Pre-treatment Sarcopenic Assessments as a Prognostic Factor for Gynaecology Cancer Outcomes: Systematic Review and Meta-Analysis

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Abstract

Introduction: Gynaecology cancers, including ovarian (OC), endometrial (EC), and cervical (CC), are prevalent with high mortality. Sarcopenia is found in 38.7% of cancer patients, adversely affecting prognosis. Computed tomography (CT) is performed routinely in oncology, yet CT assessments of sarcopenia are not commonly used to measure prognosis. This systematic review and meta-analysis aimed to evaluate the prognostic potential of pre-treatment sarcopenia assessments on overall survival (OS) and progression free survival (PFS) in gynaecology cancer.

Methodology: Four electronic databases were systematically searched from 2000 to May 2020 in English: Ovid Medline, EMBASE, Web of Science, and CINAHL plus. Titles and abstracts were screened, eligible full-texts were reviewed, and data from included studies was extracted. Meta-analyses were conducted on homogenous survival data, heterogenous data were narratively reported.

Results: The initial search yielded 767 results; 27 studies were included in the systematic review (n=4286), all published between 2015-2020. Meta-analysis of unadjusted results revealed a negative effect of pre-treatment sarcopenia on OS in OC (HR:1.40, 1.20-1.64, P<0.0001) (n=10), EC (HR:1.42, 0.97-2.10, P=0.07) (n=4) and CC (HR:1.10, 0.93-1.31, P=0.28) (n=5), and a negative effect on PFS in OC (HR:1.28, 1.11-1.46, P=0.0005) (n=8), EC (HR:1.51, 1.03-2.20, P=0.03) (n=2) and CC (HR:1.14, 0.85-1.53, P=0.37) (n=2). Longitudinal analysis indicated negative effects of muscle loss on survival. Overall, there was a high risk of bias.

Conclusion: Pre-treatment sarcopenia negatively affected survival in gynaecology cancers. Incorporating such assessments into cancer management may be beneficial. Heterogeneity in sarcopenia assessments makes data interpretation challenging. Further research in prospective studies is required.

Introduction

Cancer is responsible for one in eight deaths worldwide (1). Ovarian cancer (OC) has the highest mortality amongst gynaecology malignancies (2). Eighty percent of cases are diagnosed at advanced stage (3), increasing the likelihood of malnutrition and bowel obstructions, and reducing overall survival (OS) (4).

Meanwhile, cervical cancer (CC) is the fourth most common female cancer in terms of incidence and mortality (5). About 13% of patients are diagnosed with advanced disease; associated with poor prognosis (6).

Endometrial cancer (EC) is the most common gynaecological cancer in high-income countries (7,8). With 5-20% of patients asymptomatic, this increases the chance of later diagnosis (9) and lower 5-year survival rates (15-58%) (10).

Malnutrition is a state of nutritional status in which a deficiency, excess, or imbalance of energy and other nutrients cause measurable adverse effects (11). Cachexia is disease-related malnutrition resulting from the systemic inflammation that occurs in response to an underlying disease, like cancer (12). Over 50% of cancer patients experience cachexia (13), and nearly one third of cancer deaths are due to cachexia (14).

Malnutrition is prevalent in gynaecology malignancies (15, 16) and is associated with increased length of hospital stay (LOS), complications, and morbidities (4, 17, 18). At least 20% of gynaecology cancer deaths may be attributable to malnutrition rather than the disease (19). The challenge with malnutrition in oncology is the lack of standard methods for timely detection and treatment (12).

Nutritional deterioration in cancer is multifactorial (20). Metabolic changes, induced directly from the tumour and indirectly from the cancer treatment, inhibit the utilisation of nutrients and accelerate nutritional decline (19, 21-23).

A key contributor to the negative outcomes of cancer-associated malnutrition is reduction in muscle mass (24). Sarcopenia is a muscular disorder characterised by the progressive loss of muscle mass, strength, and function. Sarcopenia is associated with poor treatment tolerance, increased complications, worse quality of life (QoL), and prognosis (25-27).

Cancer is a major cause of sarcopenia, with 20-70% of cancer patients described as sarcopenic (20). A systematic review of 35 cancer studies identified 38.6% of patients with pre-treatment sarcopenia (28). For OC, Aust et al. (29) reported 39% and Huang et al. (30) found 33.8% had pre-treatment sarcopenia. Meanwhile, Ganju et al. (31) found 54% of EC patients, and Lee et al. (32) reported 51% of CC patients had pre-treatment sarcopenia. Evidently, sarcopenia is prevalent in gynaecology malignancies.

The test used to identify sarcopenia depends on patient mobility and accessibility of resources. CT images of the third lumbar vertebra (L3) are the standard for measuring body composition and identifying sarcopenia (33). The skeletal muscle index (SMI), skeletal muscle density (SMD), and muscle attenuation (MA) are calculated from CT and commonly used to identify sarcopenia (31, 34). Psoas muscle measurements are also used, though this is controversial (33).

To date, there are no universally defined cut-off points for sarcopenia measured by CT, despite it being a well-recognised approach (35). Prado et al. (36) was the first to establish sex-specific cut-offs for SMI by CT, now commonly used in sarcopenia studies.

Using sarcopenia assessments to predict cancer prognosis is fairly novel, yet holds great potential. A systematic review of 37 cancer studies found low SMI was associated with worse outcomes (37). Additionally, a systematic review of 35 cancer studies established sarcopenia was an independent predictor of postoperative complications, chemotherapy-induced toxicity, and poor OS (28).

In light of this, the main objective of this systematic review and meta-analysis is to identify all studies that measure pre-treatment sarcopenia by CT in patients with gynaecology malignancies, and its association with OS and PFS. Gynaecology malignancies encompass some of the most common and debilitating female cancers. Malnutrition and sarcopenia are prevalent in gynaecology cancer and have detrimental impacts on survival. Moreover, CT scans are routine in diagnosis, staging, and monitoring of gynaecology cancer, so these

could be used to concurrently assess body composition without placing additional burden on patients or adding to care costs (33). The aim is therefore to highlight the importance of incorporating nutritional assessments, including sarcopenia assessments, into gynaecology cancer management, to identify malnutrition as early as possible.

