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The impact of myosteatosis on outcomes following surgery for gastrointestinal malignancy: a meta-analysis

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ABSTRACT

Introduction The aim of this review was to evaluate the impact of preoperative myosteatosis on long-term outcomes following surgery for gastrointestinal malignancy.

Methods We conducted a systematic search of the electronic information sources, including PubMed MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and AMED. Studies were included if they reported the impact of preoperatively defined myosteatosis, or a similar term, on long-term survival outcomes following surgery for gastrointestinal malignancy. A subgroup analysis was performed for those studies reporting outcomes for colorectal cancer patients only.

Findings Thirty-nine full-text articles were reviewed for inclusion, with 19 being retained after the inclusion criteria were applied. The total number of included patients across all studies was 14,481. Patients with myosteatosis had significantly poorer overall survival, according to univariate (hazard ratio (HR) 1.82, 95% confidence interval (CI) 1.67–1.99) and multivariable (HR 1.66, 95% CI 1.49–1.86) analysis. This was also demonstrated for cancer-specific survival (univariate HR 1.62, 95% CI 1.18–2.22; multivariable HR 1.73, 95% CI 1.48–2.03) and recurrence-free survival (univariate HR 1.28, 95% CI 1.10–1.48; multivariable HR 1.38, 95% CI 1.07–1.77).

Conclusions This meta-analysis demonstrates that patients with preoperative myosteatosis have poorer long-term survival outcomes following surgery for gastrointestinal malignancy. Therefore, myosteatosis should be used for preoperative optimisation and as a prognostic tool before surgery. More standardised definitions of myosteatosis and further cohort studies of patients with non-colorectal malignancies are required.

KEYWORDS
Myosteatosis – Malignancy – Survival – Meta-analysis

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Introduction

In the age of personalised medicine, it remains essential that preoperative risk assessment is as detailed as possible.[1] A fundamental aspect of this is the assessment of nutritional status, which can be facilitated by body composition analysis.[2] Myosteatosis, the deposition of intramuscular fat, is an early change that occurs before the onset of functional decline and the development of metabolic alterations such as obesity and diabetes.[3] The muscle appears with a low radiation attenuation which reflects the deposition of fat within myocytes.[4] This has been shown to occur with or without excess extracellular deposition of adipocytes.[4] Thus, myosteatosis has subsequently been shown to decrease muscle quality and functional status significantly.[5]

Since the 1990s, enhanced recovery after surgery programmes have become an essential focus of perioperative management.[6] A key element of an enhanced recovery after surgery programme is a focus on the optimisation of preoperative nutrition; however, this has remained a challenge.[7] The ability to accurately and reliably identify patients with myosteatosis and other poor nutritional states, who would be defined as being of a less than adequate nutritional state, would allow for more accurate optimisation of preoperative and postoperative nutrition.[8]

Body composition parameters such as sarcopenia have been extensively demonstrated to significantly increase the risk of immediate postoperative complications and decrease overall survival (OS).[9–13] In recent literature, myosteatosis has been shown to result in lower long-term outcomes for all cancer patients[14] and specifically colorectal cancer patients,[15] regardless of management options or cancer stage. All patients now have cross-sectional imaging, usually in the form of a computed tomography (CT) scan, prior to any operative interventions for gastrointestinal malignancy for staging and planning purposes.[16] Therefore, myosteatosis may be assessed using these cross-sectional views and can then be analysed for an association with outcomes.

This review aims to assess the impact of myosteatosis on long-term outcomes for those patients undergoing surgery with curative intent for a gastrointestinal malignancy.

Methods

Literature search strategy

In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines, a systematic review of all published research on myosteatosis was performed. Using both Medical Subject Heading (MeSH) terms and free-text terms, the databases PubMed MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and AMED were searched for relevant articles on 17 June 2020. A review of the reference lists of all relevant studies lists was performed to identify any articles missed by the search terms. Our methodology respected the standards of PRISMA statement. The flow chart for the literature search process is shown in Figure 1.

Study selection

Three reviewers carefully assessed the title and abstract of articles found as a result of the literature search. Following initial screening, full-text articles were reviewed to confirm eligibility. Discrepancies in this process were resolved by discussion between the authors. Several inclusion criteria were used to assess eligibility. To be included, a study had to have analysed myosteatosis, or an equivalent term, using CT imaging and should have included patients with a malignancy of the gastrointestinal system, undergoing surgery with curative intent. Studies with any definition of myosteatosis were included because of the previous lack of a well-defined definition and variation based on populations.

