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Low Muscle Mass and Treatment Tolerance in Patients With Upper Gastrointestinal Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Upper gastrointestinal (GI) cancers carry notable mortality risks. While systemic therapies are vital for their management, they are often hindered by adverse events (AE), which can compromise their effectiveness. The presence of low skeletal muscle mass (LSMM) may be linked with the prevalence of AE and could potentially undermine treatment tolerance by impacting drug metabolism. The primary objective of this systematic review and meta-analysis was to evaluate the association between LSMM and the risk of grades 3 and 4 AE and treatment discontinuation.

Methods: Studies investigating the association between skeletal muscle mass and AE or treatment tolerability in adult patients diagnosed with upper GI cancer scheduled to undergo systemic treatment were eligible. The primary outcomes were grades 3 and 4 AE and treatment discontinuations. Four electronic databases were systematically searched with no date restrictions on 10 October 2022. Data were analysed via random-effects meta-analyses, and the risk of bias was assessed using the risk of bias in non-randomised studies—of exposure (ROBINS-E) appraisal tool.

Results: We identified 50 eligible publications from 49 studies. Our meta-analyses revealed evidence of a higher risk of grades 3 and 4 AE (RR 1.44, 95% CI 1.23–1.68, $N = 13$) and treatment discontinuation (RR 2.39, 95% CI 1.87–3.07, $N = 11$) in LSMM versus non-LSMM. Secondary analyses revealed an increased risk of fatigue, febrile neutropenia, intestinal pneumonia, stomatitis and thrombocytopenia in LSMM. However, 92% of studies assessing grades 3 and 4 AE and 73% of studies examining treatment discontinuation had a very high risk of bias.

Conclusions: LSMM in patients with upper GI cancer is associated with a higher risk of grades 3 and 4 AE and the discontinuation of systemic cancer treatment. The high risk of bias should be considered in the interpretation of these findings. Further evaluation of the association between LSMM and treatment tolerability in confirmatory, prospective studies is needed.

E. N. Stanhope and Thomsen S. N. are joint lead authors.

1 | Introduction

Upper gastrointestinal (GI) cancers, including cancers of the oesophagus, stomach, liver, gallbladder and pancreas, are among the most fatal malignancies, with 5-year survival rates ranging 3%–20% for all stages. Systemic therapies (i.e., chemotherapies, immunotherapies, targeted therapies and chemoradiotherapies) are key treatments in the management of upper GI cancers and improve survival in both resectable [1–3] and unresectable [4–6] disease. The administration of systemic therapies, however, is often compromised by the occurrence of adverse events, which not only can lead to short- and long-term morbidity but also treatment modifications, including dose reductions, delays or discontinuation with potential negative implications for treatment efficacy and disease survival [7, 8]. Thus, the identification of modifiable risk factors of treatment tolerability is important to improve individualised dosing of systemic therapies and inform the development of targeted adjunct treatments and interventions.

Low skeletal muscle mass (LSMM) has emerged as an independent negative prognostic factor in many forms of cancer [9]. LSMM is prevalent in patients with upper GI cancer, particularly in advanced disease stages [10] and is associated with higher a risk of postoperative complications [11] and poor survival [12]. Further, LSMM has been proposed to reduce the tolerability of systemic anticancer therapies through altered pharmacokinetics, including changes in drug biodistribution, metabolism and clearance [13, 14]. Accordingly, previous systematic reviews have evaluated the association between LSMM and the tolerability of systemic treatments; however, the results of these reviews are equivocal and limited by small sample sizes [15–17]. Therefore, we performed the present systematic review and meta-analysis with the primary objective to evaluate the association between LSMM and grades 3 and 4 adverse events and systemic treatment discontinuation in patients with upper GI cancer undergoing systemic therapies.

2 | Methods

This study was prospectively registered at PROSPERO (CRD42020146201) on 28 April 2020 and is reported in accordance with the PRISMA statement [18] (Data S1). The manuscript does not contain patient data.

2.1 | Eligibility Criteria

2.1.1 | Participants and Study Designs

We included retrospective and prospective studies investigating the association between skeletal muscle mass and adverse events or treatment tolerability in adult (age ≥ 18 years) patients diagnosed with upper GI cancer scheduled to undergo chemotherapy, immunotherapy, targeted therapy or chemoradiation. Upper GI included the following cancers, categorised according to the International Classification of diseases code 10 (ICD C10) [19]: oesophagus (C15), stomach (C16), liver and intrahepatic bile ducts (C22), gallbladder (C23), unspecified and other parts of the biliary tract (C24) and pancreas (C25). Studies were eligible if they (1) reported the association between adverse event or treatment tolerability and muscle mass on a continuous scale or (2) compared adverse events or treatment tolerability in participants with non-LSMM versus LSMM, defined using a specified threshold. No restrictions were made regarding the mode of assessment of adverse events, treatment tolerability or muscle mass. Studies were excluded if participants without upper GI cancer were included, unless separate data were available.

2.1.2 | Outcomes

The primary outcomes of this study were grades 3 and 4 adverse events (all types combined) and treatment discontinuation. Secondary outcomes were individual types of adverse events and dose reductions, dose delays and relative dose intensity of systemic treatment.

2.2 | Search Methods for Identification of Trials

We included data from published, peer-reviewed journal articles. Systematic searches for eligible studies were performed on MEDLINE (1946 to 10 October 2022), Web of Science (1997 to 10 October 2022), EMBASE (1974 to 10 October 2022) and CINAHL (1981 to 10 October 2022). We used a search string consisting of four blocks of controlled vocabularies and free text words related to cancer, systemic cancer treatment, muscle mass and adverse events and tolerability. No publication date restrictions were imposed (Data S2).

2.3 | Study Selection and Data Collection

Study selection was managed via the software Rayyan [20]. After deduplication, titles and abstracts were screened independently by a minimum of two authors (S.N.T., E.N.S., C.M.F. and I.M.L.). After excluding clearly ineligible records, the full texts of the remaining records were screened independently by a minimum of two authors (S.N.T., E.N.S., C.M.F. and I.M.L.). Selection disagreements were resolved through discussion with a third assessor.

Three authors (S.N.T., E.N.S. and I.M.L.) independently extracted data from the eligible studies. These data included the year of publication, the country of the research, the study design and the cancer site, categorised according to ICD codes (oesophagus [C15], stomach [C16], liver and intrahepatic bile ducts [C22], gallbladder [C23], unspecified and other parts of the biliary tract [C24] and pancreas [C25]). Moreover, the authors collected information on participant characteristics, including age and sex, type of systemic treatment (i.e., chemotherapy, chemoradiotherapy, immunotherapy and targeted therapy) and the treatment regimens. Data extraction disagreements were resolved by discussion involving the third assessor.

The assessment of muscle mass was documented, including the method of assessment (e.g., computerised tomography [CT] scans or bioelectrical impedance analysis), the specific

timepoints at which assessments were conducted and the parameter used to define low muscle mass. The prevalence of low muscle mass was determined and recorded. Lastly, the authors recorded specific definitions and methodologies used for assessing adverse events and treatment tolerability in the included studies.

2.4 | Risk of Bias in Individual Studies

Risk of bias was assessed independently by two authors (S.N.T. and E.N.S.) using the ROBINS-E [21], with disagreements being resolved by discussion with a third author (I.M.L.). Our hypothetical target trial was specified prior to the risk of bias assessment and is available on our Open Science Framework (OSF) page (https://osf.io/cqw8s/). For confounding variables, we considered sex, age, cancer grade/stage, comorbidities, socioeconomic status and treatment type.