Methods

Eligibility Criteria

The PICOTS (population, index, comparator, outcome(s), timing, setting) system was used to identify the inclusion/exclusion criteria of this review (Appendix 1) (38). Observational studies of ovarian (OC), cervical (CC), or endometrial cancer (EC) patients (primary or secondary) undergoing treatment were included. The prognostic factor of interest was pre-treatment sarcopenia assessments (skeletal muscle or psoas muscle measurements) and the primary outcome was overall survival (OS). Studies published only as an abstract or not available in English were excluded. Studies must not have altered treatment based on sarcopenia assessment results.

Search strategy

A scoping review was carried out to identify the available literature and finalise the research question. A comprehensive search strategy was developed for the systematic search with three key components; sarcopenia, gynaecology cancer, prognosis (Appendix 2). The search was limited to identify articles studying adults and published from 1st of January 2000 until 31st of May 2020. The search was conducted using four electronic databases; Ovid Medline, EMBASE, Web of Science and CINAHL plus. Additional references were identified through hand searching.

Study Selection

After the search was conducted and references collected, duplicates were removed. Screening of titles and abstracts was carried to remove studies outside the inclusion criteria. Full-text screening was carried out to remove studies where the abstract was not sufficient to permit inclusion (Figure 1). This was done independently by the first author, then the fourth author reviewed each step of the process.

Data Extraction

The first author extracted the following data from the included studies and collected it using Microsoft Excel (version 16.16.24):

- General information (first author, year of publication, type of study, location, duration of study, country, continent, sample size)
- Patient characteristics (age, cancer site, cancer stage, treatment undertaken, BMI)
- Pre-treatment sarcopenia assessment (timing, imaging method, muscle measurement, cut-off, prevalence of sarcopenia)
- Duration of follow up
- Outcomes (definitions and methods of measurement)
  - Overall survival
  - Progression free survival
  - 1/3/5-year survival estimates
  - Post-treatment complications
  - Length of stay
- Longitudinal analysis
  - Change in sarcopenia and effect on survival outcomes

Statistical Analysis, Heterogeneity and Quality Assessment

Analysis was carried out by the first author. Microsoft Excel was used for descriptive statistics, and Review Manager 5 for meta-analysis. A generic inverse variance random-effects model was used to pool unadjusted hazard ratios (HR) for OS (overall survival) and PFS (progression free survival). Most studies provided this from cox-proportional regression analysis. Where studies did not publish the HR and standard error (SE), data from results reported in text, tables, and Kaplan-Meier (K-M) curves were retrieved, and an established

calculator based on statistical methods for recovering survival data was used (Appendix 3). It was intended to pool HRs from multivariable analysis, as adjusted results reveal the prognostic value of the factor independent of other prognostic factors (38). However, as it is recommended that adjusted results should only be used if very similar covariates have been adjusted for, multivariable analysis could not be used (Appendix 4).

Meta-analyses were conducted separately for each cancer with subgroup analysis of sarcopenia assessments. Sensitivity analyses were carried out to explore hypotheses, not to form definitive conclusions.

Statistical heterogeneity was quantified using the I^2 statistic (I^2 >50% = moderate heterogeneity; I2 >80% = considerable heterogeneity) (39). The quality of the studies (risk of bias) was assessed using the Quality of Prognostic Studies (QUIPS) tool (40).

Publication bias was assessed using funnel plots and Egger's and Begg's tests (78-80). A funnel plot was created where effect sizes were more than 10 (81). This is a scatter plot of the effect estimates from individual studies against a measurement of the study's sample size or precision. Resemblance of a symmetrical inverted funnel supports that findings are due to sampling variation alone; thus, absence of bias (81).

Results

Included Studies

The search yielded 767 results, reduced to 513 after duplicate removal. Overall, 27 studies were included (Figure 1).

Table 1 presents details of included studies (29-32, 35, 41-62). Studies were published between 2015-2020, with data collection between 2000-2017. Sample sizes ranged from 55 (60) to 323 patients (41). Studies comprised female patients aged 15-91.5 years with ovarian (OC), cervical (CC), or endometrial cancer (EC) from American, European and Asian cohorts. Follow up time ranged from 12 to 165 months.

Some studies by similar groups of authors partially used the same populations. To avoid duplication in meta-analysis, the study with the greatest number of participants was used for results reported in overlapping studies.

Patient Characteristics

A total of 4286 female patients with a mean age range of 50.5-65.9 years were included. Fourteen studies included only OC patients (8 endometrial ovarian cancer), six EC, and six CC. One study (55) included a combination of CC (55%), EC (26.8%), and OC (16.4%).

Sarcopenia Assessments

All studies used a CT scan at L3 or 4 to quantify skeletal or psoas muscle area, which were used to determine measurements for sarcopenia assessment. The majority of studies (n=23) used an automatic software and HU range of -29-150 (Appendix 5). All CT scans were carried out pre-treatment, though proximities to treatment varied.

This review revealed 12 types of muscle quantity and quality assessments, several studies used multiple measurements to assess sarcopenia.

Sarcopenia Cut-off Values

Several SMI (skeletal muscle index) and SMD (skeletal muscle density) cut-offs were derived from previously established cut-offs (36, 63-65). Others were self-determined by cohort tertiles or statistical methods (Appendix 6).

Pre-treatment Sarcopenia Prevalence

Nineteen studies reported the prevalence of sarcopenia by low SMI (mean: 38.3%, range: 11-66%) (Table 1, Appendix 7). Eight studies reported low SMD prevalence (mean: 39.3%, range: 21.1-80%). The prevalence of low PI (psoas muscle index) was reported in two studies (mean: 53.7%, range: 50-57.5%). The highest mean prevalence of sarcopenia by SMI and SMD were both found in EC (Appendix 7).

Survival Outcomes Measured

Overall survival (OS) was reported in 25 studies, two did not report OS but reported 1-year survival (1YS) (44, 56). Progression free survival (PFS) was reported in 17 studies, details of

the measurements grouped under PFS can be found in Appendix 8. Other survival outcomes measured included 3-year survival (3YS), 3-year PFS (3Y PFS), 5-year survival (5YS) and 5-year PFS (5Y PFS).

Quality Assessment of Included Studies

Overall, there was a high risk of bias for 3 out of the 5 categories according to the QUIPS tool (Appendix 9-10).

