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# Low Skeletal Muscle Mass Predicts Relevant Outcomes in Palliative Urological Oncology: A Systematic Review and Meta-Analysis

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**Keywords**
Meta-analysis · Systematic review · Sarcopenia · Low skeletal muscle mass

**Abstract**
***Introduction:*** Low skeletal muscle mass (LSMM) can be assessed by cross-sectional imaging. LSMM is associated with several clinically relevant factors in various disorders with predictive and prognostic implications. ***Methods:*** Our aim was to establish the effect of computed tomography (CT)-defined LSMM on mortality in renal cell cancer (RCC) and urothelial carcinoma (UC) undergoing palliative treatment. The MEDLINE library, Cochrane, and SCOPUS databases were screened for the associations between CT-defined LSMM up to May 2022. In total, 11 studies were suitable for the analysis. ***Results:*** The included studies comprised 481 patients with RCC and 394 patients with UC. The pooled hazard ratio for the association between LSMM and overall survival was 1.64 (95% CI: 0.90–2.99), $p = 0.10$ in univariable analysis and 1.55 (95% CI: 0.91–2.63), $p = 0.10$ in multivariable analysis for RCC. For UC, the pooled hazard ratio was 2.75 (95% CI: 1.77–4.28), $p < 0.00001$ in univariable, and 2.77 (95% CI: 1.91–4.02), $p < 0.00001$ in multivariable analysis. For progression-free survival, it was 2.02 (95% CI: 1.24–3.27), $p = 0.004$ for RCC and 2.43 (95% CI: 1.59–3.74), $p < 0.0001$ for UC (univariable analysis). ***Conclusions:*** CT-defined LSMM predicts OS and PFS in RCC and UC in the palliative setting. The effect was higher in UC. Therefore, LSMM assessment should be included as a relevant prognostic biomarker in clinical routine.



## Introduction

Sarcopenia is a condition of muscle loss and low muscle function [1–3]. It can be defined by computed tomography (CT) as low skeletal muscle mass (LSMM) [3–5]. LSMM can be caused by aging or secondary due to diseases, malnutrition, and inactivity.

The frequency of LSMM increases with age, ranging from 5 to 13% in the general population and over 50% of patients over 80 years of age [6]. LSMM is especially useful for prognosis stratification and treatment prediction in oncologic patients [7]. In clinical practice, CT is usu-

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ally employed to quantify muscle areas and provide reliable data of LSMM [3–5].

Notably, LSMM can be estimated as a by-product of CT images as oncological patients are routinely scanned for staging purposes. One axial CT slice of the L3 intervertebral height is employed to quantify the muscle area of the paraspinal, abdominal wall, and psoas muscle. Then, the skeletal muscle index (SMI) is calculated by dividing the muscle mass by the square body height [3–5].

Nowadays, a semiautomatically approach is preferred for LSMM measurement. It employs defined Hounsfield-units to measure the amount of muscle and fat area of the CT slide.

Renal cell carcinoma (RCC) is the ninth most common cancer worldwide [8]. The median progression-free survival (PFS) in patients with metastatic disease is about 6 months, with a median overall survival (OS) of 12–16 months [8]. The treatment of RCC and urothelial carcinoma (UC) has changed significantly over the last years with the advent of targeted therapies such as tyrosine kinase inhibitors and immunotherapies [9, 10]. There were already some promising reports regarding sarcopenia assessment in patients with RCC, which could show that patients with sarcopenia have worse outcome compared to non-sarcopenic patients [11, 12].

Similar results have been reported for UCs for the prognostic relevance of LSMM in the palliative setting [9]. Yet, despite the promising nature of these preliminary reports, these are predominantly based on retrospective single-center studies and reliable data are still missing to this date. Therefore, the purpose of the present systematic review and meta-analysis was to assess associations between LSMM and unfavorable outcomes in RCC and urothelial cancer patients in advanced tumor stages.

## Materials and Methods

*Search Strategy*

The MEDLINE library, Cochrane, and SCOPUS databases were screened for LSMM assessment in RCC and UC patients up to May 2022. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the analysis [13]. The paper acquisition is summarized in Figure 1.

The following search words were used: "renal cell cancer" OR "renal cell carcinoma" OR "urothelial carcinoma" OR "urothelial cancer" AND "sarcopenia" OR "low skeletal muscle mass" OR "muscle mass" OR "body composition." In total, 11 studies were suitable for the analysis and were included into the present study [14–24]. The primary aims of the meta-analysis and systematic review were the influences of LSMM on overall survival, progression-free survival measured as hazard ratios, and odds ratios including 95% confidence intervals.

*Inclusion and Exclusion Criteria*

Inclusion criteria were (1) histological proven RCC/UC, (2) LSMM/sarcopenia defined by cross-sectional imaging, and (3) reported odds ratio or hazard ratio with confidence interval (CI). Exclusion criteria were (1) systematic reviews, (2) case reports, (3) non-English language, and (4) sarcopenia/LSMM identified on other modalities than CT and or MRI.

