REVIEW ARTICLE

Sarcopenia and long-term survival outcomes after local therapy for colorectal liver metastasis: a meta-analysis

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Abstract

Background: Sarcopenia is defined as either low pre-operative muscle mass or low muscle density on abdominal CT imaging. It has been associated with worse short-term outcomes after surgery for colorectal liver metastases. This study aimed to evaluate whether sarcopenia also impacts long-term survival outcomes in these patients.

Methods: A random-effects meta-analysis was conducted following the PRISMA guidelines. Overall survival (OS) and disease-free survival (DFS) outcomes were evaluated.

Results: Eleven studies were included, ten reporting on the impact of low muscle mass and four on low muscle density. Sample sizes ranged between 47 and 539 (2124 patients in total). Altogether, 897 (42%) patients were considered sarcopenic, although definitions varied between studies. Median follow-up was 21–74 months. Low muscle mass (hazard ration (HR) 1.35, 95%CI 1.08–1.68) and low muscle density (HR 1.97, 95%CI 1.07–3.62) were associated with impaired OS. Low muscle mass (pooled HR 1.17, 95% CI 0.94–1.46) and low muscle density (pooled HR 1.13, 95%CI 0.85–1.50) were not associated with impaired RFS.

Discussion: Sarcopenia is associated with poorer OS, but not RFS, in patients with CRLM. Additional studies with standardized sarcopenia definitions are needed to better assess the impact of sarcopenia in patients with CRLM.

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Introduction

Colorectal cancer is the second cause of cancer mortality worldwide.[1] Fifteen percent of colorectal cancer patients present with colorectal liver metastasis (CRLM) upon diagnosis, while another fifteen percent will develop metachronous CRLM.[2] When resectable, local therapy (i.e., surgery of ablative therapy) is the gold standard treatment for CRLM, resulting in a five-year survival of 40–60%.[3] Cure is merely reached in one fifth of patients with CRLM after resection.[4,5]

In order to assess the prognosis of patients with CRLM, numerous risk models have been proposed. These models mainly consist of oncological characteristics, such as the size and number of CRLM, the presence of extrahepatic disease, and the lymph node status of the primary tumour. A moderately accurate prediction of survival outcomes is achieved using these models.[6] Novel cancer related biomarkers could improve the prediction of long-term outcomes, but general patient health characteristics could also play an important role.

Sarcopenia has emerged as a potential prognostic factor in surgical oncology. Sarcopenia defined as a combination of decreased muscle mass and muscle function. Muscle mass can be measured via CT scans. An alternative for muscle mass is muscle density measurement, which can be measured on CT scans as well.[7] Commonly used measurements for muscle mass are Skeletal Muscle Index (SMI) or Psoas Muscle Index (PMI). This is a method which is easily available without additional costs using routinely performed CT examinations. Muscle density can be measured as Intramuscular Adipose tissue Content (IMAC) or the Hounsfield Unit Average Calculation (HUAC). Low muscle

density, represented by low HUAC or high IMAC implies fatty infiltration of muscle tissue and is an indicator of low muscle quality.[8] A state of sarcopenia has been associated with worse short-term outcomes and long-term outcomes in various gastrointestinal cancers.[9,10]

In order to determine whether a sarcopenic state also impairs long-term survival outcomes in patients undergoing local therapy (i.e. resection and/or ablation) with curative intent for CRLM, this study aims to systematically assess and meta-analyze available literature evaluating sarcopenia in light of overall- and recurrence-free survival after local therapy for CRLM.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A systematic literature search of Embase, Medline Ovid, Cochrane central, Web of science and Top 50 Google Scholar was performed by an experienced librarian on the 21st of December 2020. Details of the search are provided in the supplementary materials.