Univariable Overall Survival Results

Twenty studies reported unadjusted results for the effect of pre-treatment sarcopenia on the primary outcome OS (12 OC, five EC and five CC). For five studies, HRs and SEs were estimated from K-M results.

Nattenmuller et al. (55) included all three cancers, so, where results were only available for the whole cohort, these were reported narratively. Results published separately for the different cancers were extracted for meta-analysis.

Ataseven et al. (41) did not report recoverable survival data for SMI and OS, and Conrad et al. (43) did not report sufficient data for CMI (central muscle index) and OS, hence neither were included in meta-analysis. Muscle assessments analysed as continuous variables were not included in meta-analysis.

Gillen et al. (45) compared patients with and without chemotherapy, thus were excluded from meta-analysis. However, multivariable results adjusted for the treatment so were reported narratively.

After removal of duplicate data and exclusion of non-homogenous studies, 17 were included in meta-analysis (ten OC, four EC, five CC).

Ovarian Cancer

Meta-Analysis of Univariable Results

Pooled results of ten OC studies showed a statistically significant overall negative effect of pre-treatment sarcopenia on OS (HR:1.40, 1.20-1.64, P=<0.0001, I^2=55%) (Figure 2).

Subgroup analyses of sarcopenia assessments showed all subgroups, apart from one (IMAT), had a negative effect on OS. Sarcopenia by SMI was the largest subgroup (n=8), and exhibited a negative effect on OS (HR:1.28, 0.96-1.70, P=0.09, I^2=58%). The SMD subgroup showed a significant negative effect (HR:1.63, 1.26-2.10, P=0.0002, I^2=59%). Low PV (psoas volume) showed the largest negative effect, though one study was in this subgroup (HR:2.88, 1.30-6.41, P=0.009).

Sensitivity Analysis of Univariable Results

Sensitivity analysis showed a similar statistically significant negative effect of sarcopenia on OS in studies where sarcopenia assessments were reported <60 days before treatment (HR:1.36, 1.15-1.60, P=0.0002, I^2=53%) (Appendix 11). Analysis of studies on EOC patients also showed a statistically significant negative effect, though wider CI's suggest increased heterogeneity and less reliability (HR:1.61, 1.29-2.01, P<0.0001, I^2=61%) (Appendix 12).

Narrative Reporting of Univariable Results not Included in Meta-Analysis

Ataseven et al. (41) results revealed no significant difference between low SMI and non-sarcopenic patients (p>0.05). Further, Conrad et al. (43) reported low CMI patients had similar OS to non-sarcopenic.

Endometrial Cancer

Meta-Analysis of Univariable Results

Pooled results of four EC studies showed an overall negative effect of pre-treatment sarcopenia on OS (HR:1.42, 0.97-2.10, P=0.07, I^2=56%) (Figure 3). The point estimates were all relatively small, CI's fairly long, and statistical heterogeneity moderate, giving less confidence that these results reflected the true effect. Subgroup analysis showed lower heterogeneity between subgroups (I^2=44.5%), and all assessments had a negative effect apart from SMG (skeletal muscle gauge).

Sensitivity Analysis of Univariable Results

Sensitivity analysis of studies that reported sarcopenia assessments were taken <60 days pre-treatment resulted in a significant negative effect on OS with low heterogeneity (HR:1.63, 1.05-2.52, P=0.03, I^2=33%) (Appendix 13). The removal of one study (55) reduced I^2 by H20%, suggesting that study provided considerable heterogeneity.

Cervical Cancer

Meta-Analysis of Univariable Results

Pooled results of five CC studies produced a marginally negative effect of pre-treatment sarcopenia on OS (HR:1.10, 0.93-1.31, P=0.28, I^2=22%) (Figure 4). The I^2 suggests a low proportion of the variation in results were due to heterogeneity, which increases certainty. Four studies crossed the line of no effect, likely due to imprecision given the size of the CI's. Further, Nattenmuller et al. (55) was weighted 54.3% of analysis and was the only study with HR <1, largely influencing the summary estimate.

Subgroup analysis showed little heterogeneity between the sarcopenia assessments (I^2=13.7%). The largest negative effect was from low PI (HR:1.57, 0.74-3.30, P=0.24, I^2=56%), though the heterogeneity was moderate between the two studies.

Multivariable Overall Survival Results

Fourteen studies reported multivariable analysis for pre-treatment sarcopenia and OS. Results are reported narratively in Appendix 14-17.

Ovarian Cancer

Nine studies reported multivariable analysis for pre-treatment sarcopenia and OS (Appendix 14). Three studies found SMI was an independent predictor and five found SMD was an independent predictor. Though, references 30 and 46 contained some of the same population.

Endometrial Cancer

Four studies reported multivariable analysis for pre-treatment sarcopenia and OS (Appendix 15). One study found sarcopenia (low SMI and SMD combined) was an independent prognostic factor (31).

Ovarian, Endometrial, and Cervical Cancer

Nattenmuller et al. (55) found low SMI in OC, CC, and EC had a slight tendency towards worse OS in the first adjusted model, whilst a slight tendency towards better in the second. The CI's were tight, suggesting reliable results (Appendix 16).

Cervical Cancer

One study reported multivariable analysis and revealed low PI was an independent predictor for OS (Appendix 17).

Univariable Progression Free Survival Results

Fifteen studies reported univariate results for pre-treatment sarcopenia and PFS, and 12 were included in meta-analysis (eight OC, two EC, two CC). For four studies, HRs and SEs were estimated from K-M results.

Ovarian Cancer

Meta-Analysis of Univariable Results

Pooled results of eight OC studies showed a statistically significant negative effect of pre-treatment sarcopenia on PFS (HR:1.28, 1.11-1.46, P=0.0005, I^2=28%) (Figure 5). Low statistical heterogeneity was supported by the narrow and overlapping CI's, permitting confidence in results.

Subgroup analysis implied no statistical heterogeneity between sarcopenia assessments (I^2=0%). The SMI subgroup was the largest (n=7) and presented a statistically significant negative effect on PFS (HR:1.30, 1.03-1.64, P=0.03, I^2=46%). The largest HR, favouring lower PFS, was in the PV subgroup which contained one study (HR:2.00, 1.11-3.60, P=0.02).