*Data Extraction*

Data extraction was performed by H.-J.M. followed by an independent evaluation of the extractions for correctness (A.S.). For each study, details regarding study design, year of publication, country of origin, patient number, patient characteristics (age and sex), diagnosis, form of treatment, LSMM definition and prevalence, muscle mass evaluation methods, threshold values, overall survival, progression free survival, and adjustment factors were extracted.

*Quality Assessment*

The quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS) [25]. Study quality assessment was conducted by two authors (H.-J.M., A.S.) and mainly included the selection of cases, comparability of the cohort, and outcome assessment of exposure to risks. A score of 0–9 was assigned to each study, and a study with a score ≥6 was considered to be of high quality.

*Data Analysis*

The meta-analysis was performed using RevMan 5.4 (2020; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index $I^2$ [26, 27]. DerSimonian and Laird random-effect models with inverse variance weights were performed without any further correction [28].

## Results

*Quality of the Included Studies*

Tables 1 and 2 give an overview of the included studies. All studies were of retrospective design. The overall risk of bias can be considered as low, as indicated by the high NOS values throughout the studies (Table 3). Differences between the LSMM definition and measurement can also cause some bias.

*Patients and Assessment of LSMM*

The 11 included studies comprised 481 patients with RCC and 394 patients with UC. There were 658 men (75.2%) and 217 women (24.8%), with a mean age of 66.2 years ranging from 59.5 to 71 years.

In all studies, the tumors were proven by histopathological investigations. Seven studies (63.6%) were performed in Asia, and two studies, respectively, (18.2%) were performed in North America and Europe.

