ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2020; **11**: 1270–1282
Published online 1 June 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12575

Prognostic impact of myosteatosis in patients with colorectal cancer: a systematic review and meta-analysis

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Abstract

Background Myosteatosis has been reported to be a novel biomarker that could predict survival outcomes in patients with colorectal cancer. However, results have been conflicting. This systematic review and meta-analysis aimed to evaluate the long-term impact of myosteatosis on the survival of these patients.

Methods A systematic search of PubMed, Embase, and Cochrane up to 27 November 2019 generated 7022 records. Studies that reported hazard ratio (HR) for overall survival, cancer-specific survival, or disease-free survival based on myosteatosis or radiodensity were included. A total of 110 full-text articles were considered for inclusion, and 14 were selected for qualitative analysis. Inverse variance method was used with random effects model for data analysis.

Results The total number of enrolled patients included in the meta-analysis was 6518 for univariate and 8572 for multivariate HR analysis, from 12 and 10 studies, respectively. Patients with myosteatosis had a significant increase in overall mortality compared with non-myosteatosis patients by both univariate analysis [HR 1.38, 95% confidence interval (CI) 1.21 to 1.58, $P < 0.00001$] and multivariate analysis (HR 1.55, 95% CI 1.23 to 1.96, $P < 0.00001$). In subgroup analysis based on studies that reported HRs of both sarcopenia and myosteatosis, the negative effect of myosteatosis on overall survival was independent of sarcopenia using univariate values (sarcopenia HR 1.48, 95% CI 1.14 to 1.91, $P = 0.003$ vs. myosteatosis HR 1.51, 95% CI 1.17 to 1.96, $P = 0.002$) and multivariate values (sarcopenia HR 1.28, 95% CI 1.09 to 1.49, $P = 0.002$ vs. myosteatosis HR 1.38, 95% CI 1.07 to 1.80, $P = 0.001$).

Conclusions This meta-analysis demonstrates that myosteatosis is associated with worse overall survival in patients with colorectal cancer. More investigation is needed to standardize the measurement protocol for myosteatosis and to further optimize its prognostic power for colorectal cancer patients.

Keywords Myosteatosis; Skeletal muscle density; Survival; Colorectal cancer

Received: 12 September 2019; Revised: 9 March 2020; Accepted: 11 March 2020
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Introduction

Post-operative tumour stage or pre-operative disease dissemination status for unresectable patients has traditionally been used to determine the prognosis of the cancer patients.[1] However, there has been an increasing interest on the extent of host tumour response as an additional indicator of cancer prognosis, such as host systemic inflammation and body composition of macromolecules.[2–4] Over the last decade, the concept of sarcopenia has gained grounds in the oncology field, where sarcopenia identified pre-operatively was found to be associated with adverse oncological outcomes and

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increased morbidity for surgical patients.[5–7] Similarly, evaluation of qualitative measures of skeletal muscles in computed tomography (CT), which is expressed in various terms such as myosteatosis, skeletal muscle radiodensity (SMD), or skeletal muscle radiation attenuation, has also been increasingly studied, particularly in patients with colorectal cancer (CRC).[8–10] Because these terms refer to the same physiological changes of skeletal muscle, we have chosen to use the term 'myosteatosis' throughout this manuscript for consistency.

Martin *et al*. [11] defined myosteatosis as a mean value less than 41 Hounsfield unit (HU) for patients with body mass index (BMI) less than 25 and a mean value less than 33 for a BMI greater than 25, using CT-defined cross-sectional skeletal muscle measurements at the third lumbar vertebra. Using these cut-offs, many investigators identified that patients with low SMD were associated with higher overall and CRC-specific mortality when compared with those with normal SMD levels.[4,8,12] A recent study has shown that myosteatosis is associated with shorter survival in multiple cancer types.[13] However, there were other studies not showing clear association between myosteatosis and survival for patients with CRC.[8,14] To reconcile these findings and to consolidate the role of myosteatosis as a possible prognostic factor in CRC, a review of the existing evidence thus far seemed timely and appropriate.

Thus, we performed an in-depth systematic review and meta-analysis to investigate the long-term impact of myosteatosis or SMD on survival in patients with CRC.

Methods

All procedures used in this study were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15]

Data sources and searches

We included articles that reported on human studies published in the English language up to 27 November 2019 from PubMed, Embase, and Cochrane Central. The full list of search terms by category is included in Supporting Information, *Appendix* S1, and the search strategy with the number of search results is provided in *Appendix* S2.

Study selection

The list of retrieved studies was initially screened by titles, abstracts, and availability of full-text article. J. K. and C. M. L. screened full-text articles of relevant studies independently, and discrepancies were resolved by discussion. Studies were selected on several inclusion criteria. First, the patient population consisted of CRC patients. Second, the primary outcomes were measured and reported as hazard ratios (HRs) of overall survival (OS) and/or disease-free survival (DFS) or cancer-specific survival (CSS) with myosteatosis or radiodensity as one of the variables. Third, previously published definitions of myosteatosis were used and identified based on decreased mean HU on radiodensity, instead of assessing changes in radiodensity pre-operative or post-operative stages. Studies that did not contain primary data, such as those only available as conference abstracts, editorials, or commentaries, were excluded. When the same patient cohort was used in multiple publications, the study that included more appropriate data for our study was included.