Outcomes

We planned to evaluate the effect of myosteatosis on OS, cancer-specific survival (CSS) or recurrence-free survival (RFS). Studies only analysing the short-term outcomes after surgery were excluded.

Definition of myosteatosis

Definitions of myosteatosis used in the individual studies are given in Table 2. Many studies used the recently defined definition of <41 Hounsfield Units (HU) if body mass index (BMI) <25 and <33 HU if BMI >25. All the included studies assessed myosteatosis by measuring a single CT slice at the third lumbar vertebra (L3). Two of the included studies used intramuscular adipose tissue content, calculated using the same lumbar vertebra but comparing it with the mean HU values of subcutaneous fat. These intramuscular adipose tissue content values are then used to define myosteatosis by using sex-specific median cut-offs. Studies that did not precisely imply myosteatosis, but instead used 'low muscle density/attenuation' were also included.

Statistical analysis

Hazard ratios (HRs) from studies eligible for meta-analysis were pooled using the generic inverse variance method, applied separately to OS, CSS and progression-free survival. Heterogeneity between studies was estimated through the chi-square test of Cochrane's Q and the I^2 statistic interpretation. Both fixed and random-effects methods were used in the meta-analysis, with the between-study variance estimated using the Dersimonian and Laird method. Analysis was conducted using the *meta package's metagen function* in R (R Core Team, 2020).[17] Subgroup analysis was performed for those studies reporting outcomes for colorectal cancer patients only.

Assessment of risk of bias

The Newcastle–Ottawa scale was used to assess the quality of the included research studies. This method analyses the selection of patient methods, study group comparability and the outcome assessment. A flow chart sheet (Table 1) entitled 'Newcastle–Ottawa Quality Assessment Form for Cohort Studies' was followed, and the overall rating was assigned accordingly.

Findings

The full texts of 39 articles were reviewed, of which 19[18–36] were included in this meta-analysis (as shown in Figure 1). The characteristics of the included studies are given in Table 2. The total number of patients included in the analysis was 14,481 (colorectal cancer, 10,890; hepatocellular cancer, 1,863; gastric cancer, 973; cholangiocarcinoma, 459; periampullary cancer, 166; oesophageal cancer, 130).

Overall survival for all cancers

Both on univariate (HR 1.82, 95% CI 1.67–1.99; 14 studies) and multivariable (random-effects model: HR 1.66, 95% CI 1.49–1.86; 14 studies) analysis, patients classified as having myosteatosis had significantly worse OS than patients who did not have myosteatosis (Figure 2a).

Cancer-specific survival for all cancers

Fewer studies contributed CSS rates compared with OS rates. These were all from studies on colorectal cancer (although not all colorectal cancer studies presented CSS results). No significant heterogeneity was detected between the studies. Both on univariate (HR 1.62, 95% CI 1.18–2.22; four studies) and multivariable analysis (HR 1.73, 95% CI 1.48–2.03; six studies), patients with myosteatosis had worse CSS compared with patients that did not have myosteatosis (Figure 2b).

Recurrence-free survival for all cancers

Patients classified as having myosteatosis had a significantly worse RFS compared with patients who did not have myosteatosis (HR 1.28, 95% CI 1.10–1.48; seven studies). Four studies contributed to the multivariable analysis of RFS. The I^2 statistic indicated moderate heterogeneity, although this was not statistically