2.5 | Data Synthesis

Meta-analyses of a given outcome were performed if reported in two or more eligible studies, and outcomes reported in one trial only were reported as raw data. Summary data of dichotomous outcomes were analysed with the Mantel–Haenszel random-effects models without continuity correction, with the Paule–Mandel estimator of τ [2] [22] and with the Hartung–Knapp adjustments [23], using risk ratios (RR) with 95% confidence intervals as the summary measure. Trials with zero events in both arms were not included [24]. We calculated prediction intervals in meta-analyses with ≥ 10 comparisons and no clear funnel plot asymmetry [24]. I^2 was provided as a measure of heterogeneity and was interpreted as follows [25]:

- 0%–40% might not be important,
- 30%–60% may represent moderate heterogeneity,
- 50%–90% may represent substantial heterogeneity,
- 75%–100% may represent considerable heterogeneity.

In case of substantial heterogeneity in our analyses of the primary outcomes, we explored its potential causes by performing subgroup (see Subgroup Analyses). All analyses were performed in R via RStudio (v1.4.1717), using the 'meta' package [26] (see Data S3 for statistical code). Contour-enhanced funnel plots were made of our primary outcomes, if ≥ 10 comparisons were made in meta-analyses [27, 28]. Funnel plot asymmetry was assessed by visual inspection and the Harbord test [28].

2.6 | Subgroup Analyses

We conducted subgroup meta-analyses of our primary outcomes based on

- cancer site, according to ICD codes (version 10); C15 oesophagus, C16 stomach, C22 liver and intrahepatic bile ducts, C23 gallbladder, C24 unspecified and other parts of the biliary tract and C25 Pancreas
- systemic cancer treatment (i.e., chemotherapy, chemoradiotherapy, immunotherapy, targeted therapy and any combination thereof)
- muscle mass assessment method (i.e., computed tomography and bioelectrical impedance analysis)

3 | Results

3.1 | Search Results

The systematic searches yielded 4694 records. After deduplicating and screening of titles and abstracts, 194 records were selected for full-text screening, and 50 publications [29–78] from 49 studies met the inclusion criteria (Figure 1).

3.2 | Description of the Eligible Studies

The characteristics of the eligible studies are summarised in Tables 1 and 2. The eligible studies included a total of 5514 participants; 1727 (31%) were women and 3787 (69%) were men. The median (IQR) sample size was 83 [64] participants, and the participants had a mean (SD) age at baseline of 67 [5] years. The most commonly studied tumour sites were pancreas ($n = 17$, 35%) [29, 32, 34, 37, 38, 40, 42, 45, 46, 48, 57, 68, 69, 71–73, 77], oesophagus ($n = 12$, 24%) [33, 41, 44, 56, 58–61, 63, 65, 76] and stomach ($n = 11$, 22%) [35, 39, 49, 50, 52–54, 62, 67, 75, 78]. The median (IQR) prevalence of LSMM was 49% (23%). Three studies were prospective [30, 51, 63]. For the assessment of skeletal muscle mass, CT scans were used in 45 (92%) studies [29–55, 58–60, 62–70, 72–78], and bioelectrical impedance analyses were used in four (8%) studies [56, 57, 61, 71]. SMI was the most commonly ($n = 42$ studies, 89%) used parameter for defining LSMM [30–38, 40–42, 46–48, 50–53, 55, 58–60, 62–78], and 24 unique thresholds were used. Most ($n = 46$, 94%) studies were retrospective [29, 31–50, 52–78]. Among the studies that assessed adverse events ($n = 38$, 78%), 36 (95%) studies used the common terminology criteria for adverse events to assess type and severity [29, 31, 32, 34–41, 43, 44, 48, 49, 51–63, 65, 67–69, 71, 73, 74, 78], whereas two (5%) studies did not report how adverse events were assessed [46, 64]. Forty (82%) studies evaluated patients receiving chemotherapy [29, 30, 32–41, 43–50, 54, 56–62, 64, 65, 67–73, 75–78]; four (8%) studies evaluated patients receiving targeted therapies [31, 55, 66, 74]; four (8%) studies evaluated patients receiving mixed types of systemic therapies [42, 52, 53, 63]; and one (2%) study evaluated patients receiving immunotherapy [51].

3.3 | Risk of Bias

A comprehensive breakdown of our risk of bias assessments for each study can be found at https://osf.io/cqw8s/. Out of the 13 studies examining grades 3 and 4 adverse events, 12 (92%) were established at having a very high risk of bias due to potential confounding factors [31, 38, 44, 46, 52, 53, 58, 59, 62, 63, 65, 66]. Emori et al. [37] was the only study of grades 3 and 4 adverse events not judged to be of very high risk of bias; however, we identified some concerns due to missing data and the selection of reported outcomes. Regarding the 11 studies that provided

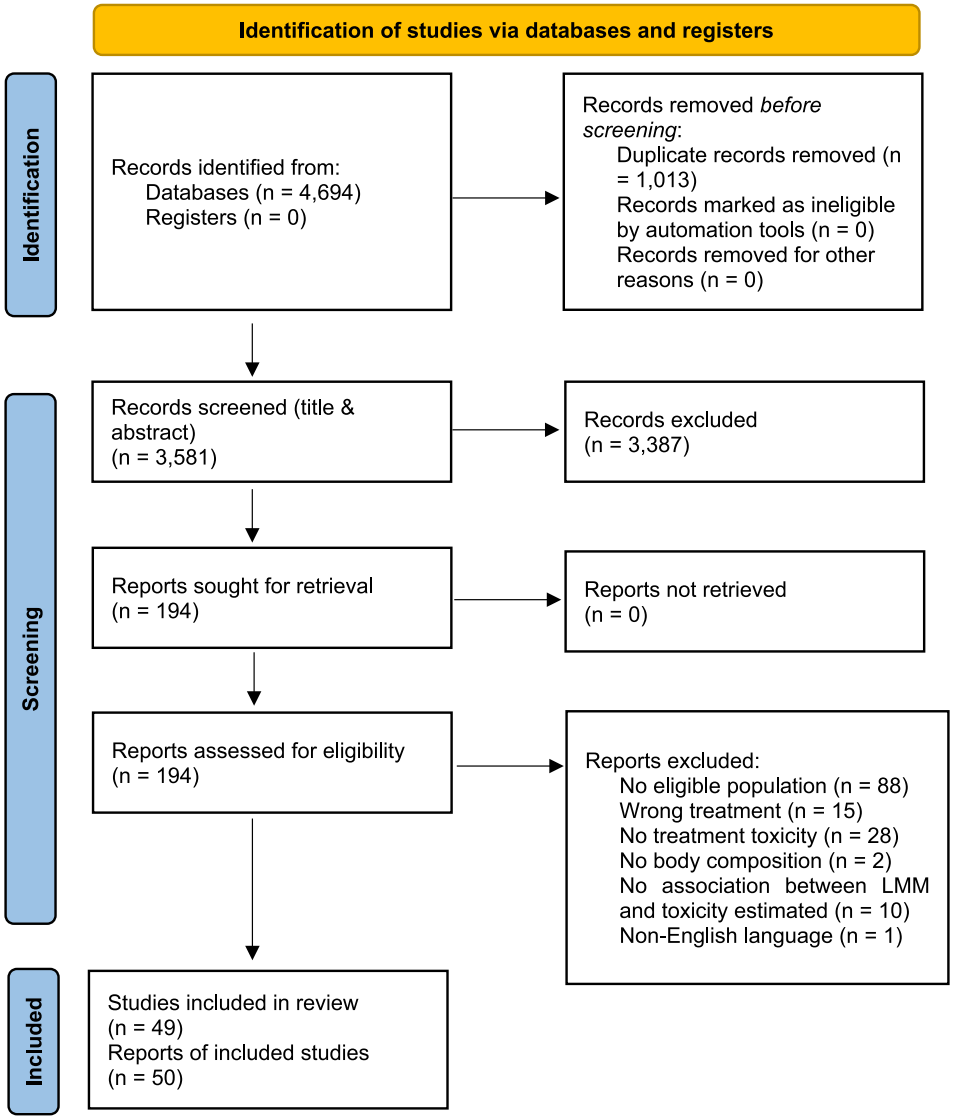


FIGURE 1 | PRIMA flow chart.