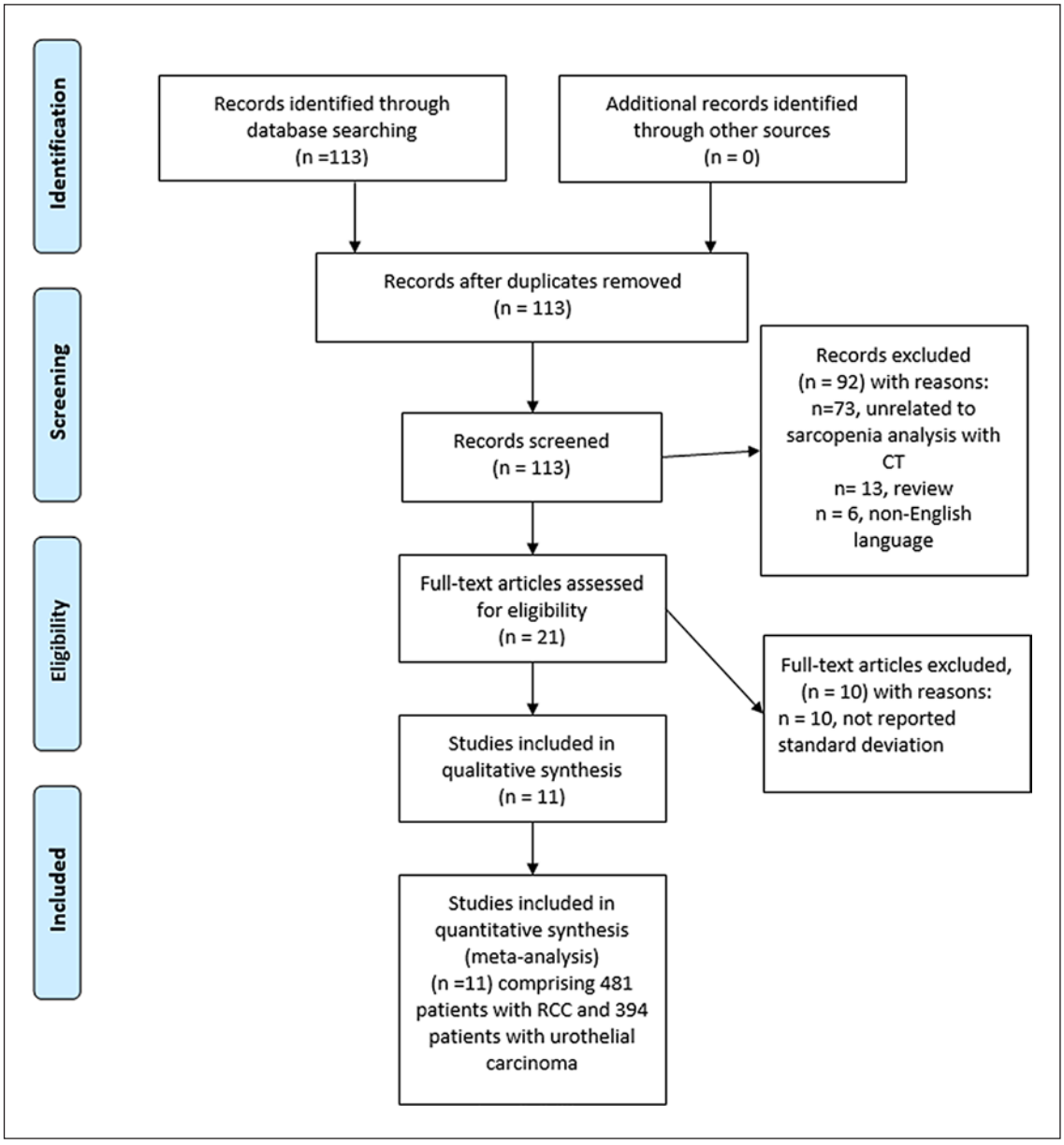


**Fig. 1.** PRISMA flow chart provides an overview of the paper acquisition. Overall, 11 studies including 481 patients with RCC and 394 patients with urothelial carcinoma were suitable for the analysis.

The SMI on the level of L3 was used in 9 studies (81.8%), and in two studies, the psoas muscle index was measured (18.2%). LSMM was diagnosed in 274 (56.9%) patients with RCC and in 149 patients (55.8%) with urothelial cancer.

*RCC*

Influence of LSMM on Overall Survival

For the analysis of associations between LSMM and overall survival (OS) (univariable analysis) 5 studies with 453 patients were suitable. The pooled hazard ratio was 1.64 (95% CI: 0.90–2.99), $p = 0.10$ (Fig. 2a). For the multivariable analysis, overall, 3 studies with 273 patients were suitable. The pooled hazard ratio was 1.55 (95% CI: 0.91–2.63), $p = 0.10$ (Fig. 2b).

Next, a sub-analysis was performed for patients only undergoing TKI. 3 studies with 250 patients, LSMM, and OS were analyzed. The pooled hazard ratio was 2.23 (95% CI: 1.08–4.58), $p = 0.03$ in the univariable analysis (Fig. 2c).

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**Table 1.** Overview of the included studies with RCC

| Authors | Country | Study design | Included patients, *n* | Mean age, years | Gender, female, *n* (%) | Treatment | Sarcopenia definition | Threshold values | Hounsfield units | LSMM frequency, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Auclin et al., (2017) [14] | France | Retrospective | 124 | 60.1 | 28 (22.6) | Everolimus | SMI, L3 | 55.4 $cm^2/m^2$ for men and 38.9 $cm^2/m^2$ for women | –25–130 | 112 (90.3) |
| Buchler et al., (2020) [15] | Czech Republic | Retrospective | 28 | 65.5 | 5 (17.9) | Cabozantinib | SMI, L3 | 55 $cm^2/m^2$ for men, 39 $cm^2/mm^2$ for women (Fearon) | Not stated | 13 (44.8) |
| Gu.et al., (2017) [16] | China | Retrospective analysis of RCT data | 101 | 59.5 | 36 (35.6) | *N* = 30 Sunitinib, *n* = 45 Sorafenib, *n* = 26 other therapy | SMI, L3 | 40.8 $cm^2/m^2$ for men, 34.9 $cm^2/m^2$ for women | –29–150 HU | 36 (35.6) |
| Ishihara et al., (2016) [17] | Japan | Retrospective | 71 | 64 | 21 (29.6) | Sunitinib | SMI, L3 | 43 $cm^2/m^2$ for men and 41 $cm^2/m^2$ for women under BMI of 25, 53 $cm^2/m^2$ for males with BMI over 25 (Martin) | –29–150 HU | 45 (63.4) |
| Lee et al., (2021) [18] | South Korea | Retrospective | 78 | 61.6 | 19 (24.4) | Sunitinib | SMI, L3 | 43 $cm^2/m^2$ for men and 41 $cm^2/m^2$ for women under BMI of 25, 53 $cm^2/m^2$ for males with BMI over 25 (Martin) | –29–150 HU | 41 (52.5) |
| Martini et al., (2021) [19] | USA | Retrospective | 79 | 61 | 19 (24.1) | Anti PD-1 monotherapy in most cases (59.5) | SMI, L3 | Not clearly stated | –29–150 HU | 27 (34.2) |

CT, computed tomography; SMI, skeletal muscle index; RCC, renal cell carcinoma; RCT, randomized controlled trial.