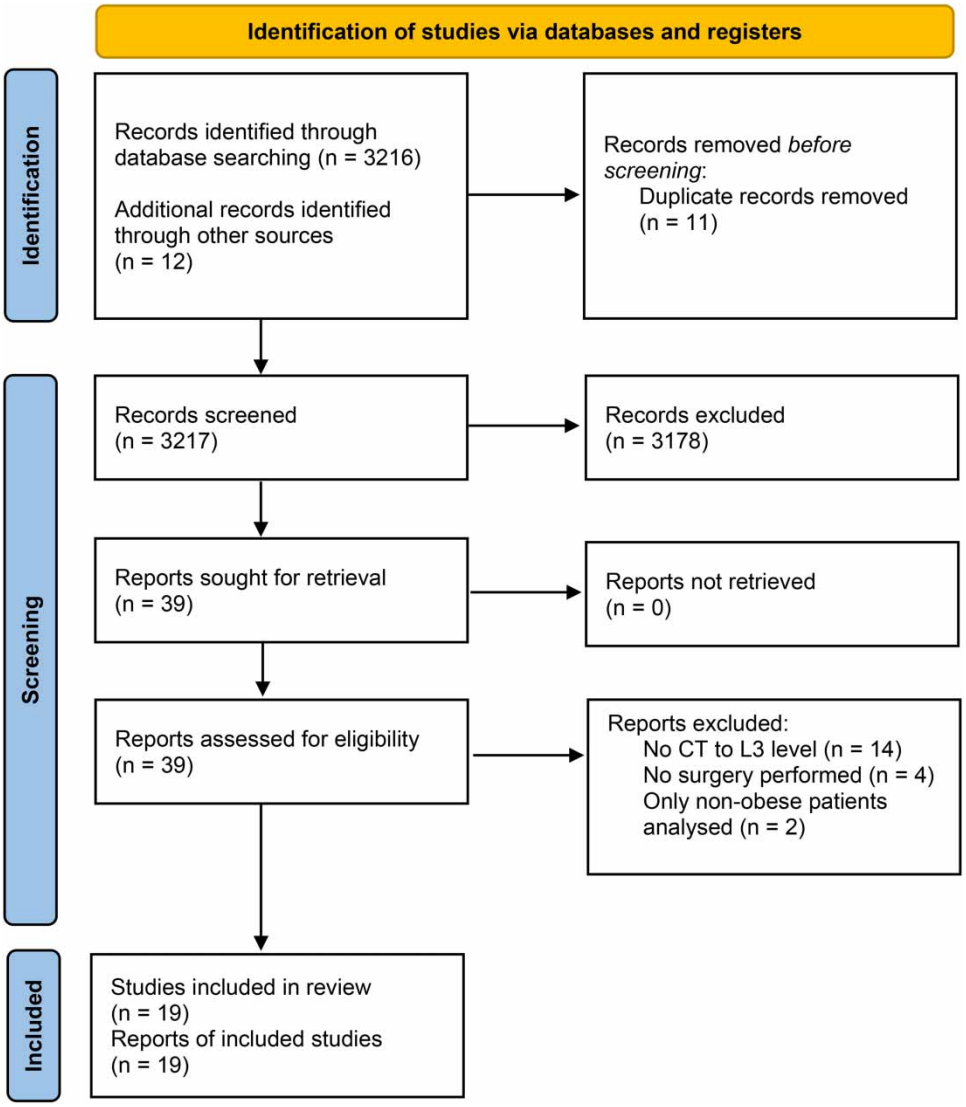

Figure 1 Study flow diagram

significant in the chi-square test of Cochrane's Q statistic. Although the confidence intervals for the fixed and random-effects estimates overlapped, taking account of heterogeneity, the random-effects estimate indicated that patients with myosteatosis had a significantly worse RFS compared with those without (HR 1.43, 95% CI 1.15–177; four studies) (Figure 2c).

Subgroup meta-analysis of studies reporting results for colorectal cancer patients

Among the subset of studies reporting results for colorectal cancer patients, heterogeneity was low according to the I^2 statistics, with little change in the estimated HRs for the meta-analysis of both univariate and multivariable-adjusted (Figure 3a) results. Because cancer-specific outcomes were reported by only a subset of studies of colorectal cancer, the meta-analysis of cancer-specific outcomes was applicable only to this group of patients (Figure 3b), and so there was no change in heterogeneity or the estimates. As measured by I^2, heterogeneity among the univariate estimates for RFS (Figure 3c) decreased slightly from 32% for all cancer types to 26% for just colorectal cancers. The point estimate for overall effect of myosteatosis was now lower, with a HR of 1.17 (95% CI 0.91–1.51) and non-significant at the 5% level, compared with all cancers. By restricting the meta-analysis to colorectal cancers, one study was lost from the meta-analysis of multivariable analyses of