Sensitivity Analysis of Univariable Results

Sensitivity analysis of EOC patients showed a similar pooled negative effect (HR:1.33, 1.15-1.54, P=0.0001, I^2=26%) (Appendix 18). Analysis of studies that reported sarcopenia assessments were carried out <60 days pre-treatment showed a similar negative effect (HR:1.24, 1.07-1.44, P=0.003, I^2=12%). Heterogeneity was lower, perhaps because few studies were included (Appendix 19).

Endometrial Cancer

Meta-Analysis of Univariable Results

Meta-analysis of two EC studies showed a statistically significant negative effect of sarcopenia on PFS (HR:1.51, 1.03-2.20, P=0.03, I^2=0%) (Figure 6). These results showed no statistical heterogeneity overall, or between subgroups, which increase the certainty that the effect estimates reflected the true effect. The subgroup CI's were quite wide, but all HRs were on the right side of the plot, indicating a consistently negative effect across the studies.

Cervical Cancer

Meta-Analysis of Univariable Results

Meta-analysis of two CC studies showed a negative effect of pre-treatment sarcopenia on PFS (HR:1.14, 0.85-1.53, P=0.37, I^2=0%) (Figure 7). One study (54) was weighted a substantially larger part of the analysis than the other, as shown by the size of the point estimates. Matsuoka et al. (54) also had much smaller CI's, giving more certainty in the results.

Multivariable Progression Free Survival Results

Eight studies reported multivariable analysis for pre-treatment sarcopenia and PFS. Results are reported narratively in Appendix 20-21.

Ovarian Cancer

Six studies reported multivariable results (Appendix 20). Three revealed SMI, and one found SMD, were independent predictors for PFS.

Endometrial Cancer

Three studies reported multivariable results and none revealed sarcopenia assessments were independent predictors of PFS (Appendix 21).

Univariable One Year Survival Results

Endometrial Cancer

Two studies analysed the effect of sarcopenia on 1YS (44, 56). Rodrigues and Chaves (56) reported K-M analysis from which SMI data was recovered, but SMD data was not sufficient so is reported narratively.

Meta-Analysis of Univariable Results

Meta-analysis of univariable data from two studies revealed a strong, statistically significant, negative effect of pre-treatment low SMI on 1YS (HR:2.55, 1.75-3.71, P=<0.00001, I^2=0%) (Appendix 22).

Narrative Reporting of Univariable Results not Included in Meta-Analysis

De Paula et al. (44) established low SMD was an independent predictor of lower 1YS (HR:2.03, 1.09-3.78, P=0.025), while Rodrigues and Chaves (56) found low SMD was significantly associated with lower 1YS (p=0.01).

Multivariable One Year Survival Results

Endometrial Cancer

De Paula et al. (44) conducted adjusted analysis which upheld that low SMI was an independent prognostic factor for reduced 1YS (HR:2.23, 1.19-4.20, P=0.012). Rodrigues and Chaves (56) created a combined model of SMI and SMD for multivariate analysis, and found this was independently associated with 1YS (HR:5.31, 1.71-16.51, P=0.004).

Three Year Survival Results

Endometrial Cancer

Ganju et al. (31) reported a 29% 3YS rate for patients with low SMI and SMD, *versus* 75% for non-sarcopenic patients.

Cervical Cancer

Yoshikawa et al. (62) reported a 33% 3YS rate for pre-treatment low PI patients, *versus* 66% for non-sarcopenic patients. Lee et al. (52) analysed 3-year DRFS (Distant recurrence free survival) and found neither low SMI nor SMD were associated with this outcome ($p>0.05$).

Five Year Survival Results

5YS was analysed by K-M analysis in five studies (Appendix 23).

Ovarian Cancer

Huang et al. (30) found a statistically significant lower 5YS rate in pre-treatment sarcopenic patients, than non-sarcopenic (SMD P=0.04, SMI P=0.03, SMG P=0.005) (Appendix 23). They established statistically significantly lower 5Y-PFS rates in patients with pre-treatment low SMI (P=0.01) and SMD (P=0.04), but not SMG (P=0.20).

Huang et al. (46) found statistically significantly lower 5YS rates in low SMD patients (p=0.02), not SMI (p=0.08), and statistically significantly lower 5Y-PFS rates in low SMI (p=0.03), not SMD (p=0.24). However, some of these results are duplications due to population overlap.

In contrast, Kim et al. (47) found no significant difference in 5YS rates, in fact, non-sarcopenic had lower 5YS rates than sarcopenic.

Endometrial Cancer

Lee et al. (51) found 5YS and 5Y-PFS were lower in sarcopenic patients, but not statistically significant (Appendix 23).

Cervical Cancer

Lee et al. (32) found 5YS rates were slightly lower in the sarcopenic patients compared to non-sarcopenic, but not statistically significant (Appendix 23).

Complications Results

Four studies analysed the risk of post-operative complications in sarcopenic and non-sarcopenic patients using t-tests, χ^2 or log-rank tests, and found no statistically significant differences. Rutten et al. (57) additionally used a binary logistic regression model to predict major complications in OC. They found low SMI and PI were not significantly predictive, while low SMD was. Conrad et al. (43) performed a ROC analysis to determine the predictive value of CMI for complications in OC, but found no association.

Length of Stay (LoS) Results

Four studies assessed LoS. Two found that sarcopenic patients had longer LoS (35, 57), while two found non-sarcopenic patients had a slightly longer LoS (43, 50). There were no statistically significant differences using t-tests, χ^2 or log-rank tests.

Change in Sarcopenia Over Treatment and Survival Results

Nine studies analysed the effect of the change in sarcopenia over treatment on survival (Appendix 24). Meta-analysis could not be performed due to heterogeneity.

Ovarian Cancer

Huang et al. (46) reported that SMI loss, not SMD, was an independent predictor for a lower OS (HR:1.04, 1.01-1.08, P=0.002) and PFS (HR:1.04, 1.01-1.06, P=0.003). Meanwhile, Bronger et al. (42) found no significant effect of SMI or SMD loss on OS ($p>0.05$). Rutten et al. (58) found SMA (skeletal muscle area) change was an independent predictor of reduced OS (HR:1.698, 1.038-2.778, P=0.035), but PA (psoas muscle area) change had no effect (HR:0.979, 0.06-1.49, P=0.921).