Data extraction

We extracted all mean HRs with 95% confidence interval (CI) for OS, DFS, and/or CSS separately, along with measurement method, location of the CT scan, and the definition of myosteatosis including references. Other clinical data collected from full-text articles included study design, study site, number of patients enrolled, basic patient demographics (age and gender), software used for muscle density measurement, and the time point of CT exam. Cohen's inter-rater κ statistics for inclusion agreement was 0.620 (95% CI 0.320 to 0.919), with strength of agreement considered 'good'.[16]

Definition of myosteatosis

Myosteatosis in most studies was defined as SMD $<$41 HU in patients with BMI $<$25 kg/m^2 and $<$33 in patients with BMI $\geq$25 mg/m^2, which was suggested by Martin *et al*.[11] For study by Dolan *et al*.[17] myosteatosis was defined by Xiao *et al*.[10] as $<$35.5 HU in men and $<$32.5 HU in women. Similarly, most studies included in our meta-analysis assessed the area of total skeletal muscle from a single image taken at the third lumbar vertebra, except Okugawa *et al*.[14] which used intramuscular adipose tissue content (IMAC) calculated from mean CT value of region of interest (ROI) of multifidus muscle (HU) divided by mean CT value of ROI of subcutaneous fat in HU and assessed the superior aspect of fourth lumbar vertebra and the psoas muscle. For the particular study, high IMAC using sex-specific median values was used to define myosteatosis.[14] The variations in the definition of myosteatosis used in the included study are summarized in *Table* 1. In this study, we included both search terms of 'low radiodensity' and 'myosteatosis' to identify the patient cohorts, and they refer to the same methods of HU measurements within CT images. To avoid confusion, we have used 'myosteatosis' throughout the manuscript to describe findings that were identified as 'myosteatosis' or 'low SMD'.

Table 1 Study characteristics

Author	Year	Country	Study design	*N*	Myosteatosis, *n* (%)	Age	CRC stage
Blauwhoff-Buskermolen *et al*.	2016	The Netherlands	Prospective	67	47 (64.2)	66.4 ± 10.6	Metastatic
Charette *et al*.	2019	Belgium	*Post hoc* analysis of two non-randomized Phase II trials	217	42 (19.3)	63.0 ± 11.0	Chemorefractory metastatic
Deng *et al*.	2018	Taiwan	Retrospective	101	NA	63.7 ± 13.7	Stages I–IV
Dolan *et al*.	2019	UK	Retrospective—from a prospective database	650	341 (52.5)	Divided to <65 (234), 65–74 (251), >74 (165)	Stages I–III
Hopkins *et al*.	2019	Canada	Retrospective—from a prospective database	968	537 (55.5)	65.8 ± 11.8	Stages I–III
Kroenke *et al*.	2018	USA	Prospective	3262	966 (29.6)	Divided to <50 (432), 50–60 (806), 60–70 (941), >70 (1083)	Stages I–III
Looijaard *et al*.	2019	The Netherlands	Retrospective	378	NA	73.4 (IQR 69.5–78.4)	Stages I–IV
Malietzis *et al*.	2016	UK	Retrospective—from a prospective database	805	625 (77.6)	Median 69 (IQR 61–77)	Stages I–IV
McSorley *et al*.	2018	UK	Retrospective—from a prospective database	322	186 (57.8)	Divided to <65 (106), 65–74 (127), >74 (89)	Stages 0–III
Okugawa *et al*.	2018	Japan	Retrospective—from a prospective database	308	153 (49.7)	Divided to <67 (159) or >67 (149)	Stages I–IV
Sabel *et al*.	2013	USA	Retrospective	302	NA	67.9 ± 12.4	Stages I–IV
Sueda *et al*.	2018	Japan	Retrospective	211	110 (52.1)	Divided to >65 (53) or <65 (53)	Stages I–III
Van Baar *et al*.	2018	The Netherlands	Prospective	1681	648 (39)	67.7 ± 10.3	Stages I–III
Van Vugt *et al*.	2018	The Netherlands	Prospective	816	523 (64.1)	Median 70	Stages I–III

NA, not applicable.

DOI: 10.1002/jcsm.12575

Table 1 (continued)

Author	Measurement location	Measurement method	Myosteatosis definition	Software used	Outcomes (univariate)	Outcomes (multivariate)	Total length of follow-up	Reference
Blauwhoff-Buskermolen *et al*.	CT L3, single	Mean HU	<41 HU (BMI < 25) <33 HU (BMI ≥ 25)	sliceOmatic v5.0	OS	OS	Total 3.5 years	Blauwhoff-Buskermolen *et al*.[27]
Charette *et al*.	CT L3, two adjacent CT slices	Mean HU	<22.5	PLANET Onco software (DOSIsoft, France)	OS	OS	NA	Charette *et al*.[30]
Deng *et al*.	CT, L4, three consecutive slides	Mean HU	NA	MATLAB v8.3	OS, PFS	None	>5 years	Deng *et al*.[32]
Dolan *et al*.	CT L3, single	Mean HU	<35.5 HU (men) <32.5 HU (women)	NIH ImageJ 1.47	None	OS	9.25 years	Dolan *et al*.[17]
Hopkins *et al*.	CT L3, single	Mean HU	<38.2 (men) and <35.7 (women) HU for BMI < 25 <31.9 (men) and <33.6 (women) HU for BMI ≥ 25	MATLAB	CSS, OS, DFS	CSS, OS	Median 5.2 years (range 0.01–10.25)	Hopkins *et al*.[31]
Kroenke *et al*.	CT L3, single	Mean HU	<35.5 HU (men) <32.5 HU (women)	sliceOmatic v5.0	None	CSS, OS	Median 6.9 years (range 0–10.9)	Kroenke *et al*.[9]
Looijaard *et al*.	CT L3, single	Mean HU, IMAT	NA	sliceOmatic v5.0	OS	OS	Median 5.3 years (IQR 3.7–6.6)	Looijaard *et al*.[33]
Malietzis *et al*.	CT L3, single	Mean HU	<41 HU (BMI < 25) <33 HU (BMI ≥ 25)	sliceOmatic v4.3	OS, DFS	None	Median 47 months (IQR 24.9–65.6)	Malietzis *et al*.[8]
McSorley *et al*.	CT L3, single	Mean HU	<41 HU (BMI < 25) <33 HU (BMI ≥ 25)	NIH ImageJ 1.47	CSS, OS	CSS, OS	Median 56 months (range 35–96)	McSorley *et al*.[4]
Okugawa *et al*.	CT, L4 (superior aspect), psoas muscle index	IMAC (intramuscular adipose tissue content)	male −0.36, female −0.24 (sex-specific median value)	AquarisNET server (TeraRecon)	CSS, DFS	None	Median 35.9 months (mean: 39.2 ± 28.6)	Okugawa *et al*.[14]
Sabel *et al*.	CT L4, single	Mean HU	No cut point indicated	MATLAB v13.0	OS, DFS	None	Median 2.81 years (mean 3.23 years)	Sabel *et al*.[34]
Sueda *et al*.	CT L3, single	Mean HU	<41 HU (BMI < 25) <33 HU (BMI ≥ 25)	SYNAPSE VINCENT analyser (Fujifilm Co., Ltd., Tokyo, Japan)	CSS, OS, DFS	CSS, OS, DFS	Median 57.6 months	Sueda *et al*.[12]
Van Baar *et al*.	CT L3, single	Mean HU	<36.4 (men) and <31.1 (women) HU for BMI < 25 <31.6 (men) and <29.3 (women) HU for BMI ≥ 25	sliceOmatic v5.0	None	CSS, OS, DFS	Median 48 months (range 0–119)	Van Baar *et al*.[28]
Van Vugt *et al*.	CT L3, single	Mean HU	<41 HU for BMI < 25 <33 HU for BMI ≥ 25	FatSeg (in-house)	OS, DFS	OS	Median 76.5	Van Vugt *et al*.[29]