Table 1 Newcastle–Ottawa scale or the assessment of cohort studies

	Selection bias assessment				Comparability	Outcome			
Author	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of study**	**Comparability of cohorts based on design or analysis**	**Assessment of the outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Result**
Hopkins *et al*, 2019[18]	•	•	•		•	•	•	•	Good
Malietzis *et al*, 2015[19]	•	•	•		•	•		•	Good
Martin *et al*, 2018[20]	•	•	•		•	•	•	•	Good
Zhuang *et al*, 2019[21]	•	•	•		•	•		•	Good
Dolan *et al*, 2018[22]	•	•	•			•	•	•	Fair
Van Vugt *et al*, 2019[23]	•	•	•		•	•	•	•	Good
Sueda *et al*, 2018[24]	•	•	•		•	•	•	•	Good
McSorley *et al*, 2018[25]	•	•	•		•	•	•	•	Good
Van Vugt *et al*, 2018[26]	•	•	•		•	•		•	Good
Van Baar *et al*, 2018[27]	•	•	•		•	•	•	•	Good
Tamandl *et al*, 2016[28]	•	•	•			•	•	•	Fair
Chakedis *et al*, 2018[29]	•	•	•		•	•		•	Good
Van Rijssen *et al*, 2017[30]	•	•	•		•	•	•	•	Good
Okumura *et al*, 2017[31]	•	•	•		•	•	•	•	Good
Shirdel *et al*, 2020[32]	•	•	•		•	•	•	•	Good
Okugawa *et al*, 2018[33]	•	•	•		•	•		•	Good
Kroenke *et al*, 2018[34]	•	•	•		•	•	•	•	Good
Fujiwara *et al*, 2015[35]	•	•	•		•	•	•	•	Good
Hamaguchi *et al*, 2019[36]	•	•	•		•	•	•	•	Good

Table 2 Characteristics of included studies

Author	Year	*n*	Type of cancer	Myosteatosis definition	Software used
Hopkins *et al*[18]	2019	968	Colorectal	<41 HU if BMI <25, <33 if BMI >25	MATLAB
Malietzis *et al*[19]	2015	805	Colorectal	<41 HU if BMI <25, <33 if BMI >25	sliceOmatic v.4.3
Martin *et al*[20]	2018	1,139	Colorectal	Age and gender dependent *z* scores (see paper)	sliceOmatic
Zhuang *et al*[21]	2019	973	Gastric	<38.5 HU in men, <28.6 HU in women	GE ADW v.4.5
Dolan *et al*[22]	2018	650	Colorectal	<35.5 HU in women, <32.5 HU in men	NIH ImageJ v.1.47
Van Vugt *et al*[23]	2019	233	Cholangiocarcinoma	<38 HU in men, <36 in women	FatSeg (in-house)
Sueda *et al*[24]	2018	211	Colorectal	<41 HU if BMI <25, <33 if BMI >25	SYNAPSE VINCENT
McSorley *et al*[25]	2018	322	Colorectal	<41 HU if BMI <25, <33 if BMI >25	NIH ImageJ v.1.47
Van Vugt *et al*[26]	2018	816	Colorectal	<41 HU if BMI <25, <33 if BMI >25	FatSeg (in-house)
Van Baar *et al*[27]	2018	1,681	Colorectal	<36.4 HU (men) and <31.1 HU (women) for BMI <25 <31.6 HU (men) and <29.3 HU (women) for BMI >25	sliceOmatic v.5.0
Tamandl *et al*[28]	2016	130	Oesophageal	<40 HU	OSIRIX v.5.0
Chakedis *et al*[29]	2018	117	Biliary	<38 HU	Aquarius iNtuition
Van Rijssen *et al*[30]	2017	166	Periampullary	<36.3 HU for males, <36.0 HU for females	sliceOmatic v.5.0
Okumura *et al*[31]	2017	109	Cholangiocarcinoma	<38.3 HU for males, <31.0 HU for females	Aquarius iNtuition
Shirdel *et al*[32]	2020	728	Colorectal	<38.5 HU for males, <36.1 HU for females	imlook4d software
Okugawa *et al*[33]	2018	308	Colorectal	IMAC: 0.36 for males, 0.24 for females	Aquarius iNtuition
Kroenke *et al*[34]	2018	3,262	Colorectal	<35.5 HU	sliceOmatic v.5.0
Fujiwara *et al*[35]	2015	1,257	Hepatocellular	<44.4 HU for males, <39.3 HU for females	sliceOmatic v.5.0
Hamaguchi *et al*[36]	2019	606	Hepatocellular	IMAC: 0.358 for males, 0.229 for females	Aquarius iNtuition

BMI = body mass index; HU = Hounsfield units; IMAC = intramuscular adipose tissue content

RFS for all cancer types and the heterogeneity decreased from 58% to 32%. Based upon just two studies of colorectal cancer, the overall HR of regression associated with myosteatosis increased from a random-effects estimate of 1.38 (95% CI 1.07–1.77) to 1.97 (95% CI 1.26–3.07), noting the wide confidence intervals of the latter and the considerable overlap with the former.