Endometrial Cancer

Lee et al. (51) reported that SMI loss had no effect, while SMD loss >5% was an independent prognostic factor for lower OS (HR:11.08, 2.43-50.58, P=0.002) and PFS

(HR:8.24, 2.32-29.23, P=0.001). Further, SMG loss was an independent predictor of reduced OS (HR:10.63, 2.45-46.21, P=0.002) and PFS (HR:11.36, 2.67-48.35, P=0.001).

Cervical Cancer

Lee et al. (32) reported in univariable analysis that SMD and SMI loss had negative effects on OS, while SMI loss >10% was an independent prognostic factor (HR:6.02, 3.04-11.93, P<0.001). Lee et al. (52) reported SMI loss >5% was an independent predictor of worse 3Y-DRFS (HR:6.31, 3.18-12.53, P=<0.001). Sanchez et al. (60) reported SMI loss >10% had a tendency towards reduced OS (HR:2.572, P=0.06). Kiyotoki et al. (48) found SMA loss >15% had negative effect on OS (HR:2.892, 0.744-11.24, P=0.125) and PFS (HR:1.619, 0.527-4.971, P=0.4). But, PA loss >15% was an independent predictor of reduced OS (HR:8.52, 2.16-33.59, P=0.002) and PFS (HR:6.0, 1.91-18.87, P=0.002).

Publication bias

Testing for publication bias has low sensitivity when meta-analysis is based on fewer than 10 effect size. Therefore, 5 meta-analyses were tested (Appendix 25). The funnel plots were symmetrical and supported by non-significant Egger's and Begg's tests in sarcopenia and OS in OC (p=0.120 and p=0.221, respectively), sarcopenia measured <60 days before treatment and OS in OC (p=0.148 and p=0.542, respectively), and sarcopenia and PFS in EOC (p=0.101 and p=0.052, respectively). With regards to PFS in OC and OS in EOC, publication bias was possibly present due to small study effects because although the funnel plot indicated asymmetry and Egger's test was significant (PFS in OC p = 0.022, OS in EOC p = 0.036), Begg's test was not (PFS in OC p = 0.112, OS in EOC p = 0.131) (Appendix 25).

Discussion

Summary of Main Findings and Relation to Existing Literature

This systematic review and meta-analysis demonstrated that pre-treatment sarcopenia had a negative effect on OS and PFS in gynaecology cancer, but was not a unanimous independent prognostic factor. This is the first meta-analysis to include all types of sarcopenia assessments and assess their effect on survival in gynaecology cancer. It is also the first to review the effect of the change in muscle over treatment on survival outcomes, generating novel findings.

In ovarian cancer (OC), pre-treatment sarcopenia had a statistically significant overall negative effect on overall survival (OS) in meta-analysis of univariate results. Low SMD (skeletal muscle density) had the largest, statistically significant, negative effect on OS in subgroup meta-analysis of univariate results. SMD was also an independent prognostic factor for OS in five studies (29, 30, 41, 46, 49) and SMI (skeletal muscle index) in three (30, 42, 46). For progression free survival (PFS), pre-treatment sarcopenia had a statistically significant overall negative effect in meta-analysis of univariate results. Low SMI had the largest, statistically significant, negative effect and was an independent prognostic factor in three studies (30, 42, 46). One study found SMD was an independent prognostic factor (46).

In endometrial cancer (EC), pre-treatment sarcopenia had an overall negative effect on OS in meta-analysis of univariate results. Low SMI and SMD combined had the largest, statistically significant, negative effect in subgroup meta-analysis, and was an independent prognostic factor for OS in one study (31). Pre-treatment sarcopenia had an overall, statistically significant, negative effect on PFS in meta-analysis of univariate results.

In cervical cancer (CC), pre-treatment sarcopenia had an overall negative effect on OS and PFS in meta-analysis of univariate results. Low PI (psoas index) was an independent prognostic factor in one study (62).

Pre-treatment low SMI had a statistically significant negative effect on 1-year survival (1YS) in meta-analysis of univariate results for EC. Similarly, 3-year survival (3YS), 5-year survival (5YS) and 5-year progression-free survival (5Y PFS) rates were mostly lower in sarcopenic compared to non-sarcopenic patients. Pre-treatment sarcopenia did not have significant effects on complications or LoS (length of stay).

Loss of muscle mass and quality over treatment had negative effects on survival. One OC study found SMI loss, not SMD, was an independent prognostic factor for lower OS and PFS (46). SMA loss was an independent prognostic factor for lower OS in two OC studies (58, 59). In one EC study, SMD and SMG (skeletal muscle gauge) loss were independent prognostic factors for lower OS and PFS (51). In CC, muscle mass loss was an independent prognostic factor in 3 studies (32, 48, 52) (Appendix 26).

Skeletal Muscle Mass

The existing literature supports the finding that pre-treatment low SMI has negative effects on survival in OC. One meta-analysis of eight studies found a significant negative effect of SMI on OS (34), while another meta-analysis of six studies reported a non-significant negative effect of low SMI on OS (66). McSharry et al. (67) reported a negative effect of low SMI on 3YS and 5YS from meta-analysis of four studies. Moreover, a review of nine studies concluded that sarcopenia was important in predicting survival, but the quality of evidence was low (27).

Systematic reviews on sarcopenia in CC and EC are lacking. However, a recent meta-analysis of 13 studies on primary OC, EC, and CC, and found that sarcopenia was associated with lower OS and PFS in the three cancers combined (68).

Skeletal Muscle Quality

A meta-analysis of 40 cancer studies found low SMD was significantly associated with lower OS in gynaecology cancer (69). This supports the current review and is upheld by other meta-analyses (34, 66) that found statistically significant negative effects of low muscle quality measurements on OS in OC. McSharry et al. (67) also reported normal MA (muscle attenuation) was associated with significantly improved 3YS and 5YS, compared to low MA. These suggest low muscle quality may be a more consistent prognostic factor than muscle quantity for OS in OC, but the quality of evidence was low.