**Table 2.** Overview of the included studies with urothelial carcinoma

| Authors | Country | Study design | Included patients, *n* | Mean age, years | Gender, female, *n* (%) | Treatment | Sarcopenia definition | Threshold values | Hounsfield units | LSMM frequency, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Fukushima et al., (2015) [20] | Japan | Retrospective | 88 | 68 | 28 (31.8) | First line chemotherapy | SMI, L3 | 43 $cm^2/m^2$ for men and 41 $cm^2/m^2$ for women under BMI of 25, 53 $cm^2/m^2$ for males with BMI over 25 (Martin) | –29 to 150 | 53 (60) |
| Fukushima et al., (2020) [21] | Japan | Retrospective | 28 | 74 | 9 (32.1) | Pembrolizomab | SMI, L3 | 43 $cm^2/m^2$ for men and 41 $cm^2/m^2$ for women under BMI of 25, 53 $cm^2/m^2$ for males with BMI over 25 (Martin) | –29 to 150 | 19 (65.5) |
| Martini et al., (2021) [22] | USA | Retrospective | 70 | 69.5 | 21 (30) | Pembrolizumab in most cases (63%) | SMI, L3 | Dichotonized | –29 to 150 HU | 23 (32.8) |
| Shimizu et al., (2020) [23] | Japan | Retrospective | 27 | 73 | 4 (14.8) | Pembrolizumab | PMI | ≤6.36 $cm^2/m^2$ for men and ≤3.92 $cm^2/m^2$ for women | Not stated | 15 (56) |
| Yumioka et al., (2020) [24] | Japan | Retrospective | 54 | 71.6 | 25 (46.3) | First line chemotherapy | PMI | 4.57 $cm^2/m^2$ for men and 3.35 $cm^2/m^2$ for women | Not stated | 39 (48.9) |

CT, computed tomography; SMI, skeletal muscle index; PMI, psoas muscle index.

**Table 3.** The quality of the studies defined by NOS scale

| Study | Is the case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate | Qualityscore |
|---|---|---|---|---|---|---|---|---|---|
| Auclin et al., (2017) [14] | * | * | * | * | * | * | * | * | 9 |
| Buchler et al., (2020) [15] | * | * | * | | | * | * | * | 6 |
| Fukushima et al., (2015) [20] | * | * | * | | * | * | * | * | 7 |
| Fukushima et al., (2020) [21] | * | * | * | * | * | * | * | * | 8 |
| Gu et al., (2017) [16] | * | * | * | * | * | * | * | * | 8 |
| Ishihara et al., (2016) [17] | * | * | * | * | * | * | * | * | 8 |
| Lee et al., (2021) [18] | * | * | | * | * | * | * | * | 7 |
| Martini et al., (2021) [19] | * | * | * | * | * | * | * | * | 8 |
| Martini et al., (2021) [22] | * | * | * | * | * | * | * | * | 8 |
| Shimizu et al., (2020) [23] | * | * | * | | * | * | * | * | 7 |
| Yumioka et al., (2020) [24] | * | * | * | | * | * | * | * | 7 |

NOS, Newcastle-Ottawa Scale.