BMI, body mass index; CRC, colorectal cancer; CSS, cancer-specific survival; CT, computed tomography; DFS, disease-free survival; HU, Hounsfield unit; IQR, inter-quartile range; L3, third lumbar; L4, fourth lumbar; NIH, National Institutes of Health; OS, overall survival; NA, not applicable.

Data synthesis and statistical analysis

Results were grouped separately according to the final outcomes by HR for myosteatosis with 95% CI of OS, CSS, or DFS. A meta-analysis was performed using a random effects model because of assumed heterogeneity between studies.[18] Random effects model allows the true effect size to differ from study to study, as it assumes that studies included in the analysis are random samples of all possible studies that meet the inclusion criteria.[19] This may be more reflective of the current meta-analysis as different studies recruited patients of varying cancer stage, ethnicity, gender proportions, and co-morbidities. We compared HR values available for OS, CSS, and DFS by univariate vs. multivariate analysis, and because most HR values were available for OS (12 studies for univariate values and 10 studies for multivariate values, respectively, as outlined in *Table* S1), we focused our meta-analysis of myosteatosis on OS.

For the data analysis, inverse variance method was used to obtain pooled HRs and 95% CIs. Statistical analysis was performed using the Review Manager software (RevMan, Version 5.3 for Windows, Oxford, UK; the Cochrane Collaboration, 2014), to calculate the summary effect size, 95% CI, and *P*-values of random and fixed effect models. Forest plots were used to visualize the results, and heterogeneity between studies was assessed using the I^2 statistic and the *P*-value from the χ^2-based Cochran's *Q* test. I^2 values reflect the percentage of variation among studies attributed to heterogeneity rather than to chance. Thus, I^2 values higher than 25%, 50%, or 75% were considered to describe low, moderate, or high heterogeneity, respectively,[20] and $\chi^2 < 0.10$ was used to define statistically significant heterogeneity.[21]

Assessment of publication bias

To check for publication bias, we generated funnel plots of log[HR] against its standard error and used Egger's regression asymmetry test. Where the asymmetry was found, the potential impact of the publication bias was assessed by the Duval and Tweedie non-parametric 'trim-and-fill' method.[22] Meta-Essentials (Version 1.4; Rotterdam, The Netherlands: Erasmus Research Institute of Management) was used to perform the Egger's regression asymmetry test.[23] All tests of significance were two sided, and *P*-values <0.05 were considered to be statistically significant.

Quality assessment

The Newcastle–Ottawa scale scoring for cohort studies for the meta-analysis of myosteatosis in CRC has already been published.[13,24] The Quality in Prognosis Studies (QUIPS) tool was used to assess the quality of the methodology of included studies, by considering each of the domains outlined by Hayden *et al*.[25] and rating for whether the study was conducted in a way to limit the potential bias (yes, no, partly, or unclear). In this systematic review, studies that were identified as having an overall high risk of bias were those that did not have clear criteria for myosteatosis and did not perform statistical analyses such as multivariate analyses to account for potential confounding factors. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[26] was performed to assess the quality of evidence for the effect of myosteatosis on the OS of CRC patients using the GRADEPro GDT software (McMaster University, 2015, developed by Evidence Prime, Inc).