data on treatment discontinuation, eight (73%) were identified as having a very high risk of bias due to potential confounding [29, 41, 47, 48, 59, 62, 65, 66, 68, 69, 72]. In Tsukagoshi et al. [72], a high risk of bias was awarded due to missing data, whereas the risk of bias assessment of Palmela et al. [62] raised some concerns both in terms of confounding and the selection of reported outcomes.

3.4 | Association Between LSMM and Treatment Tolerability

3.4.1 | Primary Outcomes

Our meta-analysis showed evidence of a higher risk of grades 3 and 4 adverse events and treatment discontinuations in LSMM versus non-LSMM, with no evidence of subgroup differences between cancer sites and type of systemic therapy (Figure 2A–D). Funnel plots and the Harbord test ($p = 0.001$) indicated funnel plot asymmetry for grades 3 and 4 adverse events, whereas we found no evidence of funnel plot asymmetry for treatment discontinuation (Data S4).

3.4.2 | Secondary Outcomes

Meta-analyses of the secondary outcomes are presented in Table 3. We found evidence of a higher risk of the following adverse events in LSMM versus non-LSMM fatigue (grades 3 and 4); febrile neutropenia; intestinal pneumonia (grades 3 and 4); stomatitis (grades 3 and 4); any type of non-hematologic AE (grades 3 and 4); thrombocytopenia (grades 3 and 4); and dose-limiting adverse events. Meta-analyses of 89 other adverse events were not performed due to a lack of studies, and these are presented as raw data in Data S4. Relative dose intensity of systemic therapy was reported in five studies, but data could not be meta-analysed due to poor reporting (Data S4).

TABLE 1 | Study, participants and the treatment characteristics of included studies.

Study (year)	Country	Design	Recruitment period	Diagnosis	*N* (% M/F)	Age (years)	Setting	Treatment details
Akahori et al. (2015) [31]	Japan	Retro	Sep 2008–Oct 2013	Pancreatic: resectable adenocarcinoma	83 (55/45)	67	NACRT	Gem
Anandavadivelan et al. (2016) [32]	Sweden	Pros	2006–2012	Oesophageal: resectable adenocarcinoma and SCC	72 (85/15)	67	NAC	Cisplatin + 5-FU
Antonelli et al. (2018) [33]	Italy	Retro	2008–2016	Hepatocellular carcinoma: advanced	96 (78/22)	Md: 69	Unclear	Sorafenib
Asama et al. (2022) [34]	Japan	Retro	Dec 2014–Aug 2016	Pancreatic: unresectable, advanced ductal adenocarcinoma	124 (54/46)	Md: 69	First-line	Gem-Nab-P
Awad et al. (2012) [35]	UK	Retro	NR	Gastroesophageal: locally advanced	47 (72/82)	63	NAC	Capecitabine/cisplatin; epirubicin/oxaliplatin; ECF; CF
Barrere et al. (2020) [36]	Brazil	Retro	Oct 2007–Sept 2015	Pancreatic	17 (65/35)	63	Unclear	Gem, cisplatinum and oxaliplatin
Catanese et al. (2021) [37]	Italy	Retro	Mar 2010–-Jan 2017	Gastroesophageal junction and gastric: localised and locally advanced adenocarcinoma	78 (72/18)	67	First-line palliative	mFOLFOX-6 and CapOX
Dijksterhuis et al. (2019) [38]	Netherlands	Retro	Jan 2010–Jul 2017	Gastroesophageal: advanced adenocarcinoma and SCC	88 (75/25)	63	First-line palliative	CapOX
Emori et al. (2022) [39]	Japan	Retro	Apr 2016–May 2020	Pancreatic: unresectable, metastatic or locally advanced ductal adenocarcinoma	84 (63/37)	≥ 65 y: 64%	First-line	Gem-Nab-P
Freckelton et al. (2019) [40]	Australia	Retro	NR	Pancreatic: metastatic ductal adenocarcinoma	52 (47/53)	65	First-line palliative	Gem-Nab-P
Hashimoto et al. (2019) [41]	Japan	Retro	Jan 2008–Dec 2018	Gastric: resectable, stages II–IV	114 (68/32)	66	NAC	S-1 + oxaliplatin/docetaxel/cisplatin

(Continues)

TABLE 1 | (Continued)

Study (year)	Country	Design	Recruitment period	Diagnosis	*N* (% M/F)	Age (years)	Setting	Treatment details
Hong et al. (2022) [42]	Republic of Korea	Retro	Jan 2009–Dec 2019	Pancreatic: metastatic ductal adenocarcinoma	636 (59/41)	Md: 60	First-line	FOLFIRINOX or Gem-based treatment
Huang et al. (2020) [43]	Taiwan	Retro	2001–2014	Oesophageal: stages IA–IIIC SCC	107 (94/6)	M: 54	NACRT	Cisplatin + 5-FU
Iede et al. (2022) [44]	Japan	Retro	Jan 2015–Mar 2020	Pancreatic: advanced	52 (44/56)	Md: 71	Second-line	Gem-Nab-P; fluoropyrimidine derivative; mFOLFIRINOX
Ishida et al. (2021) [46]	Japan	Retro	Jan 2010–Mar 2017	Oesophageal: stages I–IV; undergoing esophagectomy;	333 (88/12)	Md: 69	NAC	ACF or DCF
Keum et al. (2020) [47]	Republic of Korea	Retro	Jan 2015–Dec 2017	Pancreatic: unresectable, localised or metastatic	106 (55/45)	Md: 58	First-line	FOLFIRINOX
Kim et al. (2021) [48]	Republic of Korea	Retro	Jan 2010–Mar 2017	Pancreas: metastatic adenocarcinoma	251 (64/36)	Md: 63	First-line palliative	Gem single or gem-based
Koch et al. (2019) [49]	Germany	Retro	NR	Gastric or gastroesophageal junction: locally advanced, stages I–III adenocarcinoma	86 (72/38)	63	NAC	FLOT (5-flurouracil, leucovorin, oxaliplatin and docetaxel); EOX; ECX
Kurita et al. (2019) [50]	Japan	Retro	2011–2017	Pancreatic: advanced	82 (73/27)	64	First- and second-line	FOLFIRINOX
Lin et al. (2021) [51]	China	Retro	Jun 2013–Jun 2018	Gastric: locally advanced, stages I–III adenocarcinoma;	213 (72/25)	Md: 60	NAC	Fluorouracil-based: S-1; capecitabine; oxaliplatin; docetaxel; FOLFOX4; ECF/ECX; FLOT
Matsui et al. (2021) [52]	Japan	Retro	Apr 2008–Apr 2017	Gastric: advanced, stages II and III; post-radical gastrectomy	263 (70/30)	65	AC	S-1
Matsumoto et al. (2022) [53]	Japan	Pros	Oct 2020–Feb 2022	Hepatocellular carcinoma: unresectable	32 (59/41)	Md: 77	First-line	Atezolizumab plus bevacizumab