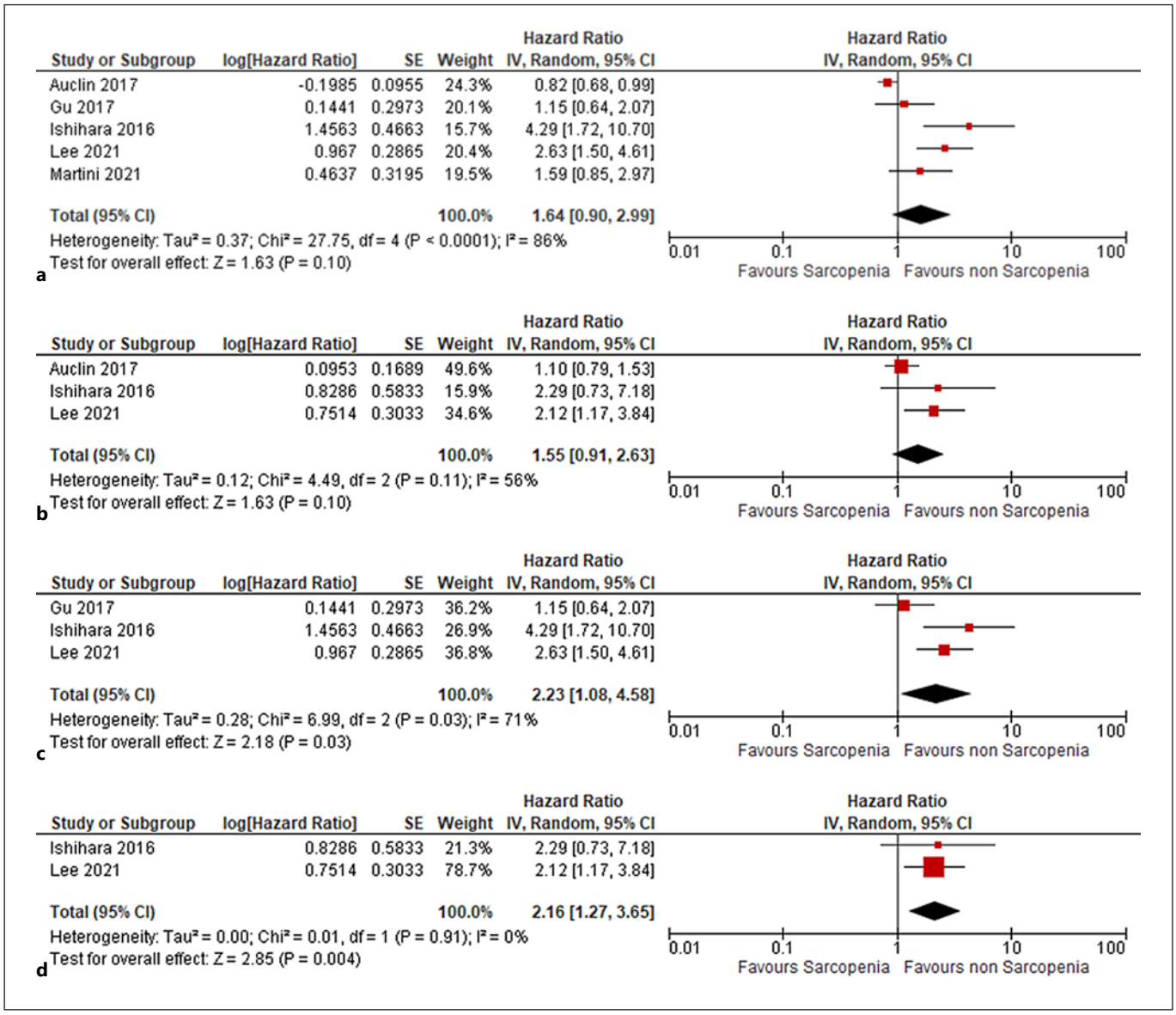


**Fig. 2.** Influence of LSMM on overall survival in RCC. **a** Univariable analysis. **b** Multivariable analysis. **c** Influence of LSMM on overall survival in RCC undergoing TKI treatment (univariable analysis). **d** Influence of LSMM on overall survival in RCC undergoing TKI treatment (multivariable analysis).

For multivariable analysis, 2 studies with 149 patients were used. The pooled hazard ratio was 2.16 (95% CI: 1.27–3.65), $p = 0.004$ (Fig. 2d).

Influence of LSMM on Progression-Free Survival

For the univariable analysis between LSMM and PFS, 4 studies with 329 patients were suitable. The pooled hazard ratio was 2.02 (95% CI: 1.24–3.27), $p = 0.004$ (Fig. 3a).

For the multivariable analysis overall, 3 studies with 177 patients were used. The pooled hazard ratio was 2.52 (95% CI: 1.62–3.93), $p < 0.0001$ (Fig. 3b).

Next, a sub-analysis was performed for patients only undergoing TKI treatment. 3 studies with 250 patients, LSMM, and PFS were analyzed. The pooled hazard ratio was 2.37 (95% CI: 1.36–4.13), $p = 0.002$ in the univariable analysis (Fig. 3c). For multivariable analysis, 3 studies with 177 patients were analyzed. The pooled hazard ratio was 2.52 (95% CI: 1.62–3.93), $p < 0.0001$ (Fig. 3d).