Results

Identification of studies and study characteristics

Our search on 27 November 2019 retrieved 7751 publications (3732 from Embase, 666 from PubMed, and 3353 from Cochrane) (*Figure* 1). After removal of duplicates, 7022 records were screened independently by the two authors (J. K. and C. M. L.), which led to exclusion of 6847 by title review, 65 abstracts, 11 review articles, editorials, and comments, 72 studies with no data on myosteatosis, and 13 with no data on the association between myosteatosis and patient survival. A total of 110 full-text articles were considered for inclusion. After full-text review of each article, 14 were selected for qualitative analysis. Among 14 included studies, nine studies were retrospective, while four studies were prospective,[9,27–29] and one study was a *post hoc* analysis of two non-randomized Phase II trials.[30]

Included studies and patient characteristics

All patients included in the study had been diagnosed with CRC, mostly between Stages I–III (seven studies) and Stages I–IV (five studies), and also at metastatic (one study) or chemorefractory status (one study). The number of patients categorized as having myosteatosis ranged from 42 to 966 or 19–78% of the study cohort, with total number of patients included in the meta-analysis being 6518 for univariate and 8572 for multivariate HR analysis for OS. Patients with myosteatosis, excluding studies that did not provide a clear definition or cut-offs for myosteatosis to determine the precise size of the myosteatosis cohort, totalled to be 3059 for univariate and 3401 for multivariate HR analysis. Time at which the CT was analysed was mostly at pre-operative evaluation, but where specified, varied between 21 days before surgery[31] to within 3 months of surgery[17] or within 4 months of chemotherapy or radiotherapy.[9]

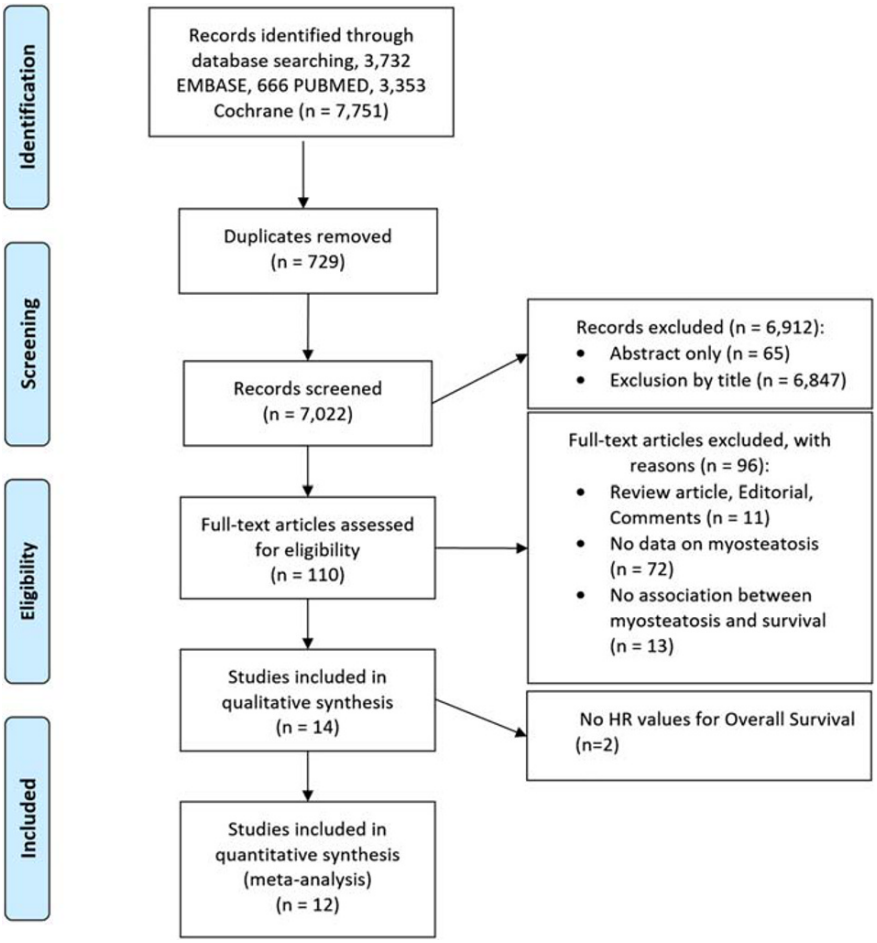


Figure 1 Flow diagram depicting the selection process for studies. HR, hazard ratio.

Myosteatosis and overall survival in colorectal cancer

Patients with myosteatosis had a significant increase in the overall mortality compared with non-myosteatosis patients by both univariate analysis (HR 1.38, 95% CI 1.21 to 1.58, $P < 0.00001$) (*Figure* 2) and multivariate analysis (HR 1.55, 95% CI 1.23 to 1.96, $P < 0.00001$) (*Figure* 3A). This indicates that myosteatosis has an independent prognostic significant effect on OS. However, a fairly large dispersion was observed

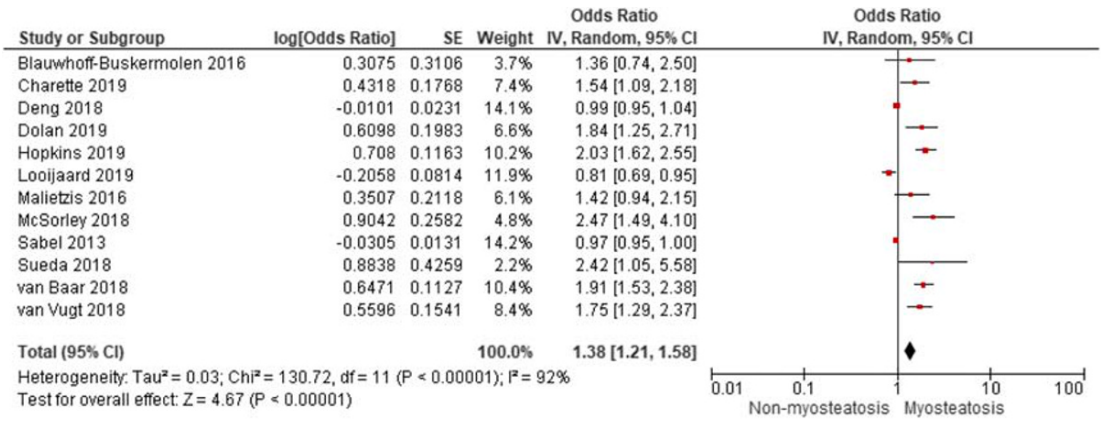
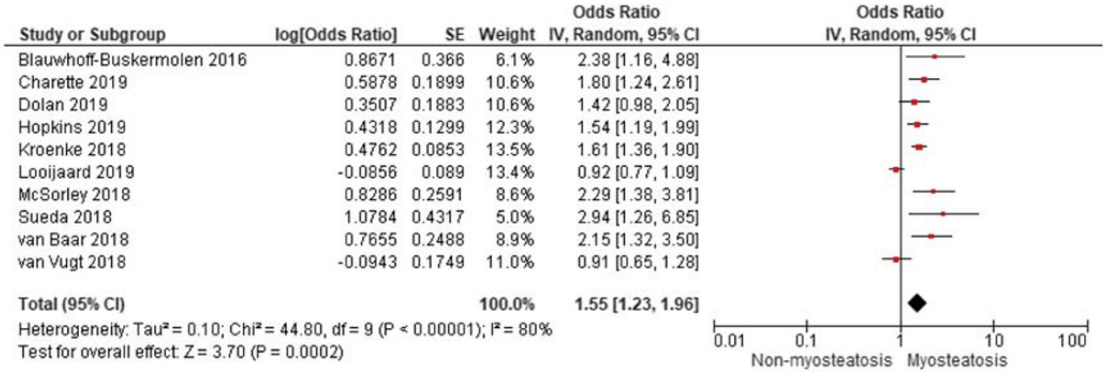