(Continues)

TABLE 1 | (Continued)

Study (year)	Country	Design	Recruitment period	Diagnosis	*N* (% M/F)	Age (years)	Setting	Treatment details
Matsunaga et al. (2021a) [54]	Japan	Retro	Jan 2008–Dec 2019	Gastric: recurrent, post-gastrectomy	67 (82/18)	68	First-line palliative	CPT-11; S-1; paclitaxel; paclitaxel + ramucirumab; S-1 + cisplatin, docetaxel, oxaliplatin or paclitaxel; capecitabine + oxaliplatin, cisplatin or trastuzumab; CPT-11 + cisplatin
Matsunaga et al. (2021b) [55]	Japan	Retro	Jan 2008–Dec 2019	Gastric: unresectable, advanced; or recurrent, post-gastrectomy	83 (74/26)	65	First-line palliative	S-1; S-1 + cisplatin, paclitaxel, oxaliplatin or docetaxel; capecitabine + oxaliplatin, cisplatin or trastuzumab; S-1 + cisplatin + docetaxel
Matsuura et al. (2021) [56]	Japan	Retro	Jan 2013–Dec 2016	Gastric: advanced adenocarcinoma	41 (68/32)	Md: 72	NAC	S-1 + cisplatin; S-1 + cisplatin + docetaxel; or S-1 + oxaliplatin
Mir et al. (2012) [57]	France	Retro	Jan 2013–Dec 2016	Hepatocellular carcinoma: advanced with Child A cirrhosis	40 (75/25)	Md: 63	Palliative	Sorafenib
Miyata et al. (2017) [58]	Japan	Retro	Jan 2013–Aug 2016	Oesophageal: stages IB–IV SCC without distant organ metastasis	94 (81/19)	64	NAC	ACF or DCF
Muramatsu et al. (2016) [59]	Japan	Retro	Nov 2012–Apr 2014	Pancreatic and biliary tract: advanced	26 (54/46)	68	AC	Gem-based; S-1; Cisplatin
Murimwa et al. (2017) [60]	USA	Retro	2008–2012	Oesophageal: locally advanced, stages IB–IIIC	56 (84/16)	63	NACRT	Cisplatin + 5-FU
Onishi et al. (2019) [61]	Japan	Retro	April 2007–Dec 2014	Oesophageal: unresectable, advanced SCC	176 (85/15)	65	AC	Cisplatin + 5-FU or DCF
Onishi et al. (2020) [62]	Japan	Retro	Jan 2013–Jun 2018	Oesophageal: advanced, stages II and III SCC in adults aged ≥ 70 years	91 (80/20)	74	NAC	Cisplatin + 5-FU; DCF; or 5-FU + nedaplatin
Ota et al. (2019) [63]	Japan	Retro	Apr 2013–Dec 2017	Oesophageal: locally advanced, stages II and III SCC	31 (87/13)	Md: 66	NAC	Cisplatin + 5-FU or DCF

(Continues)

TABLE 1 | (Continued)

Study (year)	Country	Design	Recruitment period	Diagnosis	*N* (% M/F)	Age (years)	Setting	Treatment details
Palmela et al. (2017) [64]	Portugal	Retro	Jan 2012–Dec 2014	Gastric or gastroesophageal junction: locally advanced, stages II and III adenocarcinoma	48 (69/31)	68	NAC	ECF; EOF; EOX; ECX; CapOx; FOLFOX; capecitabine; or DCF
Panje et al. (2019) [65]	Switzerland	Pro	May 2010–Dec 2013	Oesophageal: resectable, locally advanced, stages II and III SCC and adenocarcinoma	61 (93/7)	Md: 61	NACRT	Docetaxel + cisplatin; docetaxel + cisplatin + cetuximab
Rinninella et al. (2021) [66]	Italy	Retro	Apr 2019–Jan 2020	Gastric and lower oesophageal: stages II and III adenocarcinoma	26 (69/31)	63	NAC	Docetaxel + oxaliplatin + leucovorin + 5-FU
Sato et al. (2018) [67]	Japan	Retro	Oct 2012–Dec 2015	Oesophageal: unresectable, locally advanced, stages IIIC SCC	48 (67/33)	Md: 68	First-line or later CRT	Cisplatin + 5-FU; 2nd line: docetaxel + cisplatin; 3rd line: S-1; 4th line: paclitaxel
Sawado et al. (2019) [68]	Japan	Retro	Jun 2009–Feb 2016	Hepatocellular Carcinoma: unresectable	82 (82/18)	69	First-line, palliative	Sorafenib
Sugiyama et al. (2018) [69]	Japan	Retro	Jan 2013–Dec 2015	Gastric: metastatic adenocarcinoma	118 (59/41)	Md: 64	First-line	Fluoropyrimidine + cisplatin; Fluoropyrimidine + oxaliplatin
Takeda et al. (2021a) [70]	Japan	Retro	Feb 2019–Apr 2020	Pancreas: resectable	62 (52/48)	Md: 71	NAC	Gem + S-1
Takeda et al. (2021b) [71]	Japan	Retro	Jan 2015–Apr 2020	Pancreatic: metastatic in adults aged ≥ 75 years	80 (44/56)	Md: 77	Palliative	Gem-Nab-P; Gem; S-1; or FOLFIRINOX
Tan et al. (2015) [71]	UK	Retro	Nov 2010–Aug 2012	Gastroesophageal: locally advanced adenocarcinoma and SCC, without metastasis	89 (75/25)	66	NAC	5-FU + cisplatin or ECX
Tozuka et al. (2022) [73]	Japan	Retro	Jan 2015–Dec 2017	Pancreatic: unresectable, advanced, stages III and IV	121 (59/41)	Md: 69	First-line	Gem-Nab-P

(Continues)

TABLE 1 | (Continued)

Study (year)	Country	Design	Recruitment period	Diagnosis	*N* (% M/F)	Age (years)	Setting	Treatment details
Tsukagoshi et al. (2021) [74]	Japan	Retro	Jan 2016–Aug 2019	Pancreatic: underwent pancreatic resection	80 (54/46)	Md: 72	AC	S-1
Uemura et al. (2021) [75]	Japan	Retro	Jun 2014–Mar 2018	Pancreatic: unresectable, advanced	69 (55/45)	Md: 63	AC	FOLFIRINOX
Uojima et al. (2020) [76]	Japan	Retro	Feb 2018–Jul 2019	Hepatocellular carcinoma: unresectable	100 (75/25)	72	Unclear	Lenvatinib
Yang et al. (2020) [77]	China	Retro	Jan 2010–Dec 2015	Gastric: D2 dissected, locally advanced adenocarcinoma	182 (67/34)	54	ACRT	5-FU; capecitabine; or S-1
Yip et al. (2014) [78]	UK	Retro	NR	Oesophageal: adenocarcinoma and SCC	35 (86/14)	61	NAC	5-FU; 5-FU + platinum; or ECX/ECF
Youn et al. (2021) [79]	Canada	Retro	2014–2017	Pancreatic: metastatic	152 (58/42)	65	First-line	Gem-Nab-P
Yu et al. (2020) [80]	Republic of Korea	Retro	Nov 2004–Apr 2008	Gastric: D2 dissected, stages IB–IVA adenocarcinoma	440 (64/36)	Md: 61	ACRT	Cisplatin + capecitabine