Skeletal Muscle Mass and Quality Combined

The evidence of the coexistence of muscle mass and quality loss in cancer elucidates why assessing combined muscle measurements are advantageous (56). Hence, SMG was derived (70). In the current review, SMG was a better predictor than SMI in one study (30), and another (31) found that low SMI and SMD combined was an independent prognostic factor for OS. Research on the potential of combining SMI and SMD as a prognostic factor in gynaecology oncology is required.

Psoas Muscle Assessments

In the current meta-analysis, sarcopenia by psoas measurements showed negative effects on survival outcomes. Rutten et al. (58) argue that PA (psoas area) is an unreliable sarcopenia assessment in gynaecology oncology as it has weak correlations with SMA (skeletal muscle area), and a lack of association with survival. Though, the opposite effect was found in a cohort of colorectal cancer patients (71).

The misrepresentation of PA may be down to its vulnerability to degenerative diseases of the lumbar spine, which causes deterioration of trunk and psoas muscle (72). This muscle atrophy is not directly due to cancer-related sarcopenia, so measurements of this area are misleading (58). Furthermore, PA at L3 only represents <10% of SMA, so changes are less visible (24). Psoas sarcopenia assessments may have some prognostic suitability, though further investigation is required.

Change in Muscle over Treatment

As sarcopenia is a complex and progressive condition, longitudinal studies would give a more comprehensive picture of skeletal muscle changes, which impact outcomes (32). Yet, few studies have investigated the effect of the change in muscle composition over treatment on gynaecology cancer survival. In the current review, most OC and CC longitudinal studies found loss of muscle mass was significantly associated with poorer OS and PFS, while muscle quality loss was not. However, methodologies varied substantially.

A patients' muscularity at one time-point is affected by several factors including age, sex, ethnicity, and tumour treatment (67, 73-74). Thus, inconsistent findings for sarcopenia and

OS reflect that muscle was only assessed at baseline. Further research is necessitated to understand the effect of muscle composition change on outcomes in gynaecology tumours.

Risk of Bias and Study Limitations

The studies in this review were classified as high risk of bias for several reasons. Predominantly, the observational and retrospective nature of the studies makes it impossible to eliminate selection bias and confounding factors.

A major limitation is that several studies did not carry out multivariate analysis if univariate produced statistically insignificant results. Selective reporting on treatment, sarcopenia assessments, and factors adjusted for in analysis, was another limitation. The follow up time varied across studies, and there was a lack of information on patients lost in follow up. Inclusion of all FIGO stages could be a limitation, as advanced cancer patients would be at higher mortality risk than early stage.

There are several causes of heterogeneity which limit the generalisation of data including sarcopenia assessments, cut-offs, nutritional status, tumour, treatments, and other strong prognostic factors. Due to heterogeneity, meta-analysis of adjusted results was not completed, despite adjusted results providing important information for prognostic reviews. Though, this is also a strength as it prevented comparison of dissimilar data and misinterpretation of results.

Strengths and Implications for Practice

This research is extremely valuable as it is the first meta-analysis to include all types of sarcopenia assessments and assess their effect on survival in gynaecology cancer. It is also the first to review the effect of the change in muscle over gynaecology cancer treatment on survival outcomes, generating novel findings.

There are many strengths to this review, including the large number of studies, variety of regions, and extensive meta-analysis with subgroup analysis. This study examined CT for sarcopenia assessments as it is routine in gynaecology oncology care for staging and check-ups, so places no extra burden or extra costs. Using CT will also identify patients at risk of poor treatment tolerance and survival, while potentially having a normal BMI.

Conclusions and Future Research

This meta-analysis provides evidence that pre-treatment sarcopenia has a statistically significant negative effect on OS and PFS in ovarian and endometrial cancers. This research has identified that skeletal muscle quality measures may be more important in predicting gynaecology survival outcomes. Additionally, it establishes that measuring the change in muscle mass over gynaecology cancer treatment may be more advantageous than a single baseline assessment. Nonetheless, there remains considerable variation in sarcopenia cut-offs and assessment methods, making interpretation for clinical practice challenging.

Future assessments require consensus on cut-off values. More large-scale longitudinal trials using CT images at several time points to assess muscle change over treatment, in concomitance with cancer progression and treatment monitoring, are needed, and should include QoL indicators. Prospective studies combining muscle function tests with CT scans would provide a more comprehensive analysis of sarcopenia. Finally, gynaecology cancer can be long-lasting, requiring several treatment interventions, thus assessments of sarcopenia must be regular to ensure early identification and should be incorporated into cancer management.

Overall, this research has highlighted that the incorporation of sarcopenia assessments into the gynaecology cancer management pathway, may have beneficial effects on survival through identifying those with increased risk of poor outcomes, who require multimodal interventions.

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Conflict of Interest

No conflicts of interest.

Author Contribution Statement

ES led the review, was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening eligible studies, extracting and analysing data, conducting meta-analysis, deriving all tables and figures.

MP supported the research process, made critical comments that helped in the interpretation of results, supported in writing sections of the report, and reviewed the final report.

SD provided expert clinical advice and reviewed the final report.

KF reviewed the final report.