Figure 2 Meta-analysis of univariate results reporting impact of myosteatosis on overall survival in patients with colorectal cancer using the random effects model. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SE, standard error.

A Overall survival using HR from multivariate analysis



B Cancer-specific survival

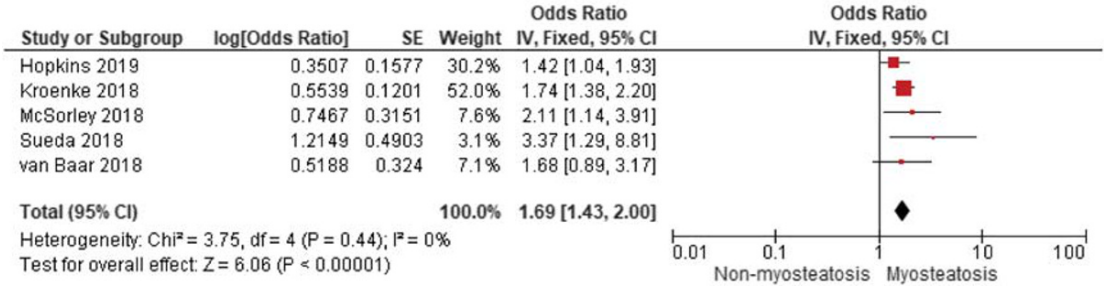


Figure 3 Meta-analysis of multivariate results reporting impact of myosteatosis on (A) overall survival and (B) cancer-specific survival in patients with colorectal cancer using the random effects model. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SE, standard error.

in both plots (I^2 = 92% and 80%, respectively). By funnel plot, publication bias was detected for univariate analysis (Egger P = 0.004) (*Figure* S2A) but not for multivariate analysis (Egger P = 0.125) (*Figure* S2B). Studies that did not show significance in the forest plot[32–34] in *Figure* 2 were largely those with no clear cut-off or definition for myosteatosis and which scored very poorly in the QUIPS assessment. For example, in Looijaard *et al.*,[33] muscle density measured in HU without any cut-off for myosteatosis was used for the HR calculation, which yielded an insignificant HR value.

Myosteatosis and cancer-specific survival and disease-free survival in colorectal cancer

We identified five studies that reported adjusted data on the effect of myosteatosis on CSS. Meta-analysis of the five adjusted studies showed a significant increase in CRC-specific mortality with the presence of myosteatosis for random effects model (HR 1.69, 95% CI 1.43 to 2.00, $P < 0.00001$) (*Figure* 3B). Heterogeneity was low among these studies (I^2 = 20%). We also performed a meta-analysis of DFS HR values, but interestingly, there was no effect of myosteatosis on DFS (HR 1.00, 95% CI 0.95 to 1.05, P = 0.88) (*Figure* S1).

Comparison of myosteatosis and sarcopenia in colorectal cancer

Using nine and seven studies that reported the impact of both sarcopenia and myosteatosis in their study cohort by univariate and multivariate analysis of HR for OS, respectively (*Table* 2), we found that sarcopenia and myosteatosis had independent negative effects on OS. *Figures* 4 and 5 show the negative effect of sarcopenia and myosteatosis using univariate values (sarcopenia HR 1.48, 95% CI 1.14 to 1.91, P = 0.003 vs. myosteatosis HR 1.51, 95% CI 1.17 to 1.96, P = 0.002) and multivariate values (sarcopenia HR 1.28, 95% CI 1.09 to 1.49, P = 0.002 vs. myosteatosis HR 1.38, 95% CI 1.07 to 1.80, P = 0.001) (*Figures* 4 and 5). Two studies [9,31]reported the effect of having both sarcopenia and myosteatosis on patient survival (HR 2.02, 95% CI 1.65 to 2.47 and HR 2.24, 95% CI 1.63 to 3.09, respectively).