Discussion

The results from this meta-analysis indicate that myosteatosis could be an independent predictor of worse long-term outcomes in those patients undergoing surgery for malignancies of the gastrointestinal tract. This was in terms of both OS and RFS in all cancers, and CSS in colorectal cancer.

Recent research has identified that body composition parameters have a significant impact on outcomes following cancer surgery.[37] Sarcopenia, the generalised loss of skeletal muscle mass and function,[38] has been shown to impact outcomes significantly and has been highlighted in numerous studies.[39–41] This has led to more extensive research into other body composition parameters. Myosteatosis, the process of fat deposition within the intra- and intermuscular compartments,[42] has been associated with poorer outcomes following surgery in oncological and non-oncological patients.[43] This increased deposition of adipose tissue is thought to lead to a range of physical and physiological abnormalities such as reduced muscle power and an increased incidence of type 2 diabetes.[44] The exact pathophysiology surrounding myosteatosis remains uncertain. However, it has been hypothesised that intermuscular fat may alter muscle metabolism and insulin sensitivity by the local secretion of inflammatory adipokines from adipocytes surrounding muscle fibres.[45] This has been shown to directly impact skeletal myocyte metabolism, which may drive myotubes into lipid oxidation and affect skeletal muscle metabolism.[46] This impact is particularly heightened when the body is in a highly catabolic state, such as during cancer or chemotherapy. When considering intramuscular fat, the exact pathophysiology remains unclear. Recent literature has shown a demonstrable difference in the level of abdominal myosteatosis when comparing patients with type 2 diabetes, prediabetes and healthy volunteers.[47]

The results of this review appear consistent across each type of gastrointestinal malignancy analysed. Most of the studies included were analysing patients undergoing