Study selection and quality assessment

Screening of the articles was performed by two researchers (YM, RW), independently. Any disagreement was solved by evaluation with a third reviewer (BG). Studies were considered eligible for inclusion when the impact of sarcopenia on overall survival (OS) or recurrence-free survival (RFS) in patients undergoing local therapy (i.e. resection and/or ablation) with curative intent for CRLM was evaluated. Non-original studies (e.g. editorials, systematic reviews), conference abstracts, and studies written in a language other than English were excluded. Methodological quality of the included studies was assessed by two researchers independently (RW and YM), using the Newcastle–Ottawa quality assessment scale[11] Disagreements were solved by consulting with a third researcher (BG). Based on the Newcastle–Ottawa Scale (NOS), studies were classified as being of low (<6 points), moderate (6–7 points) or high quality (>7 points).

Data extraction

Data were extracted by two researchers (RW, YM). Extracted data consisted of author, year of publication, number of patients, country where the trial was conducted, median age of patients, proportion of sarcopenic patients, type of sarcopenia assessment, cutoff level and its origin, follow-up duration, OS outcomes (5-year Kaplan–Meier estimates, hazard ratios (HRs) and 95% confidence intervals (95%CI)), and RFS outcomes (5-year Kaplan–Meier estimates, hazard ratios (HRs) and 95% confidence intervals (95%CI)).

Quantitative analysis

Multivariable HRs were used for pooling when available, and univariable in its absence. When HRs were not reported, these were calculated using methods described by Tierney et al.[12] OS and RFS were evaluated separately for low muscle mass and low muscle density. The Chi^2-test and Higgins I^2-test were used to asses study heterogeneity. Heterogeneity was considered low when I^2 = 0-40%; moderate when I^2 = 30-60% and substantial when I^2 > 50% with a p-value < 0.10. In the absence of a universal assessment method and definition of sarcopenia, it was expected that the heterogeneity between the studies was at least moderate. Therefore, a random effects model was applied to pool OS and RFS estimates.[13] Publication bias was evaluated through funnel plots. A two-tailed p-value below 0.05 was considered statistically significant. Statistical analyses were performed using Review Manager (version 5.4.1).[14]

Results

Study selection

Fig. 1 displays the screening process of the study. After removal of duplicates, 416 articles were evaluated on title and abstract. Ultimately, 63 studies were reviewed full-text, of which eleven were deemed eligible for inclusion.

Study characteristics and quality assessment

The study characteristics are presented in Table 1. In total, the studies reported on 2124 patients with CRLM. The sample size of the included studies ranged from 47 to 539 patients.[15–25] Median follow-up ranged between 21 and 74 months. Four studies did not report on follow-up duration.[16,17,22,23] Median or mean follow-up did not exceed 36 months in five studies.[15,18–20,25] None of the studies reported significant differences in tumour characteristics between the sarcopenic and non-sarcopenic patients. The baseline characteristics of the sarcopenic and non-sarcopenic groups in the various studies are displayed in the supplementary materials, table 4.

To measure skeletal muscle mass, eight studies used the skeletal muscle index (SMI)[15,17,19–21,23–25] and two studies used the psoas muscle index (PMI).[16,22] The level of measurement was at the height of the third lumbar vertebra (L3) for all studies. To measure skeletal muscle density, three studies used the intra-muscular adipose tissue content (IMAC), measured at the level of the umbilicus[16,17,23] and one study used the Hounsfield unit average calculation (HUAC) measured at the height of the fourth lumbar vertebra (L4) endplate.[18] Six studies used pre-defined cut-off levels based on previous literature,[15,17,19–21,24] while in five studies receiver operating curves, optimal stratification or sensitivity analysis were used to define the optimal cut-off.[16,18,22,23,25] The references used for the cutoff values are Prado et al. (2008),[26] Nishikawa et al. (2016)[27] and Martin et al. (2013).[28] The prevalence of sarcopenia ranged from 16% to 65% per study. Overall, 897 (42%) patients were considered to be sarcopenic.