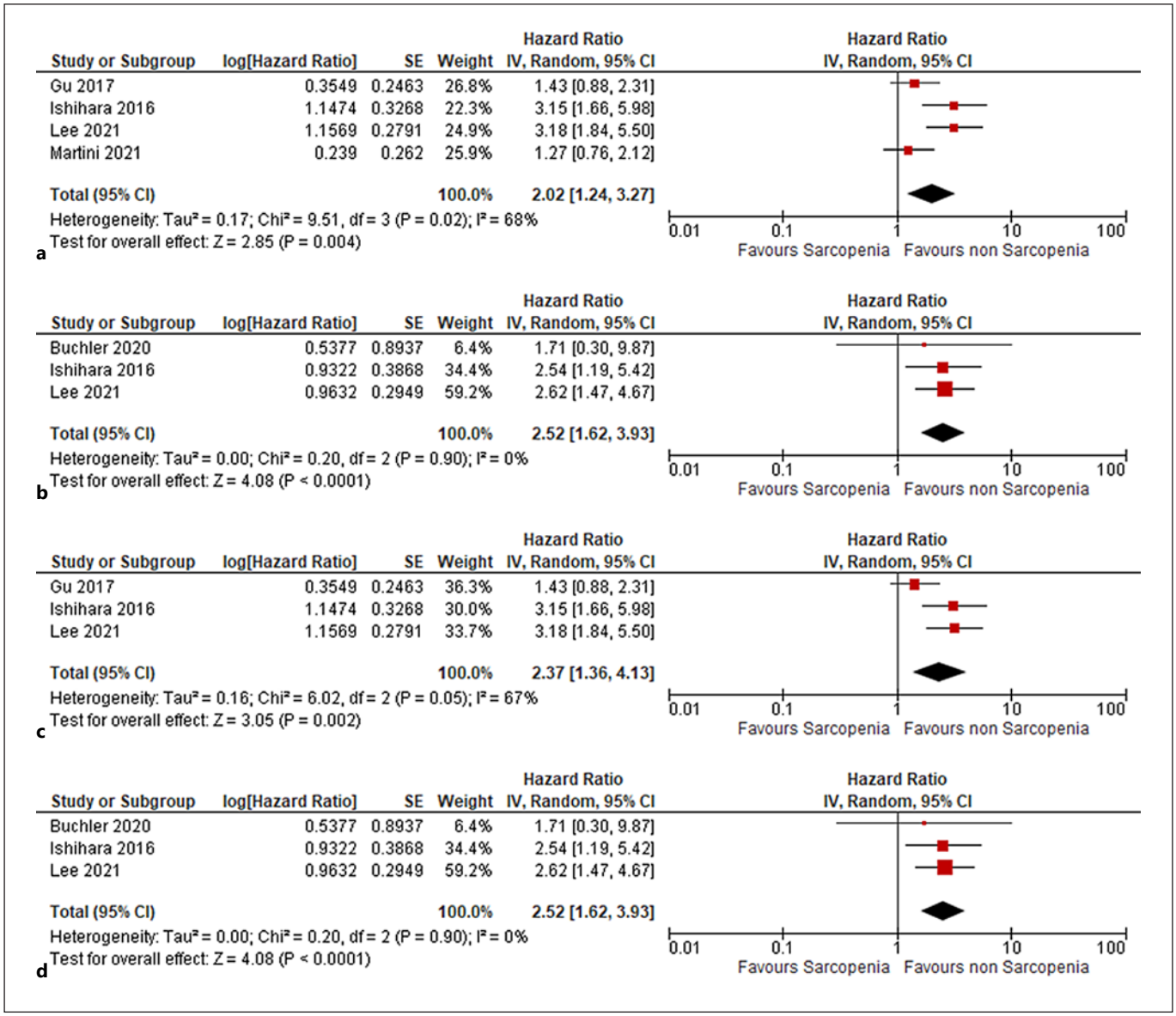


**Fig. 3.** Associations between LSMM and progression-free survival in RCC. **a** Univariable analysis **b** Multivariable analysis. **c** Influence of LSMM on progression free survival in RCC undergoing TKI treatment (univariable analysis). **d** Influence of LSMM on progression free survival in RCC undergoing TKI treatment (multivariable analysis).

*Urothelial Carcinoma*

Influence of LSMM on Overall Survival

For the analysis of associations between LSMM and OS (univariable analysis), 3 studies with 150 patients were suitable. The pooled hazard ratio was 2.75 (95% CI: 1.77–4.28), $p < 0.00001$ (Fig. 4a). For the multivariable analysis, overall, 4 studies with 232 patients were suitable. The pooled hazard ratio was 2.77 (95% CI: 1.91–4.02), $p < 0.00001$ (Fig. 4b). In a univariable sub-analysis for patients undergoing immunotherapy (2 studies with 97 patients), the pooled hazard ratio was 2.79 (95% CI: 1.64–4.74), $p = 0.0001$ (Fig. 4c) and for patients undergoing chemotherapy (3 studies with 205 patients), the pooled hazard ratio was 2.67 (95% CI: 1.80–3.95), $p < 0.00001$ (Fig. 4d).

Influence of LSMM on Progression-Free Survival

For the univariable analysis between LSMM and PFS, 3 studies with 125 patients were suitable. The pooled hazard ratio was 2.43 (95% CI: 1.59–3.74), $p < 0.0001$ (Fig. 5).