Abbreviations: 5-FU; 5-fluorouracil, AC; adjuvant chemotherapy, ACF adriamycin, CAPOX; capecitabine oxaliplatin, CF; cisplatin, fluorouracil, CPT-11; irinotecan, DCF; docetaxel, cisplatin, 5-fluorouracil, ECF; epirubicin, cisplatin, 5-fluorouracil, ECX; epirubicin, cisplatin, capecitabine, EOF; epirubacin, fluorouracil, oxaliplatin, EOX; epirubicin, oxaliplatin, capecitabine, FOLFIRINOX; 5-fluorouracil, irinotecan, oxaliplatin, FOLFOX; folinic acid, 5-fluoroaracil, oxaliplatin, FLOT; fluorouracil, folinic acid, oxaliplatin, docetaxel, Gem-Nab-P; gemcitabine and nab-paclitaxel, NAC; neoadjuvant chemotherapy, NACRT; neoadjuvant chemoradiotherapy, Pros; prospective, retro; retrospective.

TABLE 2 | Skeletal muscle mass, adverse events and chemotherapy dose-related measurement details.

Study (year)	SMM measurement; software	LSMM parameter	LSMM cut-off value	LSMM at baseline (%)	Adverse event measurement	Systemic treatment-related measures
Akahori et al. (2015) [31]	CT-L3; Synapse Vincent	MA	Lower quartile of HU values	MA: 20%	Grades 3 and 4 AE via CTCAE v4	Dose incompletion
Anandavadivelan et al. (2016) [32]	CT-L3; Image J	SMI	Men: $< 52.4\,cm^2/m^2$; Women: $< 38.5\,cm^2/m^2$.	43	None	DLT
Antonelli et al. (2018) [33]	CT-L3; Slice-O-Matic 5.0	SMI	Men: $53\,cm^2/m^2$ and BMI ≥ 25 or $43\,cm^2/m^2$ and BMI < 25; Women: $41\,cm^2/m^2$ for women.	49	None	Dose reduction
Asama et al. (2022) [34]	CT-L3; Slice-O-Matic 4.3	SMI	Men: $< 42\,cm^2/m^2$; women: $< 38\,cm^2/m^2$.	51	Grades 3 and 4 AE via CTCAE v4	Dose reduction
Awad et al. (2012) [35]	CT-L3; Slice-O-Matic	SMI	Men: $< 52.4\,cm^2/m^2$; women: $< 38.5\,cm^2/m^2$.	57	None	Treatment completion
Barrere et al. (2020) [36]	CT-L3; Slice-O-Matic 4.3	SMI	Men: $< 52.4\,cm^2/m^2$; women: $< 38.5\,cm^2/m^2$.	47	Gastrointestinal events via CTCAE v2	None
Catanese et al. (2021) [37]	CT-L3; GE advantage workstation 4.7	SMI	Men: $< 53\,cm^2/m^2$ and BMI ≥ 25 or $< 43\,cm^2/m^2$ and BMI < 25; women: $< 41\,cm^2/m^2$ for women.	34	All grades AEs and grades 3 and 4 AE via CTCAE v4	None
Dijksterhuis et al. (2019) [38]	CT-L3; Slice-O-Matic	SMI	Men: $< 53\,cm^2/m^2$and BMI ≥ 25 or $< 43\,cm^2/m^2$ and BMI < 25; women: $< 41\,cm^2/m^2$ for women.	49	Grades 2–4 and 3 and 4 AEs via CTCAE v4	None
Emori et al. (2022) [39]	CT-L3; Synapse Vincent	SMI	Men: $< 42\,cm^2/m^2$; women: $< 38\,cm^2/m^2$.	50	Grades 3 and 4 AE via CTCAE v4	RDI
Freckelton et al. (2019) [40]	CT-L3; Slice-O-Matic	SMI	Men: $< 52.4\,cm^2/m^2$; women: $< 38.5\,cm^2/m^2$.	58	Grades 2–4 and 3 and 4 AE via CTCAE v4	Dose reduction

(Continues)

TABLE 2 | (Continued)

Study (year)	SMM measurement; software	LSMM parameter	LSMM cut-off value	LSMM at baseline (%)	Adverse event measurement	Systemic treatment-related measures
Hashimoto et al. (2019) [41]	CT-L3; Synapse Vincent	PMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	50	Grades 3 and 4 haematological and grades 2–4 non-haematological AE via CTCAE v4	None
Hong et al. (2022) [42]	CT-L3; NR	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	34	Grades 3 and 4 AE via CTCAE v5	Treatment-modifying toxicity: AE leading to dose reduction, delayed administration, drug skip or discontinuation
Huang et al. (2020) [43]	CT-L3; OsiriX	SMI	Men: $<52.4\,cm^2/m^2$; women: $<38.5\,cm^2/m^2$.	67	Grades 3 and 4 AE via CTCAE v4	Treatment discontinuation
Iede et al. (2022) [44]	CT-L3; Synapse Vincent	SMI	Prado 2009	54	None	RDI
Ishida et al. (2021) [46]	CT-L3; Synapse Vincent	PMI	Men: $<6.36\,cm^2/m^2$; women: $<3.92\,cm^2/m^2$.	31	Grades 3 and 4 AE via CTCAE v4	Dose reduction
Keum et al. (2020) [47]	CT-L3; Image J	SMI	NR	19	Febrile neutropenia	None
Kim et al. (2021) [48]	CT-L3; Advantage windows workstation 4.6	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	41	Grades 3 and 4 toxicities (measure NR)	None
Koch et al. (2019) [49]	CT-L3; Slice-O-Matic	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	36	None	Treatment discontinuations; dose reduction
Kurita et al. (2019) [50]	CT-L3; Synapse Vincent	SMI	Optimum stratification	51	Grades 3 and 4 haematological, grade 3 non-haematological AE via CTCAE v4	Treatment discontinuations; time to treatment failure

(Continues)

TABLE 2 | (Continued)