Quality assessment of the studies is displayed in the supplementary materials. Four studies (36%) were considered to

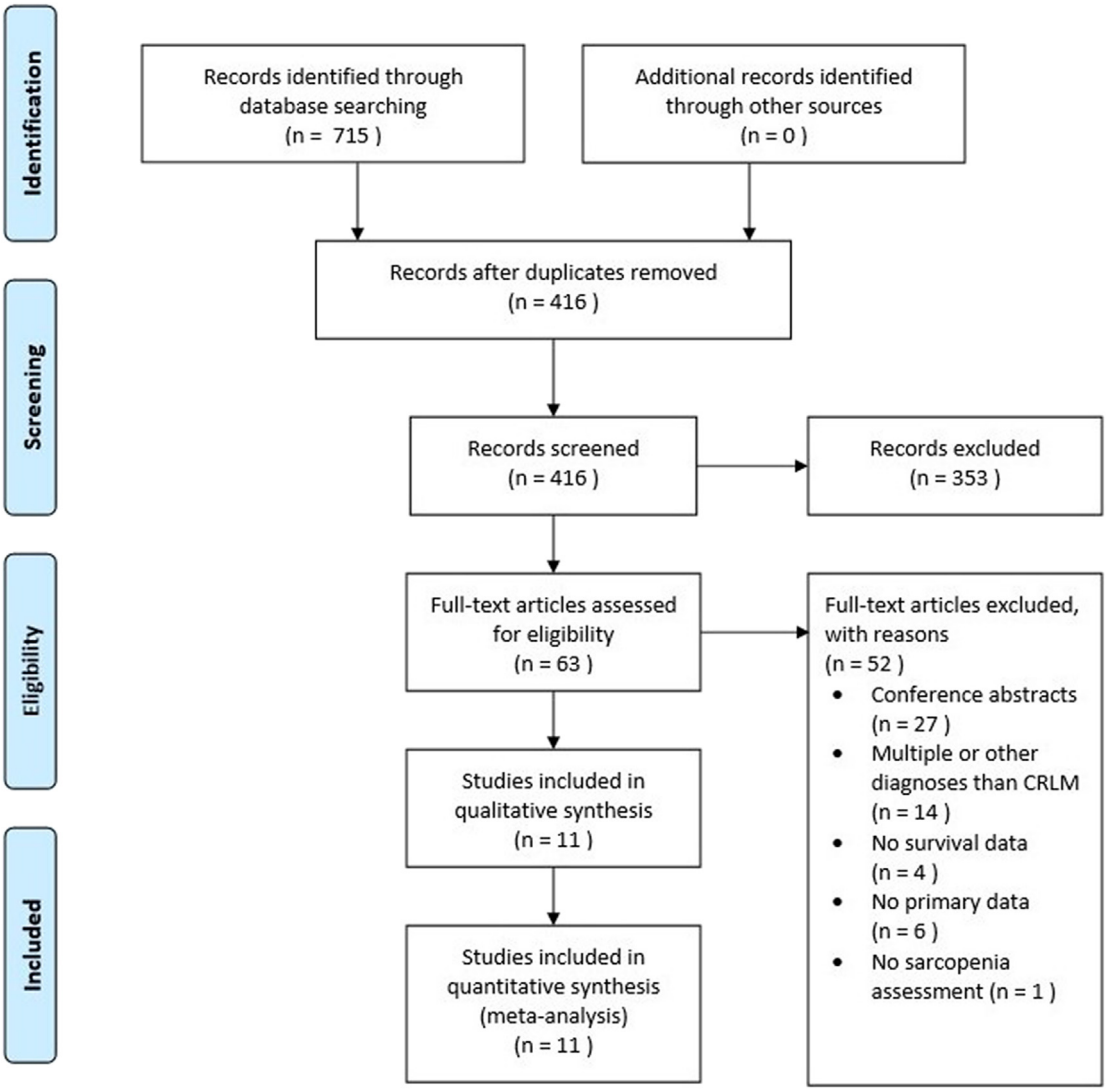

Figure 1 PRISMA flowchart of selection and screening procedures

be of moderate to good quality, these all evaluated muscle mass but not muscle density.[15,21,24,25] Multivariable analysis of the effect of sarcopenia was not performed in seven studies.[16–19,21–23] The remaining studies included a multivariable analysis, but did not correct for all appropriate confounders.[15,20,24,25] The majority of studies scored poorly on the outcome indicator of the NOS. Most studies had a follow-up period of less than 36 months or did not describe median follow-up (N = 9)[15–20,22,23,25]. Of the four studies scoring moderate to good quality three had inappropriate correction in their multivariate model[15,24,25] and one had no multivariate analysis at all.[21] Among these four studies median follow-up did not exceed 36 months in two of the studies.[15,25] Funnel plots did not indicate the presence of publication bias in any of the analyses (Supplementary, Figs. 1).