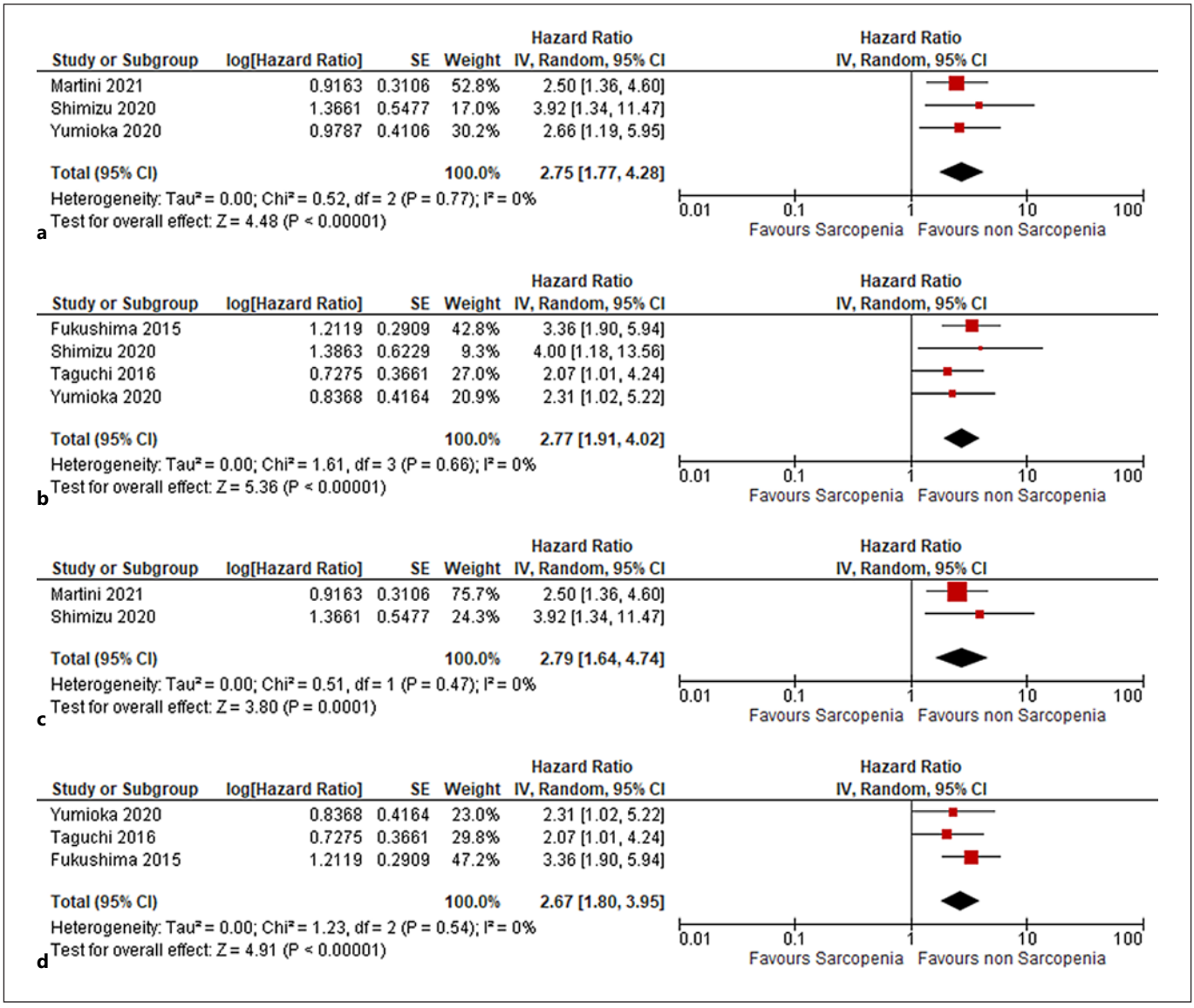


**Fig. 4.** Influence of LSMM on overall survival in urothelial carcinoma. **a** Univariable analysis. **b** Multivariable analysis. **c** Influence of LSMM on overall survival in urothelial carcinoma treated with immunotherapy (univariable analysis). **d** Effect of LSMM on overall survival in urothelial carcinoma undergoing chemotherapy (univariable analysis).

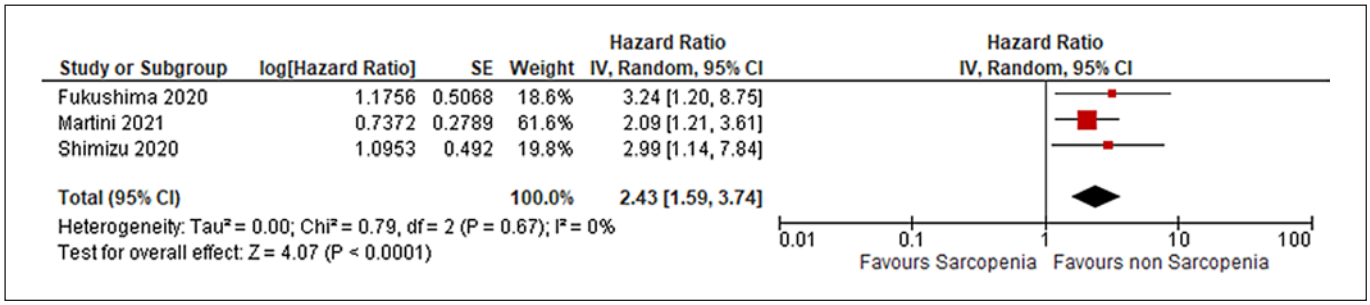


**Fig. 5.** Effect of LSMM on progression-free survival in urothelial carcinoma (univariable analysis).

## Discussion

This meta-analysis elucidated the associations between LSMM derived from CT images and overall survival and progression-free survival in RCC and UC patients. As shown, there were strong associations in univariable as well as in multivariable analyses, which was shown for conventional chemotherapy, TKI therapy, as well as immunotherapy. The effect of LSMM on OS was stronger in UC compared to RCC and seems to be of greater importance for TKI and immunotherapy than conventional chemotherapy.