Study (year)	SMM measurement; software	LSMM parameter	LSMM cut-off value	LSMM at baseline (%)	Adverse event measurement	Systemic treatment-related measures
Lin et al. (2021) [51]	CT-L3; Slice-O-Matic 5.0	SMI, SMD	ROC analysis	NR	Grades 3 and 4 AE via CTCAE v4	None
Matsui et al. (2021) [52]	CT-L3; Ziostation	SMI	Median of sample	50	None	Treatment failure
Matsumoto et al. (2022) [53]	CT-L3; Slice-O-Matic 5.0	SMI	Men: $<42\,cm^2/m^2$; women: $<38\,cm^2/m^2$	44	AE per type per grade via CTCAE v5	RDI; dose reduction or discontinuation
Matsunaga et al. (2021a) [54]	CT-L3; Synapse Vincent	SMI	Median for each sex	33	Grades 3 and 4 AE via CTCAE v4	None
Matsunaga et al. (2021b) [55]	CT-L3; Synapse Vincent	SMI	ROC analysis	51	Grades 3 and 4 haematological AE, GI AE (NG), and febrile neutropenia (NG) via CTCAE v4.0	None
Matsuura et al. (2021) [56]	CT-L3; Synapse Vincent	PMI	Median of sample	50	Grades 3 and 4 adverse events via CTCAE v4	None
Mir et al. (2012) [57]	CT-L3; Image J	SMI	Men: $<54.4\,cm^2/m^2$; women: $<38.5\,cm^2/m^2$.	28	Grades 0–4 and Grade 3 AE via CTCAE v3	DLT: dose reduction, temporary or permanent or discontinuation of treatment due to AE
Miyata et al. (2017) [58]	BIA; InBody720	SM	$<90\%$ of the 'standard' SMM	47	Grades 0–4 toxicities via CTCAE v4	None
Muramatsu et al. (2016) [59]	BIA; Karada Scan HBF-37	% SMM	None	NR	Grade ≥ 2 hematotoxicity via CTCAE v4.03	RDI
Murimwa et al. (2017) [60]	CT-L4; Pinnacle3 TPS version 9.8	SMI	Median of sample	41	Grades 3 and 4 AE via CTCAE v4	None
Onishi et al. (2019) [61]	CT-L3; Synapse Vincent	SMI	Men: $<52.4\,cm^2/m^2$; women: $<38.5\,cm^2/m^2$.	57	Grades 3 and 4 AE via CTCAE v4	Treatment discontinuation
Onishi et al. (2020) [62]	CT-L3; Synapse Vincent	SMI	Men: $<42\,cm^2/m^2$; women: $<38\,cm^2/m^2$.	76	Grades 3 and 4 AE via CTCAE v4	Treatment discontinuation
Ota et al. (2019) [63]	BIA; InBody 720	SMI[a]	Men: $<7.0\,kg/m^2$; women: $<5.7\,kg/m^2$.	52	Grades 3 and 4 AE via CTCAE v4	None

(Continues)

TABLE 2 | (Continued)

Study (year)	SMM measurement; software	LSMM parameter	LSMM cut-off value	LSMM at baseline (%)	Adverse event measurement	Systemic treatment-related measures
Palmela et al. (2017) [64]	CT-L3; NR	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $41\,cm^2/m^2$ for women.	23	Grades 2–4 AE via CTCAE (version NR)	DLT: grades 3 and 4 AE leading to physician-ordered dose reduction or termination of therapy
Panje et al. (2019) [65]	CT-L3; Slice-O-Matic	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	30	Grades 3 and 4 AE via CTCAE v4	None
Rinninella et al. (2021) [66]	CT-L3; Slice-O-Matic	SMI	Men: $<55\,cm^2/m^2$; women $<39\,cm^2/m^2$.	73	Grade ≥ 2 AE (measure NR)	Chemotherapy delay; chemotherapy completion
Sato et al. (2018) [67]	CT-L3; Synapse Vincent	SMI	Men: $<52.4\,cm^2/m^2$; women: $<38.5\,cm^2/m^2$.	71	Grades 3 and 4 AE via CTCAE v4	Dose reduction; dose discontinuation
Sawado et al. (2019) [68]	CT-L3; Synapse Vincent	SMI	Men $\leq 36.2\,cm^2/m^2$; women: $\leq 29.6\,cm^2/m^2$.	20	Grades 3 and 4 AE and SAE (measure NR)	Dose discontinuation
Sugiyama et al. (2018) [69]	CT-L3; Synapse Vincent	SMI	Men: $<52.4\,cm^2/m^2$; women: $<38.5\,cm^2/m^2$.	89	0–4 grades and grades 3 and 4 AE via CTCAE v4	Time to treatment failure
Takeda et al. (2021a) [70]	CT-L3; Synapse Vincent 5.2	SMI	Men: $<53\,cm^2/m^2$and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	40	0–4 grades and grades 3 and 4 AE via CTCAE v5	RDI; treatment delay; dose reduction
Takeda et al. (2021b) [71]	CT-L3; Synapse Vincent 5.2	SMI	Men: $<53\,cm^2/m^2$ and BMI ≥ 25 or $<43\,cm^2/m^2$ and BMI <25; women: $<41\,cm^2/m^2$ for women.	76	Grade 4 haematological and grade 3 non-haematological AE via CTCAE v5	RDI; treatment discontinuation; treatment delay; dose reduction; time to treatment failure

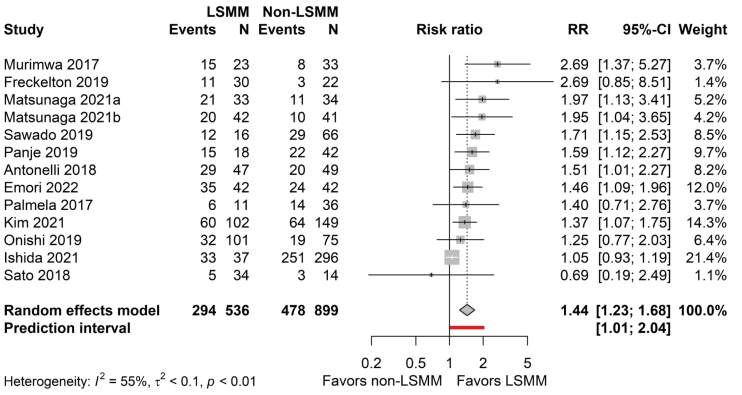
(Continues)

TABLE 2 | (Continued)

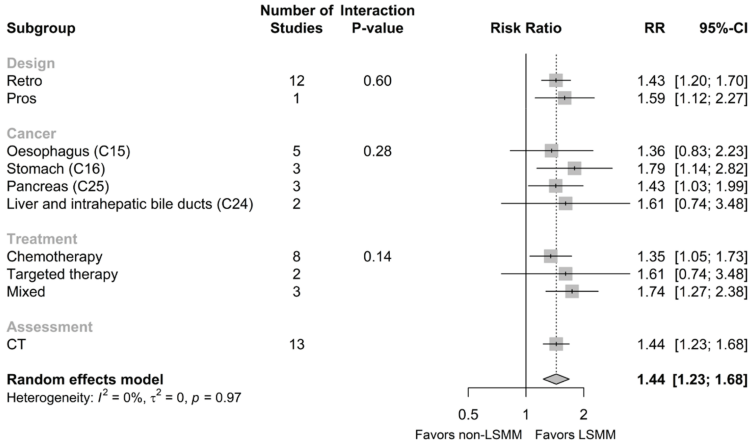
Study (year)	SMM measurement; software	LSMM parameter	LSMM cut-off value	LSMM at baseline (%)	Adverse event measurement	Systemic treatment-related measures
Tan et al. (2015) [71]	CT-L3; Slice-O-Matic 4.3	SMI	Men: < 52.4 cm^2/m^2; women: < 38.5 cm^2/m^2.	49	None	DLT: postponement of treatment, dose reduction, or definitive interruption of chemotherapy due to intolerable AE
Tozuka et al. (2022) [73]	BIA; InBody 720	SMI	Men: < 8.87 kg/m^2; women: < 6.42 kg/m^2.	33	All grades and grades 3 and 4 AE via CTCAE v5	RDI; dose reductions; dose discontinuations
Tsukagoshi et al. (2021) [74]	CT-L3; Synapse Vincent	SMI	Men: < 42 cm^2/m^2; women: < 38 cm^2/m^2	70	None	Dose discontinuations
Uemura et al. (2021) [75]	CT-L3; Synapse Vincent 4.0	SMI	Men: < 7.0 kg/m^2; women: < 5.7 kg/m^2.	48	Grades 3 and 4 serious AE via CTCAE v4	Dose reduction
Uojima et al. (2020) [76]	CT-L3; Slice-O-Matic 5.0	SMI	Men: < 42 cm^2/m^2; women: < 38 cm^2/m^2.	41	Grades 3 and 4 SAE via CTCAE v4; hospitalisation due to AE	Time to treatment failure
Yang et al. (2020) [77]	CT-L3; MIM Software	SMI	Men: < 52.4 cm^2/m^2; women: < 38.5 cm^2/m^2.	74	CTCAE v5	DLT: grades 3 and 4 toxicity, dose reduction or interruption of therapy
Yip et al. (2014) [78]	CT-L3; Syngo Multimodality workplace	SMI	Men: < 52.4 cm^2/m^2; women: < 38.5 cm^2/m^2.	26	None	Dose reduction
Youn et al. (2021) [79]	CT-L3; Slice-O-Matic 5.0	SMI	Men: < 53 cm^2/m^2 and BMI ≥ 25 or < 43 cm2/m2 and BMI < 25; women: < 41 cm^2/m^2.	63	None	DLT: dose reduction or discontinuation due to AE
Yu et al. (2020) [80]	CT-L3; In-house, open-source software	SMI	Men: < 6.58 kg/m^2; women 4.59 kg/m^2.	17	Grades 1–4 AE via the CTCAE v2	None