The impact of low muscle mass on survival outcomes

The outcomes for the ten studies (N = 1942) evaluating the association of muscle mass with OS are displayed in Fig. 2a[15–17,19–25] Three studies found a lower OS in sarcopenic patients.[15,20,25] Overall, low muscle mass was associated with poorer OS (pooled HR 1.35, 95%CI 1.08–1.68, p 0.007). There was substantial heterogeneity between studies, with an I^2 of 52% (p 0.03). When pooling results from the two studies that excluded patients who died within 90 days after surgery, pooled HR for OS remained similar (1.48, 95%CI 0.98–2.23, p 0.06) (Supplementary, Figs. 2).

Fig. 2b displays the outcomes of the seven studies (N = 1505) evaluating RFS and muscle mass.[17,19,20,23,25] One study found worse RFS in sarcopenic patients.[25] After pooling the studies, low muscle mass did not result in impaired RFS (pooled HR 1.17,

Table 1 Study characteristics

Author	Year	Country	Test	cutoff level men (cm^2/m^2)	cutoff level women (cm^2/m^2)	Basis cutoff	N	Sarcopenic
Eriksson	2017	SE	L3 SMI	52.4	38.5	Prado et al., 2008	225	147 (65%)
Horii	2020	JPN	L3 PMI + IMAC	6.0	4.0	ROC	115	64 (56%)
Kobayashi	2018	JPN	L3 SMI + IMAC	40.31	30.88	Nishikawa et al., 2016	124	24 (19%)
Liu	2020	CN	L4 HUAC	22[a]	22[a]	ROC	182	48 (26%)
Lodewick	2015	NL	L3 SMI	43 & 53[b]	41	Martin et al., 2013	171	80 (47%)
Lv	2019	CN	L3 SMI	43	41	Martin et al., 2013	539	309 (57%)
Okuno	2019	USA	L3 SMI	43 & 53[b]	41	Martin et al., 2013	169	61 (36%)
Peng	2011	USA	L3 PMI	5.0	5.0	sensitivity analysis	259	41 (17%)
Shiozawa	2020	JPN	L3 SMI + IMAC	39.4	41.5	ROC	47	25 (53%)
Van Dijk	2019	CA	L3 SMI VAT	z-scores	z-scores	Martin et al., 2013	97	60 (56%)
Van Vledder	2012	NL	L3 SMI	43.75	41.10	optimal stratification	196	38 (19%)

SMI = skeletal muscle index, PMI = psoas muscle index, IMAC = intramuscular adipose tissue content, HUAC = Hounsfield unit average calculation.
[a] Hounsfield units.
[b] Cutoff levels were split for men with BMI<25 and BMI≥25.

95%CI 0.94–1.46, p 0.15). Moderate heterogeneity was present between studies (I^2 = 44%, p 0.10).

The impact of low muscle density on survival outcomes

Overall survival data was available in four studies (N = 464) evaluating muscle density (Fig. 3a).[16–18,23] Two studies showed worse OS in sarcopenic patients.[16,17] After pooling the data, low muscle density was associated with poorer OS (pooled HR 1.97, 95%CI 1.07–3.62, p = 0.03). Moderate heterogeneity existed with an I^2 of 47% (p = 0.13). RFS data was available in three studies including a total of 169 patients.[17,18,23] Low muscle density did not result in impaired RFS (pooled HR 1.13, 95%CI 0.85–1.50, p 0.41) (Fig. 3b). There was low heterogeneity between the studies, with an I^2 of 0% (p = 0.74).