Notably, LSMM has a high frequency in RCC and UC alike. These findings highlight the utter importance of the assessment of body composition in patients with RCC to provide a novel biomarker in clinical routine.

The topic of body composition is an important field of recent research [1–7]. Promising prognostic implications of LSMM assessment were shown throughout medicine, especially in the field of oncology [1–7, 29]. LSMM assessment is a by-product of cross-sectional imaging and can easily be calculated without additional scan time or cost [4, 5].

It can be presumed that especially elderly patients with primary sarcopenia are more at risk for associated muscle wasting than patients without. LSMM may be associated with an increased risk of toxicity of chemotherapeutic drugs due to the administration of a fixed drug dose, resulting in a higher dose per kg lean tissue, which was also shown for several tumor entities [30].

Considerably, there are also great variations between studies in regard to the estimation of different body composition parameters [5]. One of the most important ones is SMI. This index uses the muscle area on the L3 level and the body height to perform a reliable estimation of LSMM. Different threshold values were proposed throughout the literature, as was also identified in the investigated studies [3, 31, 32]. This can result in considerably heterogeneity throughout the studies.

Most commonly, a semiautomatically measurement was performed utilizing Hounsfield unit thresholds to quantify the muscle and fat areas. One can assume that the semiautomatically approach might be more reliable and have less interreader variability.

Moreover, there might be differences caused by the different patient samples and treatments. We also performed sub-analyses to account for different tumor stages and treatment choices, as it was possible. The patient samples might also have slightly different associated risk factors and co-morbidities, which should be considered with care when discussing the present results.

For RCC, it is known that obesity defined by a BMI over 25 is a protective factor with a longer median OS compared with underweight or normal patients (25.6 vs. 17.1 months) [22, 33]. This can be one link between the identified associations between LSMM and mortality in the present analysis.

Already established prognostic factors in RCC are pathologic stage, lymph node status, and histologic grade [34]. For metastasized UC, the presence of liver metastasis, poor performance status, high C-reactive protein, and high neutrophil-lymphocyte ratio were independent prognostic factors under immunotherapy [35]. It would be interesting to study whether LSMM could be added as another independent prognostic factor.

There is an ongoing trend to combine different clinical factors into a model to accurately predict survival. Clearly, better results can be expected when clinical, pathological, and serum markers can provide complementary information. One important next goal is to include body composition derived from CT images into clinical prognostic scores, which should be addressed by future studies. The present analysis gives insight that LSMM assessment is clinically important in RCC and UC patients undergoing chemotherapy, TKI treatment and immunotherapy.

The importance of muscle mass quantification based on imaging has a great clinical relevance. As such, one important point for the diagnosis of malnutrition is the LSMM assessment with the proposed threshold values [35, 36]. In clinical routine, early diagnosis of malnutrition could provide better nutritional support for advanced cancer patients as part of multimodal therapeutic approaches to maintain or build skeletal muscle mass [35, 36]. The present results might indicate that LSMM assessment is of greater importance in patients undergoing TKI and immunotherapy. Yet, there are no systematic data before elucidated distinctive differences of LSMM in patients undergoing different systematic treatment regimes. Contrary, there is good data of the importance of LSMM assessment in patients undergoing surgical treatment for RCC and UC alike, as LSMM is a risk factor for postoperative complications.

The present meta-analysis has several limitations to address. First, it is comprised of published studies with inhomogeneities between studies in regard of measurements and different patient samples. Sarcopenia definitions were different according to different published threshold values. However, most studies used common investigated sarcopenia assessments. Second, there is the restriction to English language. However, no substantial

publication bias was identified for the present analysis. Third, defined clinical outcomes were slightly different between studies, resulting in possible bias.

## Conclusion

CT-defined LSMM has a high prevalence in patients with RCC and UCs in the palliative setting and influences OS and PFS. The effect was higher in urothelial carcinomas and in patients undergoing treatment with TKI and immunotherapy. Therefore, LSMM assessment should be included as a relevant prognostic biomarker into clinical routine in palliative urological oncology.

## Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published data.

## Conflict of Interest Statement

The authors have no conflict of interests to declare.


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No funding was received for this work.


## Author Contributions

Hans-Jonas Meyer: data analysis and manuscript writing. Alexey Surov: data analysis and manuscript writing/editing. Andreas Wienke: data analysis, statistical analysis, and manuscript editing. Marina Zamsheva: data collection and statistical analysis.

## Data Availability Statement

Data generated and used for the study are not publicly available because it contains information that may compromise the privacy of our study participants.

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