Abbreviations: AEs; adverse events, BIA; bioelectrical impedance analysis, BMI; body mass index, DLT; dose-limiting toxicity, MA; muscle attenuations, NR; not reported, PMI; psoas muscle index, RDI; relative dose intensity, SMD; skeletal muscle density, SMI; skeletal muscle index, SMM; skeletal muscle mass, TTF: time to treatment failure.
[a]SMI calculated via ASM/height.

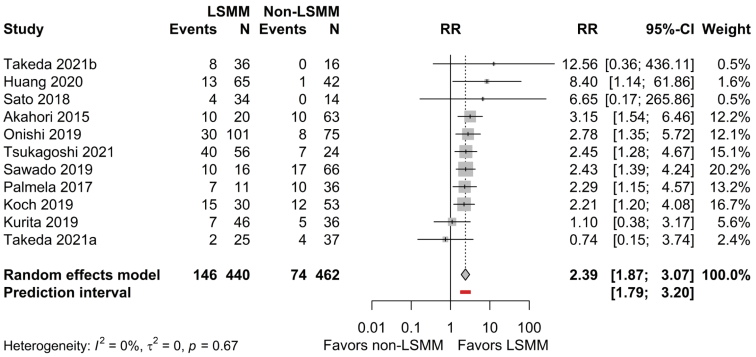
A) Meta-analysis of grade 3-4 adverse events



B) Subgroup meta-analyses of grade 3-4 adverse events



C) Meta-analysis of treatment discontinuation



D) Subgroup meta-analyses of treatment discontinuation

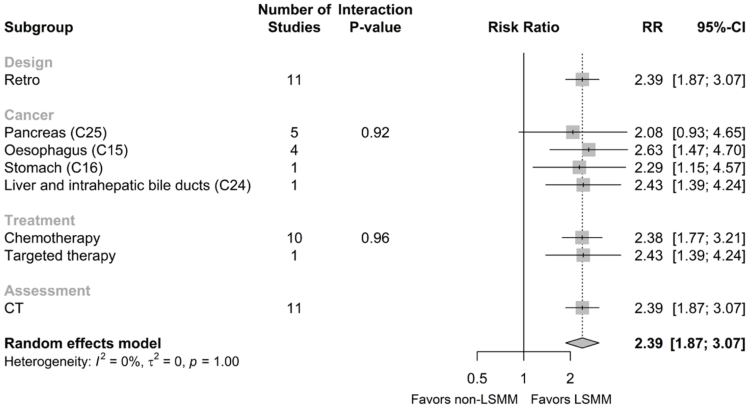


FIGURE 2 | Legend on next page.

FIGURE 2 | Meta analyses of (A) grades 3 and 4 AE (all types combined), (B) subgroup analysis of grades 3 and 4 AE, (C) discontinuations of systemic cancer treatment and (D) subgroup analysis of discontinuations of systemic cancer treatment RR; risk ratio, CI; confidence interval, CT; computed tomography, LSMM; low skeletal muscle mass, Retro; retrospective.

TABLE 3 | Meta-analyses of secondary outcomes.

		LSMM		Non-LSMM			
Outcome	**Comparisons**	**Events**	***N***	**Events**	***N***	I^2	**RR (95% CI)**
Nonhaematologic							
Anorexia, all G	4 [61, 69, 71, 73]	95	271	35	206	0	1.34 [0.91; 1.98]
Anorexia, G3 and 4	6 [62, 69–71, 73, 75]	18	307	64	539	0	0.83 [0.43; 1.59]
AST/ALT ratio, G3 and 4	2 [70, 71]	7	61	1	53	45	1.96 [0.00; > 1000]
Constipation, all G	2 [71, 73]	28	65	49	118	0	0.91 [0.25; 3.27]
Constipation, G3 and 4	5 [70, 71, 73, 80]	2	176	2	499	0	4.90 [0.72; 33.27]
Diarrhoea, all G	5 [57, 68–70, 73]	40	197	51	226	45	0.93 [0.41; 2.08]
Diarrhoea, G3 and 4	13 [43, 46, 48, 57, 62, 63, 68–71, 73, 75, 80]	30	592	100	1205	0	1.40 [0.92; 2.13]
Fatigue, all G	3 [68–70]	54	146	28	116	0	1.19 [0.71; 2.00]
Fatigue, G3 and 4	4 [39, 48, 69, 71]	28	326	21	323	0	**1.59 [1.07; 2.37]**
Febrile neutropenia	8 [39, 43, 46, 54, 55, 61, 63, 71]	62	372	152	561	0	**1.39 [1.03; 1.87]**
Gastrointestinal, G3 and 4	2 [54, 55]	19	75	5	75	0	3.76 [0.41; 34.44]
Hypertension, all G	2 [57, 68]	4	27	18	98	0	0.72 [0.07; 7.00]
Hypertension, G3 and 4	2 [57, 68]	1	27	4	95	39	1.22 [0.00; > 1000]
Intestinal pneumonia, G3 and 4	2 [39, 75]	4	75	1	78	0	**3.03 [2.53; 3.63]**
Loss of appetite, G3 and 4	2 [39, 68]	4	58	3	108	47	2.57 [0.00; > 1000]
Malaise, G3and 4	2 [62, 73]	2	71	7	141	0	0.60 [0.07; 5.11]
Nausea, all G	3 [69, 70, 73]	80	170	22	131	53	1.74 [0.38; 8.06]
Nausea, G3and 4	5 [63, 69, 73, 80]	14	236	49	474	0	1.07 [0.63; 1.81]
Peripheral neuropathy, G3 and4	3 [73, 75, 76]	14	106	19	153	0	1.06 [0.55; 2.05]
Stomatitis, G3 and 4	3 [70, 71, 80]	3	136	4	418	0	**2.67 [1.45; 4.89]**
Vomiting, G3 and 4	3 [75, 80]	2	108	14	401	0	0.79 [0.04; 15.57]
Any non-hematologic adverse event, G3 and 4	6 [34, 39, 50, 70, 71, 75]	53	245	36	228	0	1.25 [0.78; 1.99]
Haematologic							
Anaemia, all G	4 [68–70, 73]	153	186	117	197	73	0.98 [0.88; 1.09]
Anaemia, G3 and 4	11 [39, 43, 48, 54, 55, 68–70, 73, 75, 80]	64	578	62	906	36	1.10 [0.64; 1.91]
Leukopenia, G3 and 4	2 [45, 73]	39	77	195	377	76	1.02 [0.03; 39.37]
Neutropenia, all G	4 [61, 69, 70, 73]	136	271	127	206	0	0.95 [0.87; 1.04]