Discussion

This meta-analysis shows that both low muscle mass and low muscle density are associated with poorer OS (pooled HR 1.35 (p = 0.007) and 1.97 (p = 0.03), respectively) in patients who underwent local therapy with curative intent for CRLM. No impact of muscle mass and density on RFS was observed (pooled HR 1.17 (p = 0.15) and 1.13 (p = 0.41), respectively).

To our best knowledge, this is the first meta-analysis to evaluate the prognostic impact of sarcopenia on long-term survival outcomes in patients with CRLM. Previous meta-analyses for several other primary malignancies, including hepatocellular carcinoma and colorectal cancer, have found a decreased OS and RFS in sarcopenic patients.[9,29–31] The effect size found in these cancers was somewhat higher (OS 1.57–1.83; RFS 1.54–1.55).[29,31] Similar to the results of this meta-analysis, reported HRs for OS were generally higher than for DFS/RFS. This suggests that sarcopenia mostly reflects an impaired performance status rather than unfavorable tumour biology. Multiple findings from previous studies lend support to this hypothesis. First, sarcopenia has been associated with cardiac disease, pulmonary disease and cognitive impairment, all potentially contributing to worse prognosis.[7] Second, sarcopenia on itself is associated with increased long-term mortality, in the absence of a malignancy.[32] Third, the presence of sarcopenia resulted in a 1.5-fold increase in the risk of major complications following hepatopancreatobiliary surgery.[33] The increased risk of complications in sarcopenic patients is not limited to oncological surgery, but also present in a variety of major non-oncological surgeries.[34–36] This is further supported by the fact that none of the studies in this meta-analysis described impactful differences in tumour characteristics between sarcopenic and non-sarcopenic patients. A possible mechanism through which sarcopenia may influence long term OS is early operative mortality, However, pooling of the two studies that excluded patients who died within 90 days after surgery,[15,21] still resulted in a comparable HR to the main OS analysis (pooled HR of 1.48, 95%CI 0.98–2.23, Supplementary Fig. 5). This result was not statistically significant (p 0.06), likely due to the small number of patients in the analysis. This suggests that sarcopenia may affect long term OS in these patients through other mechanisms than early postoperative mortality alone. However, given the small sample size in this comparison, this result should be interpreted with caution. One of these mechanisms may be reduced chemotherapy tolerance in sarcopenic patients.[37–39] This may lead to worse survival outcomes as they are more likely to receive reduced doses and fewer cycles of chemotherapy compared to non-sarcopenic patients. The included studies in this meta-analysis did not report enough information on the chemotherapy regimens. No conclusions can be drawn on chemotherapy tolerance of sarcopenic patients in the current study population.