Quality assessment

The 14 studies were assessed for each of the six domains of the QUIPS tool, where a rating of 'yes' means that the study was designed and conducted to sufficiently limit the potential biases within that domain. 'Unclear' denotes that the answer

Table 2 Studies that report both sarcopenia and myosteatosis and the respective HR for OS

For OS	Univariate		Multivariate		
Study	Sarcopenia (HR, 95% CI)	Myosteatosis (HR, 95% CI)	Sarcopenia (HR, 95% CI)	Myosteatosis (HR, 95% CI)	Combined sarcopenia and myosteatosis (HR, 95% CI)
Charette *et al.*[30]	2.06 (1.45 to 2.93)	1.54 (1.09 to 2.18)	1.49 (1.04 to 2.15)	1.80 (1.24 to 2.61)	
Deng *et al.*[32]	0.93 (0.84 to 1.02)	0.99 (0.95 to 1.04)	NA	NA	
Dolan *et al.*[17]	1.74 (1.21 to 2.49)	1.84 (1.25 to 2.72)	1.50 (1.04 to 2.18)	1.42 (0.98 to 2.05)	
Hopkins *et al.*[31]	2.01 (1.67 to 2.50)	2.03 (1.61 to 2.54)	1.45 (1.15 to 1.84)	1.54 (1.19 to 1.98)	2.24 (1.63 to 3.09)
Kroenke *et al.*[9]	NA	NA	1.30 (1.07 to 1.57)	1.63 (1.30 to 2.05)	2.02 (1.65 to 2.47)
Looijaard *et al.*[33]	0.953 (0.812 to 1.119)	0.814 (0.694 to 0.955)	0.998 (0.840 to 1.187)	0.918 (0.771 to 1.093)	
Malietzis *et al.*[8]	1.77 (1.32 to 2.38)	1.42 (1.09 to 2.50)	1.70 (1.25 to 2.31)	NA	
McSorley *et al.*[4]	1.40 (0.88 to 2.24)	2.47 (1.49 to 4.10)	NA	2.29 (1.38 to 3.81)	
Okugawa *et al.*[14]	NA	NA	NA	NA	
Sabel *et al.*[34]	NA	0.97 (0.95 to 1.00)	NA	NA	
Sueda *et al.*[12]	2.14 (0.99 to 4.97)	2.42 (1.10 to 5.84)	2.29 (1.04 to 5.41)	2.94 (1.32 to 7.17)	
Van Baar *et al.*[28]	NA	NA	NA	1.91 (1.53 to 2.38)	
Van Vugt *et al.*[29]	1.35 (1.03 to 1.76)	1.75 (1.29 to 2.36)	1.06 (0.80 to 1.42)	0.91 (0.65 to 1.29)	

CI, confidence interval; HR, hazard ratio; OS, overall survival; NA, not applicable.

to the item was not reported clearly, and 'partly' similarly indicates that the item was not fully addressed. Most studies were retrospective cohort studies from prospectively maintained databases, with well-defined collection period and detailed description of the patient populations. However, one study[32] did not provide sufficient baseline characteristics of the cohort, and four studies either did not provide clear definition of myosteatosis[32–34] or had very small proportion of the study

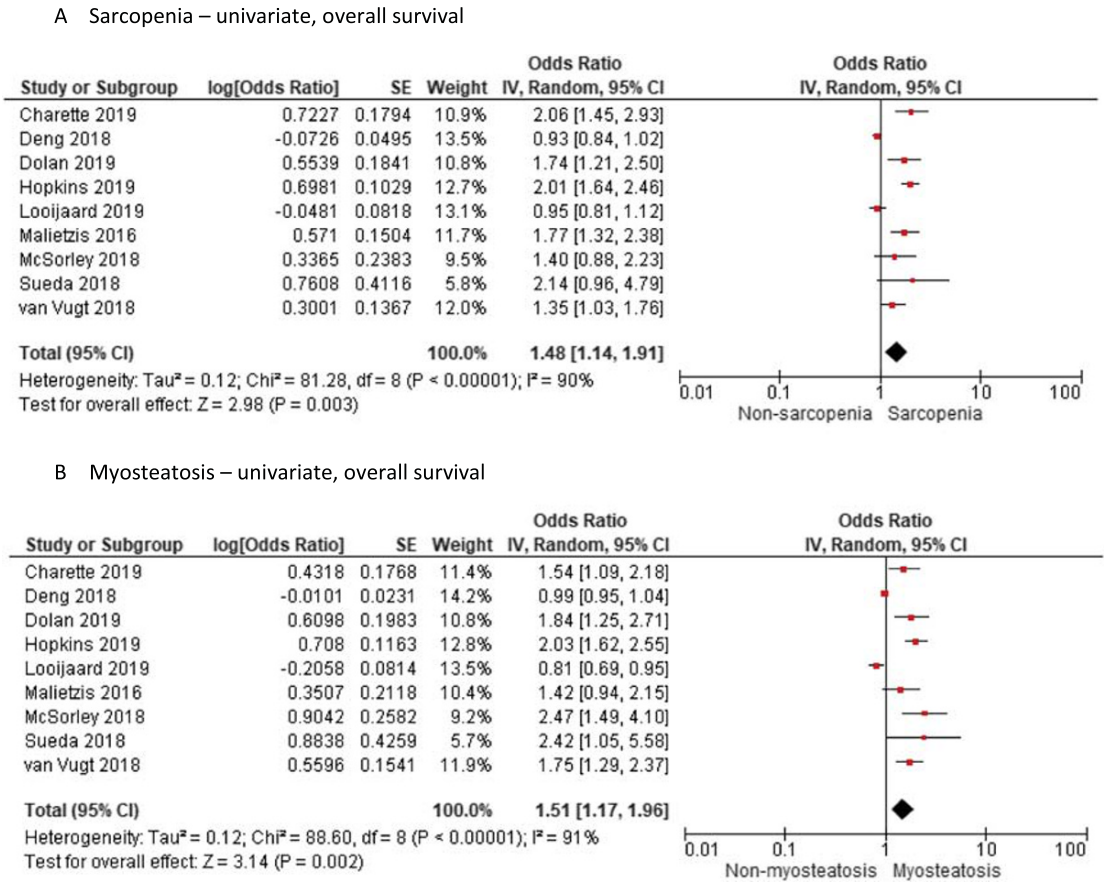
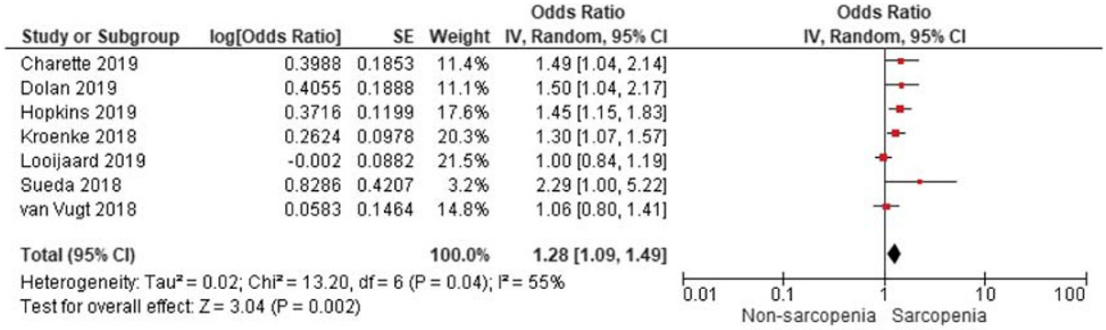