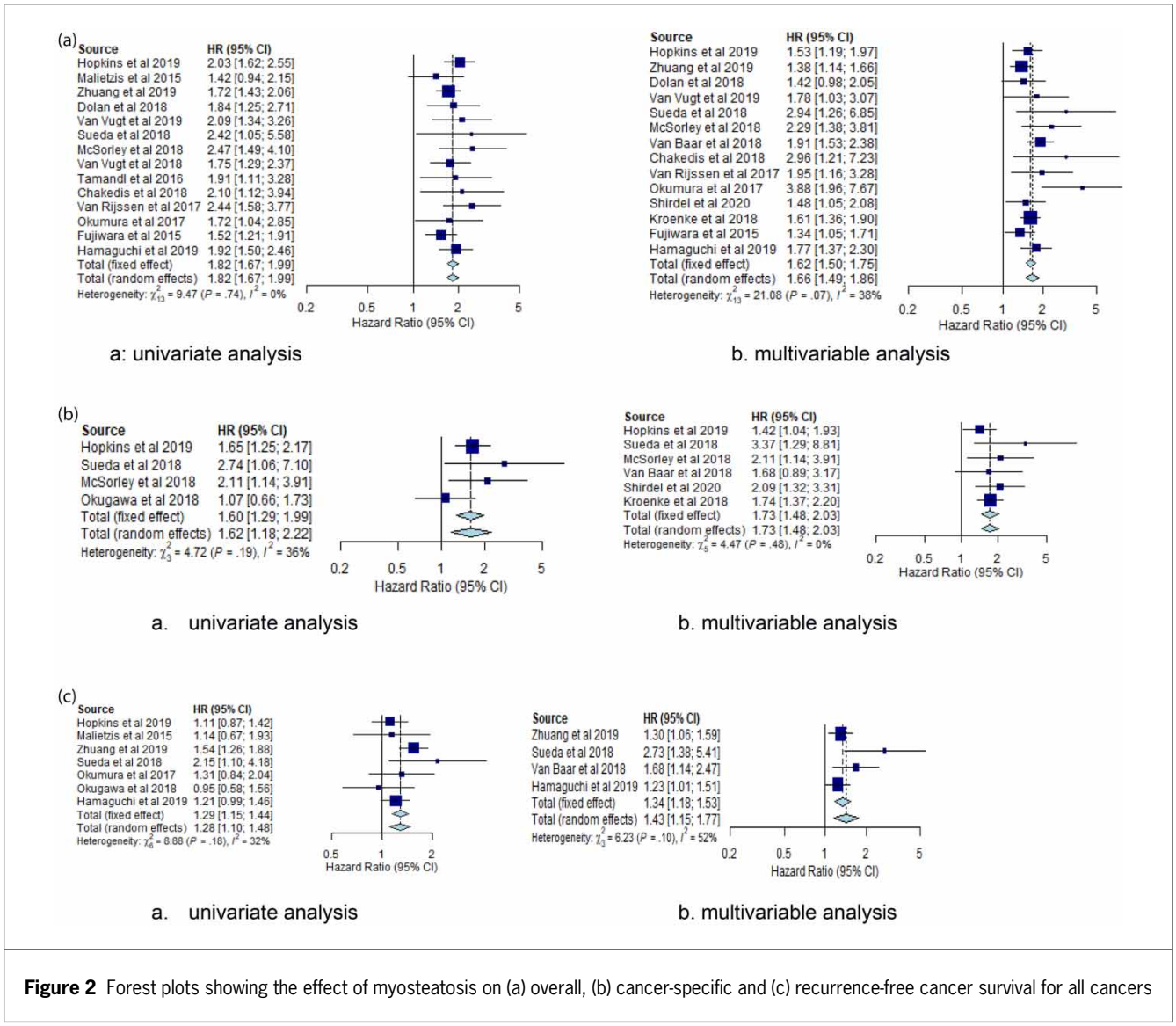

Figure 2 Forest plots showing the effect of myosteatosis on (a) overall, (b) cancer-specific and (c) recurrence-free cancer survival for all cancers

surgery for colorectal cancer, with a paucity of published research analysing the impact in pancreatic and oesophageal cancer patients. Patients with oesophageal and pancreatic malignancies have a high likelihood of being in a poor nutritional state before surgery, so further research is needed to assess the impact of body composition abnormalities on outcomes following oesophagectomy or pancreatectomy.

A potential limitation of this review is the varying cut-off points within the sampled studies. Although recent studies have adopted a more consistent definition of myosteatosis of <41 HU if BMI <25 and <33 if BMI >25, many studies used population defined cut-offs. Notwithstanding variation in definitions, little or no heterogeneity was detected between studies in our meta-analysis. There remains a lack of defined cut-off points within body composition research due to a range of different factors, including population differences.[5] Future research would be enhanced by the development of clearly defined parameters, which would allow for a more consistent field of statistics.

Further to this, assessing intermuscular adipose tissue is tricky when a single slice at the third lumbar vertebra is applied with conventional CT analysis. Adipose tissue may be distributed unevenly within a muscle, and an observer would have to evaluate the entire muscle to quantify the amount of intermuscular adipose tissue. It is also possible that patients with cancer may have low radiodensity with or without adipose tissue deposition and the alternative, a high amount of intermuscular fat without low muscle radiodensity.[48] Therefore, the definition of myosteatosis that prevails in the literature remains complex and