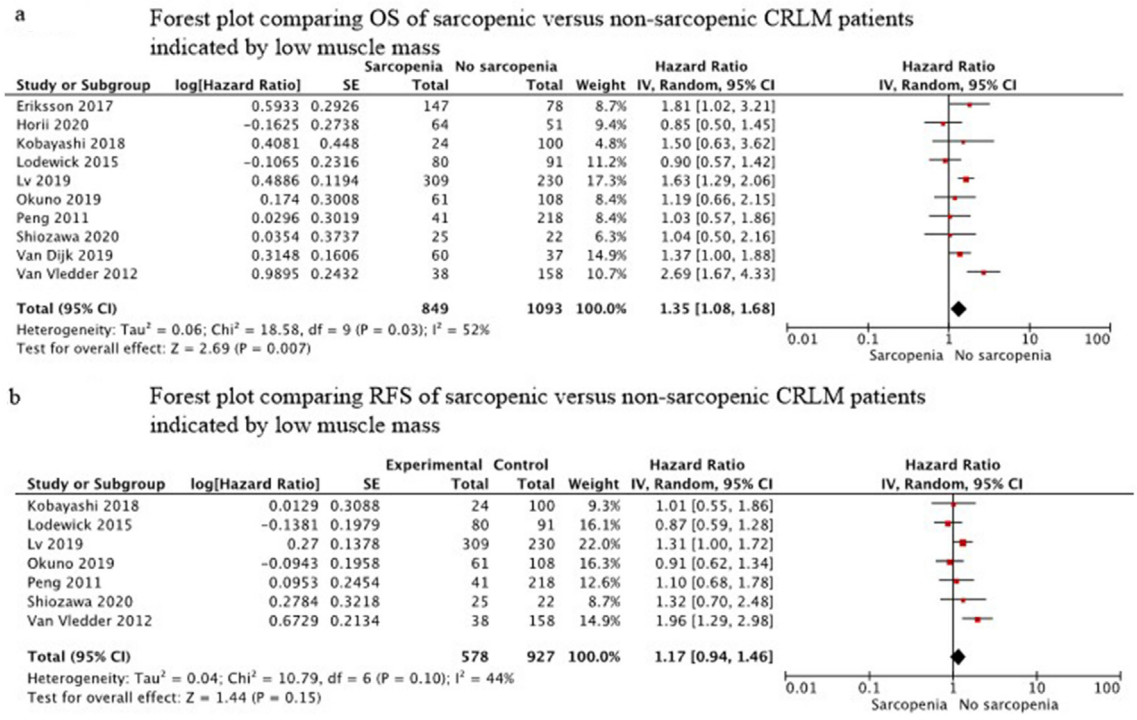

Figure 2 Forest plot comparing OS(a) and RFS(b) of sarcopenic versus non-sarcopenic CRLM patients indicated by low muscle mass

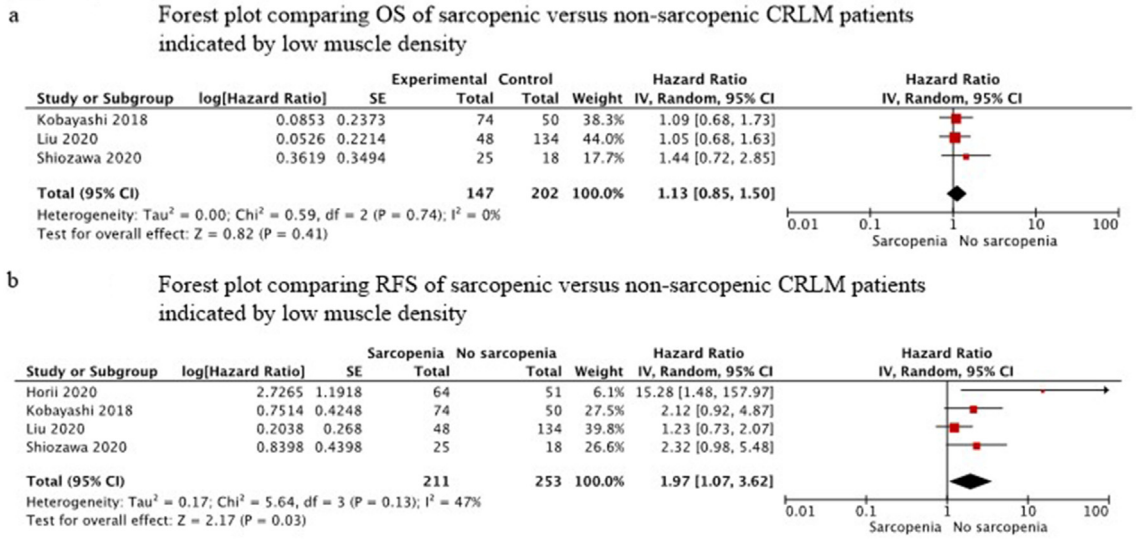

Figure 3 Forest plot comparing OS(a) and RFS (b) of sarcopenic versus non-sarcopenic CRLM patients indicated by low muscle density

Patients with CRLM make up a relatively unique population of patients with metastatic disease. They frequently undergo resection with curative intent compared to patients with metastases from other gastrointestinal malignancies.[40] There are multiple reviews discussing the role of sarcopenia in patients undergoing resection of the primary tumor in non-metastatic gastrointestinal malignancies. However, it is not clear whether these results are applicable to patients with CRLM. There are indications that the presence of metastatic disease may promote sarcopenia.[41] Thus, sarcopenia may play a larger role in the prognosis of patients who undergo resection for metastatic colorectal cancer compared to those with non-metastatic disease.[42]

