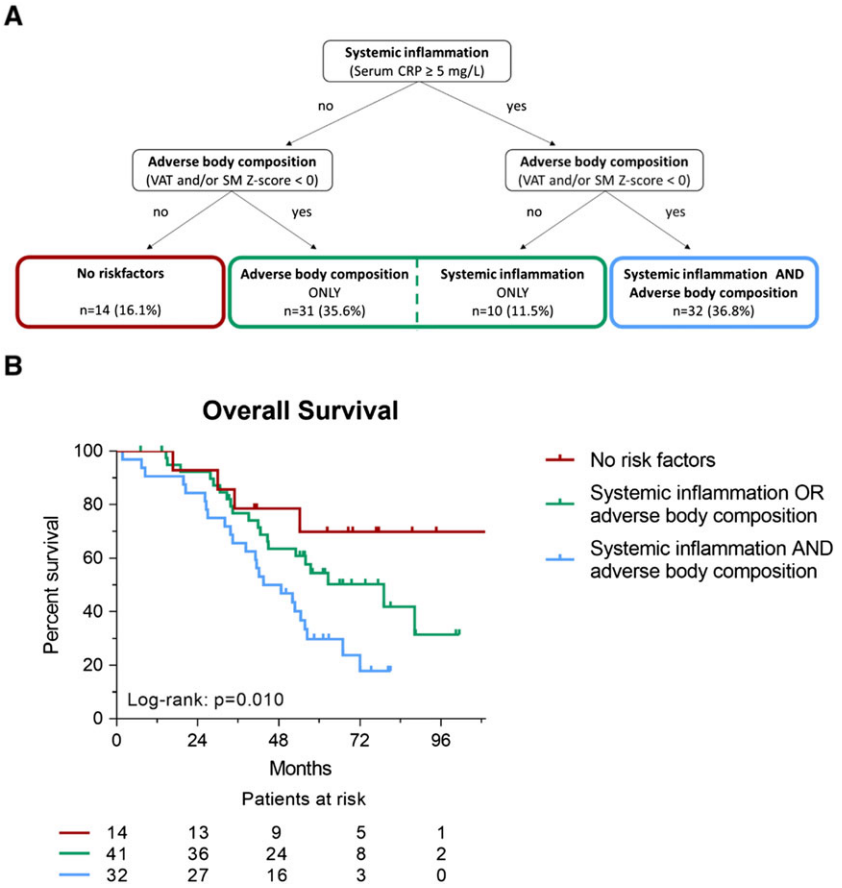
Figure 4 Effect of combinations of risk factors on overall survival. (A) Flow diagram illustrating the derivation of phenotypes used for survival analysis. Four phenotypes were identified by categorizing the study population by systemic inflammation (CRP level ≥ 5 mg/L) and adverse body composition (low VAT and/or SM Z-score). (B) Kaplan–Meier curve illustrating survival differences based on host risk factors. CRP, C-reactive protein; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.



described the deleterious effects of low muscle mass (sarcopenia) and low visceral fat in patients with resected CRLM. These body composition phenotypes can exist independently from systemic inflammation; when inflammation coexists with sarcopenia and/or low visceral fat reserves, prognosis is especially poor. Moreover, the effects appear to be independent of the effects of the Fong clinical prognostic score, primarily a function of tumour biology.

The relationship between systemic inflammation and body composition is complex and requires further study. One prominent theory is that systemic inflammation induces changes in body composition, such as a reduction in SM mass and adipose tissue mass.[26] Cytokines associated with the acute phase response, such as tumour necrosis factor-α, IL-1, and IL-6 can inhibit myocyte and adipocyte differentiation *in vitro*,[27,28] induce E3 ligases involved in muscle atrophy through the ubiquitin proteasome pathway,[29] and induce lipolysis of white adipose tissue.[30] Elevated CRP is a sign of an ongoing acute phase response, which is associated with elevated systemic cytokine levels and increased whole-body protein breakdown as we have previously shown.[5,31] Therefore, we expected that elevated CRP levels would be tightly coupled to sarcopenia and changes in adipose tissue distribution. However, elevated CRP was only detected in about half of patients with sarcopenia and/or low VAT, the two-body composition variables most closely linked to prognosis. Conversely, those body composition features were only present in ~76% of patients with elevated CRP.