(Continues)

TABLE 3 | (Continued)

Outcome	Comparisons	LSMM		Non-LSMM		I^2	RR (95% CI)
		Events	*N*	Events	*N*		
Neutropenia, G3 and 4	11 [39, 46, 48, 54, 55, 62, 63, 69, 70, 73, 75]	223	506	451	804	24	1.05 [0.89; 1.23]
Pancytopenia, G3 and 4	2 [39, 68]	4	58	4	108	0	1.21 [0.02; 61.55]
Thrombocytopenia, all G	4 [69–71, 73]	93	186	102	197	10	0.96 [0.71; 1.29]
Thrombocytopenia, G3 and 4	13 [39, 43, 46, 48, 54, 55, 63, 68, 70, 73, 75, 80]	44	526	43	1204	0	**1.87 [1.27; 2.74]**
Hematologic AE, G3 and 4	5 [34, 39, 50, 70, 75]	147	209	131	212	59	1.16 [0.84; 1.60]
Treatment tolerability							
Dose reductions	6 [34, 40, 49, 64, 67, 73]	36	208	51	267	34	0.96 [0.53; 1.72]
	4 [57, 64, 72, 79]	85	161	53	167	0	**1.84 [1.30; 2.61]**

Abbreviations: ALT; alanine transaminase, AST; aspartate transaminase, CI; confidence interval, G; grade, RR; risk ratio. Statistically significant associations are in bold.

4 | Discussion

Our main goal in conducting this review was to assess the association between LSMM and the risk of grades 3 and 4 adverse events, and the discontinuation of systemic treatment in patients with upper GI cancer who are receiving systemic therapies. The results of our meta-analysis indicated a higher likelihood of grades 3 and 4 adverse events (RR 1.44, 95% CI 1.23 to 1.68, $N=13$) and the treatment discontinuations (RR 2.39, 95% CI 1.87 to 3.07, $N=11$) in individuals with upper GI cancers, who have LSMM compared to those without LSMM. This trend remains consistent across various subgroups, including tumour site and the type of systemic treatments received.

Secondary analyses revealed that fatigue (grades 3 and 4), febrile neutropenia, intestinal pneumonia (grades 3 and 4), stomatitis (grades 3 and 4), thrombocytopenia and dose-limiting adverse events exhibit a higher likelihood of occurrence in LSMM compared to non-LSMM. No differences were observed concerning other categories of haematological or non-haematological adverse events; however, the analysis of individual types of adverse events was limited due to the availability of eligible studies, resulting in wide confidence intervals and low statistical power. Our ability to carry out further analysis on 89 adverse events was not possible due to the limited availability of studies.

Our primary findings support the general notion that muscle mass is a prognostic factor in the general oncology setting [9]; yet some of our findings disagree with similar systematic reviews and meta-analyses [16, 17]. Rizzo et al. [17] found that the association between LSMM and AEs is uncertain in patients with pancreatic cancer, whereas our subgroup meta-analysis of pancreatic cancer revealed evidence of a higher risk of AEs in patients with LSMM. However, in the Rizzo study [17], the data analysis was based on the vote counting of studies with statistically significant findings. Such approach is generally discouraged and may be misleading as it ignores the magnitude of the effect estimate and the variance of individual studies [25]. In another systematic review [16], Guo et al. reported a higher risk of AEs in patients with hepatocellular cancer; in contrast, our subgroup meta-analysis revealed no evidence of such an association. The difference between our study and Guo et al. may be related to the outcome eligibility criteria. The Guo study [16] merged grades 3 and 4 events, dose-limiting events and serious events, which resulted in a higher number of eligible studies. In contrast, given the potential distinct clinical implications of grades 3 and 4 AEs and serious AEs, we strictly separated these types of events in our analyses.

The completeness of the available evidence in this review was limited. The majority of eligible studies included patients undergoing chemotherapy, leaving a significant gap in our understanding of the association between LSMM and other therapeutic regimens. The lack of data pertaining to these specific treatment modalities indicates a notable uncertainty in the broader applicability of LSMM in the context of different therapeutic approaches. Further, most of the meta-analyses on individual types of adverse events had small sample sizes and were likely underpowered, leading to imprecise estimates of effect and making it difficult to detect meaningful associations.

Overall, the assessment of the risk of bias in this study reveals a very high level of uncertainty in the reported findings. The most prominent contributor to this high risk of bias is the lack of statistical adjustment for confounding variables, such as sex, age, cancer grade/stage, comorbidities, socioeconomic status and treatment type, in the included studies. The absence of such adjustments can make it challenging to differentiate between the true effect of LSMM and the influence of other factors that might confound this relationship. Compounding this issue, the absence of pre-registered study protocols and the unavailability of statistical analysis plans raise concerns about the potential for data-driven decisions, such as choice of LSMM threshold and merging of severities or types of AEs. In addition, the retrospective nature of the included studies adds uncertainty, as the quality and completeness of the data collected cannot be guaranteed.

Our analysis revealed a limited number of prospective studies, specifically only three, in the eligible body of literature. To advance our understanding of the temporal relationship between LSMM and the risk of grades 3 and 4 adverse events and the discontinuation of systemic treatment, future research opportunities should prioritise prospective studies that not only delve into this relationship but also rigorously control for important confounding variables, such as sex, age, cancer grade/stage, comorbidities, socioeconomic status, and treatment type.

Building upon the insights generated from our review, a promising area for future research includes the evaluation of interventions aimed at addressing LSMM, such as structured exercise interventions [79], tailored nutritional interventions [80] and pharmacological approaches, such as myostatin/ActR2 signalling inhibitors, exercise mimetics and anabolic hormones [81]. These research opportunities have the potential to not just improve our comprehension of how LSMM affects systemic treatment results but also to offer valuable insights for shaping the standard of care and enhancing treatment protocols.

Limitations of this study should be considered in the interpretation of our findings. Although we preregistered our study, the specific methods of data synthesis were not specified in detail. In addition, we added treatment discontinuation as a primary outcome after the preregistration of our protocol.

In conclusion, our systematic review and meta-analysis suggest that LSMM in patients with upper GI cancer is associated with a higher risk of grades 3 and 4 adverse events and the discontinuation of systemic cancer treatment. In addition, we found that LSMM was associated with some types of adverse events, such as fatigue and febrile neutropenia. The interpretation of our findings should take into account the high risk of bias primarily due to potential confounding factors, and the limited sample sizes within specific analyses included in our study. Our study warrants further evaluation of the association between LSMM and treatment tolerability in confirmatory, prospective studies that adequately control for confounding variables.

Author Contributions

I. M. Lahart: conceptualization, data curation, methodology, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.