Figure 4 Meta-analysis of univariate results reporting impact of (A) sarcopenia and (B) myosteatosis by random effects model in studies that report both findings in the same study cohort. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SE, standard error.

A Sarcopenia – multivariate, overall survival



B Myosteatosis – multivariate, overall survival

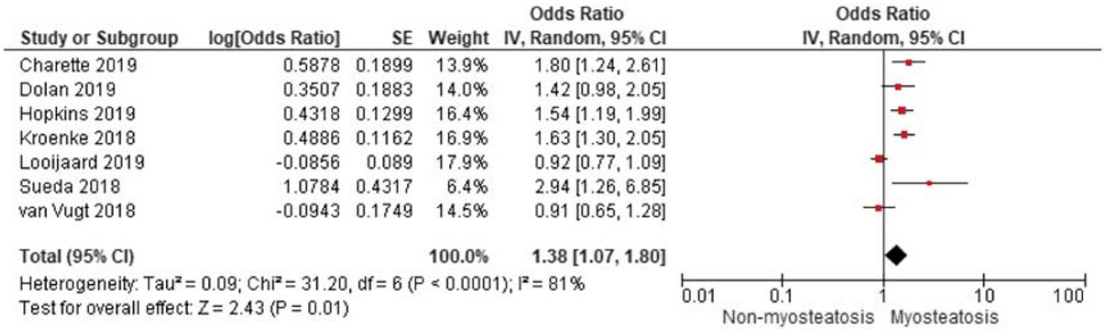


Figure 5 Meta-analysis of multivariate results reporting impact of (A) sarcopenia and (B) myosteatosis by random effects model in studies that report both findings in the same study cohort. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SE, standard error.

cohort with myosteatosis,[30] which affected both study attrition and prognostic factor measurement. Outcome measurement was judged to be clearly defined by all studies for overall mortality. For confounding measurement, minimum requirements were set as that the results were adjusted for age, gender, and disease stage. Studies adjusted for less or different factors were denoted as 'partly'.[14,27,33,34] Regarding statistical approach, four studies did not include multivariate analyses and were judged as with high potential for this bias.[8,14,32,34] One study was noted as 'partly' for the statistical approach domain[33] as muscle density without cut-off was used in the analysis. Three studies were judged to be at an overall high risk of bias,[32–34] given inadequate definition or measurement of myosteatosis and 'partly/unclear' or high risk of bias for the confounding measurement and statistical approach (*Table* S2). The GRADE assessment of studies included in the meta-analysis is provided in *Table* 3, which gave 'Low' score on the overall certainty of evidence as there were no randomized controlled trial studies and mostly retrospective studies.

Discussion

This systematic review and meta-analysis demonstrate that myosteatosis measured in pre-treatment periods could be used as an independent predictor of worse survival outcomes in patients with CRC.

Sarcopenia has been increasingly recognized not only as a prognosticator of adverse outcomes but also as a predictor of post-operative morbidity.[7,31,32,35–37] Even in CRC, the negative impact of sarcopenia on survival has been increasingly investigated.[38–40] Intramuscular fat accumulation, referred to as 'myosteatosis', is an early change within the muscle architecture, associated with significantly decreased muscle quality.[41] In addition to the loss of muscle mass, however, the concept of sarcopenia has been extended to include muscle quality and function.[42] Recent studies looking at the effect of skeletal muscle mass and/or composition on the survival of CRC patients have found that patients with both sarcopenia and myosteatosis have worse OS than those patients with sarcopenia or myosteatosis alone.[9,31] However, there are also studies reporting no prognostic impact of myosteatosis in patients with CRC,[27,34] which prompted us to look into whether myosteatosis was an independent risk factor as in the case for sarcopenia. Although there was a large meta-analysis looking at myosteatosis and prognosis in multiple cancer types,[13] detailed analysis is still required for CRC because of its prevalence and controversies of the outcomes.