The cause of systemic inflammation in CRC is unknown. We considered that HMGB1 protein could be involved, as it has been demonstrated that administration of HMGB1 protein caused elaboration of IL-1β and IL-6 in a mouse model of CRC, which was associated with metabolic changes in muscle that mimicked cachexia.[32] The inflammatory and metabolic response was abrogated by blockade of HMGB1. *In vitro* studies demonstrate that HMGB1 is a multifunctional protein that has growth factor functions and also encourages proliferation, invasion, and metastasis of cancer cells, including CRC cells.[33,34] High mobility group box 1 appears to be released by necrotic cells,[34] but little other than that is known

about what causes its release. The few *in vivo* studies on human CRC have demonstrated that serum HMGB1 levels are increased in CRC,[10] and overexpression is associated with a worse prognosis.[35] We have demonstrated that, in our clinical series, HMGB1 levels are elevated in individuals who have high CRP levels. The source of HMGB1 still requires elucidation.

The effects of sarcopenia on prognosis were not entirely surprising. While others have not reported such an association,[14,16] van Vledder *et al*.[15] did report an association between low muscle mass and survival. Some of the discrepancy could be due to the definition of sarcopenia. Cachexia is not a prominent feature of patients undergoing resection for CRLM, and it is possible that the effect is only apparent in individuals with the most overt degree of muscle atrophy. Very low muscle attenuation was also uncommonly identified in this cohort, which may be why we did not see a relationship between low muscle radiation attenuation and survival. In other tumour types, low muscle attenuation, which isthought to reflect fat infiltration (myosteatosis), is associated with a poor prognosis.[12,13,36] Other studies in (non-metastatic) CRC also did not find an effect of myosteatosis on survival.[18,37,38] As in the present study, others have demonstrated a correlation between myosteatosis and a host systemic inflammatory response.[18,38] This indicates that the prognostic effects of body composition parameters such as sarcopenia and myosteatosis vary among different cancer types.

The true strength of the present paper was the extensive description of the incidence of various body composition features and their co-relationship with systemic inflammation. One limitation of our study is that body composition features and systemic inflammation were evaluated at single time points (i.e. prior to resection). Because of this, it is difficult to distinguish body composition features that are constitutional from those that are secondary to the disease state. It will be important in future efforts to understand how body composition and systemic inflammation evolve with the disease state, as well as with treatment.

While there is extensive ongoing research on body composition and inflammation, the question is whether this could be applied clinically. Currently, it is uncommon for clinical radiologists to report on body composition variables, and measuring CRP is not yet a standard of care. There are a number of obstacles to translating this to the clinic. First, extensive international data sets are needed to provide a clinically useful framework, as body composition features greatly vary among sex, age, ethnicity, and tumour type.[12,36] It will be important to gain a better understanding of how body composition and inflammation vary with the disease state and with treatment. Also, host features can have independent as well as co-dependent associations with outcome such as body composition with systemic inflammation (present study), but also body mass index with body composition[12] or weight loss.[39] For these reasons, we consider it premature to enmesh this with normal clinical care, although (like the Fong score) the presence of numerous adverse prognostic features could represent an argument to administer upfront chemotherapy. In our opinion, the true value of our observations is that we have recognized independent host-derived features that can adversely affect survival in addition to tumour-derived features. This should spur further research on the mechanisms responsible for the appearance of each of these features, so that more specific interventions can be devised.

In conclusion, we have demonstrated that the host phenotype does have a strong effect on prognosis independent of tumour biology. Systemic inflammation combined with low muscle mass and/or low VAT reserves has the most profound effects on prognosis. While larger studies will be required to verify these findings, we have clearly shown that systemic inflammation and body composition features, while often coexistent, can appear independently.

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Conflict of interest

All authors declare that they have no conflict of interest.

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