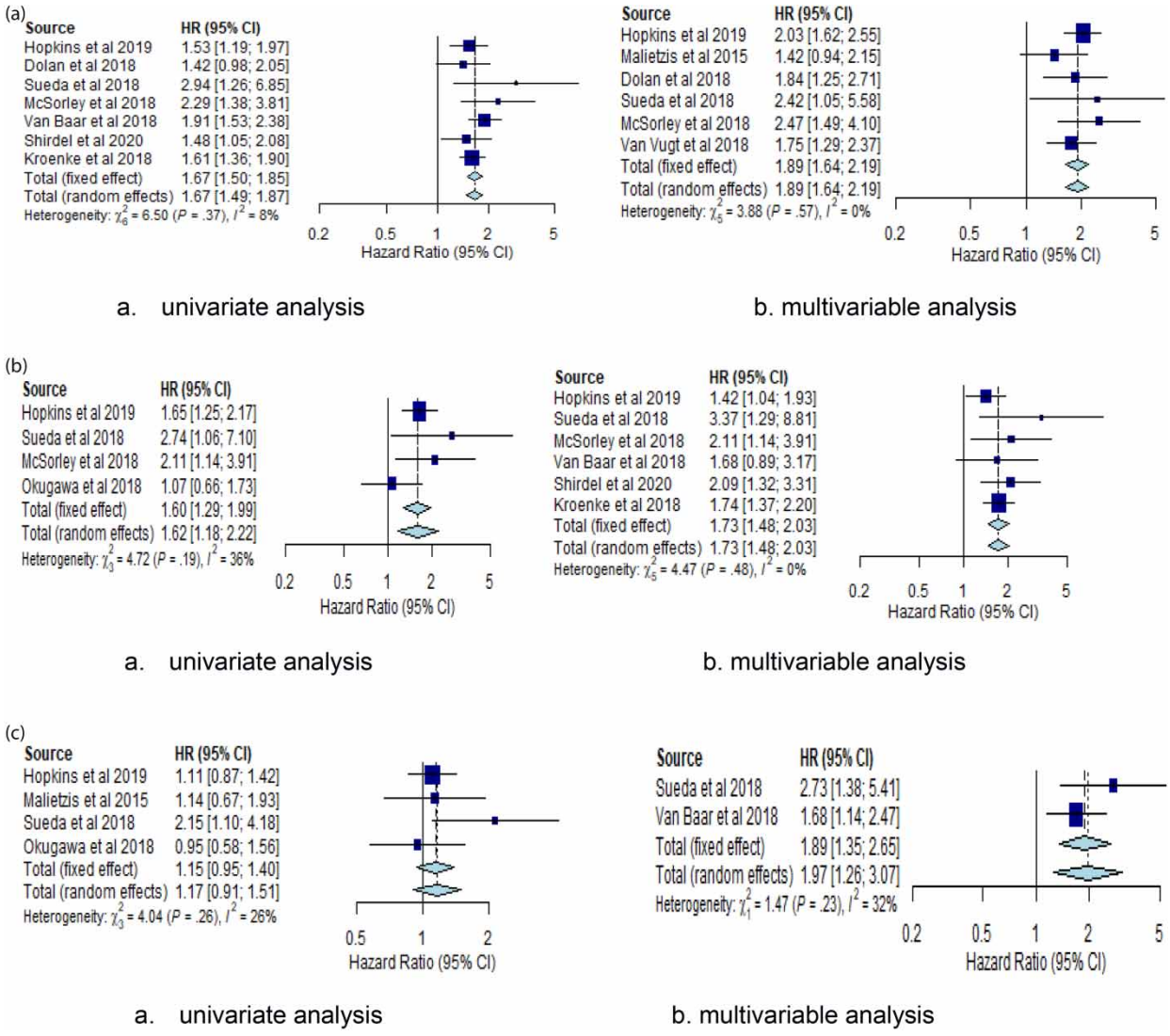

Figure 3 Forest plots showing the effect of myosteatosis on (a) overall, (b) cancer-specific and (c) recurrence-free cancer survival in colorectal cancer

assumes a homogeneous distribution of fatty deposition within the muscle, whereas adipose tissue may be distributed unevenly within a muscle.

Another limitation inherent in analysing observational data is potential confounding bias and the correlation between the exposure of interest (here, myosteatosis) and other adjusted prognostic factors in the eligible studies. Therefore, the final estimates should be interpreted with caution. However, the results consistently indicate myosteatosis as a strong predictor of poor prognosis.

To our knowledge, this is the first meta-analysis to analyse the impact of myosteatosis on the long-term outcomes of patients undergoing resectional surgery for gastrointestinal malignancy with curative intent. Recent reviews have identified that myosteatosis is associated with significantly poorer outcomes following cancer treatment[14] and in the treatment of colorectal cancer alone,[15] including those who did not have surgery and those who were treated with the best supportive care. Gastrointestinal malignancy is well known to be particularly associated with weight loss and a poor nutritional state, so the results of this review add to a growing body of evidence that myosteatosis identification can be used for both prognostication and preoperative optimisation.

Conclusions

This review demonstrates that myosteatosis is an independent predictor of worse long-term outcomes following surgery for gastrointestinal malignancy. Because all patients have preoperative CT scans before surgery, myosteatosis should be utilised in prognostic tools when assessing a patient's suitability for major surgery. This study also highlights the paucity of research analysing the impact of myosteatosis on outcomes following surgery for non-colorectal tumours. Further research should focus on understanding the impact that this may have on those cancers which were under-represented within this review.

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