The exact pathogenesis of myosteatosis or its relationship to sarcopenia is not clearly understood, though some clinical data suggest that there may be a common mechanism to

Table 3 GRADE assessment of studies included in the meta-analysis for overall survival

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Myosteatosis	Non-myosteatosis	Relative (95% CI)	Absolute (95% CI)	Certainty
Univariate analysis											
12	Observational studies	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected All plausible residual confounding would reduce the demonstrated effect[a]	3059/6518 (46.9%)	3459/6518 (53.1%)	HR 1.38 (1.21 to 1.58)	117 more per 1000 (from 69 more to 167 more)	⊕⊕○○ Low
Multivariate analysis											
10	Observational studies	Not serious	Not serious	Not serious	Not serious	None	3401/8572 (39.7%)	5171/8572 (60.3%)	HR 1.55 (1.23 to 1.96)	158 more per 1000 (from 76 more to 233 more)	⊕⊕○○ Low

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HR, hazard ratio.
[a]Funnel plot is not symmetrical, and Egger regression has a significant *P*-value of 0.004.

sarcopenia and myosteatosis. Systemic inflammatory response in patients with CRC, for example, has been associated with both sarcopenia and myosteatosis, with high neutrophil-to-lymphocyte ratio being an independent predictor of reduced muscle mass (odds ratio 1.78, 95% CI 1.29 to 2.45) and myosteatosis (odds ratio 1.60, 95% CI 1.03 to 2.45).[8] It is thought that anti-tumour proteins and the pro-inflammatory cytokines such as interleukin-1β[43] against cancer contribute to systemic inflammation and muscle wasting, cachexia, and sarcopenia.[44] The basic mechanism of myosteatosis and its relation to survival outcome might be important to identify the most appropriate intervention at the time of diagnosis such as anti-inflammatory medications, which may improve long-term survival outcomes,[31] and future interventional studies such as means of increasing muscle mass before surgery may be helpful. The exact pathogenesis of myosteatosis and how it differs in different cancer types are also subjected to further investigation.

Although our analysis revealed the association of myosteatosis with worse survival, there are several issues on the use of myosteatosis as a significant and standardized prognostic factor in patients with CRC. Firstly, there is currently no unified or validated consensus on the definition of myosteatosis. Most of the included studies used <41 HU in patients with BMI <25 kg/m^2 and <33 in patients with BMI ≥ 25 mg/m^2 as a cut-off value of radiodensity,[11] but others have also used <35.5 HU in men and <32.5 HU in women[10] or IMAC calculation,[14] or their own criteria (22.5 HU).[30] The clinical significance of myosteatosis may vary depending on which criteria are used, and future studies should correlate myosteatosis with measurements of muscle function. For instance, in a study using their own cut-off of 22.5 HU, muscle density was found to be an important prognostic factor in the multivariate analysis (HR 1.8, 95% CI 1.24 to 2.61), but when using the cut-off values originated from Martin *et al.*[11] which were generated from mixed group of cancers and mostly from poor prognosis, low muscle density was not associated with OS (HR 1.25, 95% CI 0.89 to 1.77).[30] Even in our study, for univariate analysis (*Figure* 2), the three studies with HR values close to 1 or on the side of favouring myosteatosis were those without clear criteria for myosteatosis. Secondly, the HU may vary depending on the phase of the CT used for measurement. One study reported that mean SMD in the unenhanced phase is significantly lower than that measured in the arterial and portal venous phase [unenhanced phase (30.9 ± 8.0 HU) vs. arterial (38.0 ± 9.9 HU) or portal venous (38.7 ± 9.2 HU) phase (both $P < 0.001$)].[45] In this meta-analysis, comparison of the CT protocol or phase could not be performed because of lack of such information. These limitations may render cross-comparison between different studies challenging.

There are also several limitations to our study. Not every study looking at the OS of CRC patient had measured SMD as one of their variables, for example, which led to their

exclusion for the purpose of our study. Similarly, myosteatosis was often not the main focus of many of the studies included, which means that the patient demographics were often not sufficiently stratified within the study population to identify potential confounding variables, other than a 'yes/no' on the presence of myosteatosis and a report on the final survival outcome in a form of meta-analysis. Other sources of variations among studies may include different cancer stage, race, and gender ratio of the patient population.

In this meta-analysis, studies including OS were more represented than those studies reporting CSS or DFS. Meta-analysis of studies that report the impact of both sarcopenia and myosteatosis in their study, myosteatosis had negative effects on OS independent from sarcopenia, by both univariate and multivariate analyses. Interestingly, however, myosteatosis did not have an effect on DFS, unlike OS or CSS. This could suggest that myosteatosis does not reflect the aggressiveness of CRC but acts mainly as an indicator of overall fragility of the host. Because myosteatosis increases with age and is known to be associated with obesity and diabetes,[46,47] it would be important to ensure matched analysis of patients in future studies. It still remains uncertain whether the worse survival outcomes for patients with myosteatosis are associated with aggressive tumour behaviour, impaired host immune defence, or a combination of both as its possible mechanism. Although an investigation of this question was beyond the scope of our study, this phenomenon might be useful in elucidating the association of myosteatosis with worse outcomes in patients with CRC.

We hereby report the association between myosteatosis and OS in CRC and that myosteatosis is an independent predictor of worse survival. More investigation is needed to standardize the measurement protocol for myosteatosis and to further optimize its prognostic power by cancer stage and patient demographics for CRC patients.

Acknowledgement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[48] We would like to thank Na Won Kim, PhD (Librarian, Yonsei University Medical Library, Seoul, Korea), for her generous help in the searching process.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Number of studies with available hazard ratios of univariate and multivariate analysis with respect to different survival outcomes including overall survival, cancer-specific survival and disease-free survival.
Table S2. Risk of Bias Assessment Using the Quality in Prognosis Studies (QUIPS) Tool
Figure S1. Meta-analysis of multivariate results reporting impact of myosteatosis on disease-free survival (DFS) in patients with colorectal cancer by random effect model. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SE, standard error
Figure S2. Funnel plot of the meta-analysis of univariate and multivariate HR of included studies indicating presence of publication bias.
Appendix 1: Search strategy
Appendix S2. Search query and number of items found

Conflict of interest

None declared.

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