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List of Tables

Table. 1. Characteristics and main findings for the 27 included studies

Study	Country	Time	Single or Multi-centre	Sample Size	Mean (±SD) age (years)	Cancer Site	FIGO Stage	Treatment	Timing of Pre-T assessme-nt	Pre-T muscle assess-ments from CT	Sarcopenia cut-offs	Prevalence of Pre-T sarcopenia (%)	Follow up (month)	Outcomes	Main Findings
Ataseven et al. 2018	Germany	2011 – 2016	Single	323	57.5 (±19.7)	EOC	III – IV	PDS, adjuvant ChT	<60 days Pre-T	SMA, SMI, SMD	SMI <38.5 cm^2/m^2 SMI <39.0 cm^2/m^2 SMI <41.0 cm^2/m^2 SMD <32 HU	29.4 33.7 47.1 21.1	54	OS	Pre-T low SMD, not SMI, was an independent prognostic factor for lower OS.
Aust et al. 2015	Austria	2004 – 2012	Single	140	60 (±13)	EOC	I – IV	PDS, adjuvant ChT	<30 days Pre-T	SMI, SMD	SMI <41.0 cm^2/m^2 SMD <39.0 HU SMI <41cm^2/m^2 + SMD <39 HU	28.9 35.0 20.0	73	OS, PFS	Pre-T low SMD, not SMI, was significantly associated with reduced OS and PFS.
Bronger et al. 2017	Germany	2003 – 2013	Single	128	62 (±15.1)	EOC	III – IV	PDS, adjuvant ChT	Median 39 weeks from diagnosis	SMA, SMI	SMI <38.5 cm^2/m^2	11.0	120	OS, PFS, Long OS	Pre-T low SMI was an independent predictor of low OS and PFS.
Conrad et al. 2018	Texas	2007 – 2015	Single	102	55 (±11)	OC	III – IV	PDS, adjuvant ChT	Pre-T	CMI	CMI <2.8 cm^2/m^2	53.9	NR (median 26)	OS, PFS, Comp, LoS	Pre-T low CMI was not associated with OS or PFS.
De Paula et al. 2019	Brazil	2008 – 2015	Single	232	64.3 (±9.6)	EC	I – IV	PDS, adjuvant ChT	<30 days Pre-T	SMI, SMD	SMI <38.9 cm^2/m^2	25.8	12	1YS	Pre-T HRSMI was significantly associated with reduced 1YS.
Ganju et al. 2020	Kansas	2007 – 2017	Single	64	Median 61.0	EC	I – IV	TH, adjuvant EBRT	Day of treatment	SMI, SMD	SMI <41.0 cm^2/m^2 SMD <41.0 HU + BMI <25 kg/m^2 SMD <33.0 HU + BMI >25 kg/m^2 SMD <37.0 HU SMI <41.0 cm^2/m^2 + SMD <37.0 HU	44.0 NR NR 80.0 32.8	128	OS, 3YS	Having both low SMI and low SMD pre-T was significantly associated with poorer OS compared with having either individual factor.
Gillen et al. 2019	Oklaho-ma	2006 – 2012	Multi	78	61.5 (±9.5)	EC	III – IV	ChT	Pre-T	PA	PA <15.0 cm^2	50.0	NR (mean 45.1)	OS, PFS	Pre-T PA was not significantly associated with OS or PFS.
Huang et al. 2020a	Taiwan	2008 – 2017	Single	147	54.5 (±10.5)	EOC	III	PDS, adjuvant ChT	Median 7 days Pre-T	SMA, SMI, SMD, SMG	SMI <39.1 cm^2/m^2 SMD <35.5 HU	34.0 32.7	63.2	OS, PFS, 5YS, 5Y-PFS	Pre-T low SMI and SMD were independent predictors of poor OS.
Huang et al. 2020b	Taiwan	2008 – 2017	Single	139	54.4 (±10.3)	EOC	III	PDS, adjuvant ChT	Pre-T	SMA, SMI, SMD	SMI <39.2 cm^2/m^2 SMD <35.5 HU	33.8 33.1	64.2	OS, PFS, 5YS, 5Y-PFS, Long OS, PFS, 5YS, 5Y-PFS	Pre-T low SMD, SMI, and SMI loss during treatment, were independent predictors of poor OS and PFS.
Kim et al. 2020	Korea	2019 – 2017	Single	197	57.5 (±10.6)	OC	III – IV	75.4% PDS + adjuvant ChT, 24.5% neoadjuvant ChT + PDS	Baseline	SMA, SMI	SMI <39.0 cm^2/m^2	42.5	60	OS, disease recurrence, 5YS	No significant association between pre-T SMI and OS or recurrence.

Study	Country	Time	Single or Multi-centre	Sample Size	Mean age (years) (±SD)	Cancer Site	FIGO Stage	Treatment	Timing of Pre-T assessment	Pre-T muscle assess-ments from CT	Sarcopenia cut-offs	Prevalence of Pre-T sarcopenia (%)	Follow up (month)	Outcomes	Main Findings
Kiyotoki et al. 2018	Japan	2004 – 2014	Single	60	52.8 (±14.3)	CC	I – IV	EBRT, BrT or CCRT	<7 days Pre-T	SMA, PA	SMA <90.29 cm^2 PA <10.07 cm^2	55.0 53.3	104	OS, PFS, Long OS, PFS	Pre-T PA was not significantly associated with OS or PFS. PA loss >15% was an independent predictor of OS and PFS.
Kumar et al. 2016	Rochest-er	2006 – 2012	Single	296	64.6 (±10.6)	EOC	III – IV	PDS, 87% with adjuvant ChT	<30 days pre-T	SMA, SMI, SMD	SMI <39.0 cm^2/m^2 SMI <39.0 cm^2/m^2 + BMI >25 kg/m^2 SMD <33.4 HU	44.6 18.9 NR	NR (mean 33.2)	OS, PFS	Pre-T low SMD was significantly associated with worse OS, not PFS.
Kuroki et al. 2015	Washing-ton	2005 – 2009	Single	122	65.9 (±10.4)	EC	I – IV	TH, 53% with adjuvant ChT/RT/CRT	<60 days Pre-T	PI	PI <4.33 cm^2/m^2 PI <4.33 cm^2/m^2 + BMI >30 kg/m^2	50.0 22.0	NR (mean 32.8)	OS, RFS, LoS, Comp	Pre-T low PI was significantly associated with decreased RFS, not OS.
Lee et al. 2018	Taiwan	2004 – 2009	Single	245	63 (±12.7)	CC	I – IV	RT or CCRT	Pre-T	SMI, SMD	SMI <41.0 cm^2/m^2 SMD <41.0 HU + BMI <25 kg/m^2 SMD <33.0 HU + BMI >25 kg/m^2 SMD <37.0 HU	51.8 NR NR 63.9	152.3	OS, 5YS, Long OS, 5YS	Pre-T low SMI and SMD were not significantly associated with lower OS. SM loss during treatment was an independent prognostic factor for reduced OS.
Lee et al. 2019	Taiwan	2008 – 2016	Multi	131	54.3 (±9.6)	EC	III	TH, adjuvant CRT	<14 days Pre-T	SMA, SMI, SMD, SMG	SMI <39.3 cm^2/m^2 SMD <35.1 HU SMG <1408.1 (no units)	33.6 33.6 NR	117	OS, PFS, 5YS, 5Y-PFS, Long OS, PFS, 5YS, 5Y-PFS	Pre-T low SMI and SMD were not significantly associated with decreased OS or PFS. SMD loss during treatment was significantly associated with poorer survival outcomes.
Lee et al. 2020	Taiwan	2004 – 2017	Multi	278	62.5 (±5.8)	CC	I – IV	RT or CCRT	Pre-T	SMI, SMD	SMI <36.3 cm^2/m^2 SMD <30.7 HU	33.1 33.1	93.1	3Y-DRFS, Long 3Y-DRFS	SMI loss >5% was independently associated with worse 3Y-DRFS, SMD loss was not.
Matsubara et al. 2019	Japan	2002 – 2017	Single	92	50.9 (±18.4)	EOC	I – IV	PDS or IDS, adjuvant ChT	Pre-T	SMA, PA, PV	SMA <92.92 cm^2 PA <9.96 cm^2 PV <195.6 cm^3	50.0 50.0 50.0	144	OS, PFS	Pre-T low PV was significantly associated with poorer PFS and OS, pre-T PA and SMA were not.
Matsuoka et al. 2019	Japan	2004 – 2018	Single	236	58.8 (±18.2)	CC	I – IV	34% RT, 66% CCRT	Pre-T	SMA, SMI, PI	SMI <36.55 cm^2/m^2 PI <3.9 cm^2/m^2	NR NR	165	OS, PFS	Pre-T low PI and SMI were not significantly associated with OS or PFS.
Nakayama et al. 2019	Japan	2006 – 2013	Single	94	58.2 (±17.2)	OC	I – IV	PDS, adjuvant ChT	<7 days Pre-T	SMI, IMAC	SMI <30.88 cm^2/m^2	66.6	NR	OS, DFS, Comp, LoS	No significant association between pre-T SMI and OS or DFS.