Although sarcopenia has been investigated for several years, universal consensus on the definition and cutoff levels was lacking. Recently, the European Working Group on Sarcopenia in

Older People (EWGSOP) has revised its definition of sarcopenia and replaced their focus from muscle mass to muscle strength.[7] In order to diagnose sarcopenia, low muscle strength must be determined, whereas low muscle quality or quantity should be used to then confirm the presence of sarcopenia. Using this revised definition, Berardi et al. recently found an almost four-fold increased odds of 90-day post-operative morbidity for sarcopenic patients undergoing hepatectomy for various malignant tumours, including CRLM (OR = 3.70). The increased odds of major complications for sarcopenic patients was even higher (OR = 5.93).[43] None of the studies included in this meta-analysis evaluated muscle strength. Using an universal definition of sarcopenia with universal cutoff levels would increase the comparability between studies and would increase the generalizability of the results. The most commonly used measurement in this meta-analysis was SMI, but then, the cutoff levels used for SMI also varied considerably. In women the cutoff level ranged from 30.9 cm^2/m^2 to 41.0 cm^2/m^2 and in men from 39.4 cm^2/m^2 to 53.0 cm^2/m^2[15,17,19–21,23–25]. Altogether, large studies should be initiated to evaluate the EWGSOP guidelines for sarcopenia in light of long-term survival outcomes.

Sarcopenia assessment is currently not part of the standard preoperative workup in patients with CRLM. Given the limited effect size and quality of evidence presented here the addition of sarcopenia as measured on CT-scans alone, without standardized cutoff values does not show potential to improve prognostication for patients undergoing local treatment of CRLM. However, currently available prediction models for CRLM only predict outcomes with moderate accuracy,[6] thus there is a need to identify new variables. Sarcopenia may be such a variable, on the condition that it is assessed using standardized, validated measurements and standard cutoff values. Importantly, preoperative sarcopenia measurements are easily assessed, since most patients with CRLM already receive routine abdominal CT examinations and the measurement of sarcopenia is relatively fast and straightforward. Adding the hand-grip-test to diagnose sarcopenia according to the revised EWSGOP guidelines is inexpensive, easily done and widely available.[7,43] In the light of the severely increased perioperative risk of sarcopenic patients determined by muscle mass and strength and the applicability of these measurements, both should preoperatively be obtained to better identify patients at high risk for adverse outcomes.[43,44]

Furthermore, sarcopenia could also be a valuable target for preoperative interventions, although it remains to be determined whether sarcopenia is modifiable. Recently, studies have shown promising results of preoperative prehabilitation programs with regards to short-term postoperative outcomes.[45,46] These studies did not measure sarcopenia, thus it is not clear whether prehabilitation could modify sarcopenia.

There are several limitations regarding the evidence presented here, mostly related to the quality of the studies used for meta-analysis. Most of the studies were limited due to short follow-up duration and small sample sizes. Additionally, no multivariable analysis was performed in the majority of studies. Although no apparent baseline differences between sarcopenic and non-sarcopenic patients were observed, confounding may have biased the main outcomes of this study. All of the limitations mentioned above are even more apparent in the studies investigating muscle density in this meta-analysis, which is why no firm conclusions can be drawn on the relationship between muscle density and the impact on long-term survival outcomes in patients with locally treated CRLM.

In summary, sarcopenia is associated with poorer long-term overall survival in patients with CRLM who underwent local therapy. This was observed for both low muscle mass (PMI or SMI) and low muscle density (IMAC or HUAC). No impaired RFS was observed, suggesting that sarcopenia mainly reflects an impaired general health status. Quality of the studies was mainly poor and definitions for sarcopenia varied considerably. Larger studies, applying the most recent EWGSOP guidelines for sarcopenia, are needed to determine whether this factor could contribute to the prognostication in patients with CRLM.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.08.947.