Study	Country	Time	Single or Multi-centre	Sample Size	Mean age (years) (±SD)	Cancer Site	FIGO Stage	Treatment	Timing of Pre-T assessment	Pre-T muscle assessments from CT	Sarcopenia cut-offs	Prevalence of Pre-T sarcopenia (%)	Follow up (month)	Outcomes	Main Findings
Nattenmuller et al. 2018	Germany	NR	Single	189	62.9 (±13.5)	CC, EC, OC	I – IV	Surgery, with CRT	Pre-T	SMI, IMFA	SMI <41.0 cm^2/m^2	34.8	77	OS	Pre-T SMI was not significantly associated with OS in all patients. In CC patients there was a significant association.
Rodrigues and Chaves, 2018	Brazil	2008 – 2014	Single	208	64.2 (±9.5)	EC	I – IV	53% surgery, 32% surgery with adjuvant ChT, 15% palliative treatment	<30 days Pre-T	SMI, SMD	SMI <42.4 cm^2/m^2 SMD <30.0 HU	50.0 NR	12	1YS	Low pre-T SMD and HRSMI were significantly associated with reduced 1YS. SMI and SMD combined was independently associated with 1YS.
Rutten et al. 2017a	Netherlands	2000 – 2015	Multi	216	63.1 (±0.8)	OC	II – IV	PDS, 29% with secondary IDS	<60 days Pre-T	SMI, SMD, IMAT	SMI <38.73 cm^2/m^2 SMD <33.67 HU IMAT <3.51 cm^2/m^2 PI <4.65 cm^2/m^2	32.4 NR NR NR	NR (mean 56.4)	OS, Comp, LoS	Low pre-T SMI and SMD were significantly associated with lower OS, PI was not.
Rutten et al. 2017b	Netherlands	2004 – 2017	Single	150	64.8 (±13.6)	OC	II – IV	Neoadjuvant ChT, IDS	Pre-T	SMA, PA	NR	NR	NR (median 23.4)	Long OS	SMA loss, not PA loss, was independently associated with lower OS.
Rutten et al. 2016	Netherlands	2000 – 2014	Single	123	66.5 (±0.8)	OC	II – IV	Neoadjuvant ChT, IDS	Pre-T	SMA, SMI, IMAT	SMI <41.5 cm^2/m^2	50.4	126.6	OS, Long OS	Pre-T SMI and SMA were not significantly associated with OS. Loss of SMA was an independent prognostic factor for lower OS.
Sanchez et al. 2019	Mexico	2013 – 2014	Single	55	50.5 (±11.4)	CC	II – IV	CCRT	<14 days Pre-T	SMI	SMI <38.5 cm^2/m^2	33.3	NR	Long OS + disease recurrence	Loss of >10% SMI was significantly associated with disease recurrence.
Staley et al. 2020	North Carolina	2000 – 2017	Single	201	60.7 (±19.5)	EOC	I – IV	ChT	Within 3 months of diagnosis	SMA, SMI	SMI <41.0 cm^2/m^2	59.2	NR	OS, PFS	Pre-T SMI was not significantly associated with OS or PFS.
Yoshikawa et al. 2020	Japan	2004 – 2017	Single	40	56.9 (±13.4)	CC	NR	CCRT	Pre-T	PI	PI <3.72 cm^2/m^2	57.5	91	OS, 3YS	Pre-T low PI was an independent prognostic factor for lower OS.

Abbreviations: BMI – body mass index, BrT – brachytherapy, CC – cervical cancer, CCRT – concurrent chemotherapy, ChT – chemotherapy, CMI – core muscle index, Comp – complications, CRT – chemoradiotherapy, DRFS – disease recurrence free survival, EBRT - pelvic external beam radiation, EC – endometrial cancer, EOC – epithelial ovarian cancer, HRSMI – high radio-density skeletal muscle index, IDS – interval debulking surgery, IMAC – intramuscular adipose tissue content, IMAT – intramuscular adipose tissue, Long – longitudinal LoS – length of stay, NR – not reported, OC – ovarian cancer, OS – overall survival, PA – psoas muscle area, PDS – primary debulking surgery, PFS – progression free survival, PI – psoas muscle index, Pre-T – Pre-treatment, PV – psoas muscle volume, RFS – recurrence free survival, RT – radiotherapy, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index, TH – total hysterectomy, 1/3/5Y PFS – 1/3/5 year progression free survival, 1/3/5 YS – 1/3/5 year survival.

Figures

Figure 1. Flow diagram depicting the selection process for the studies.

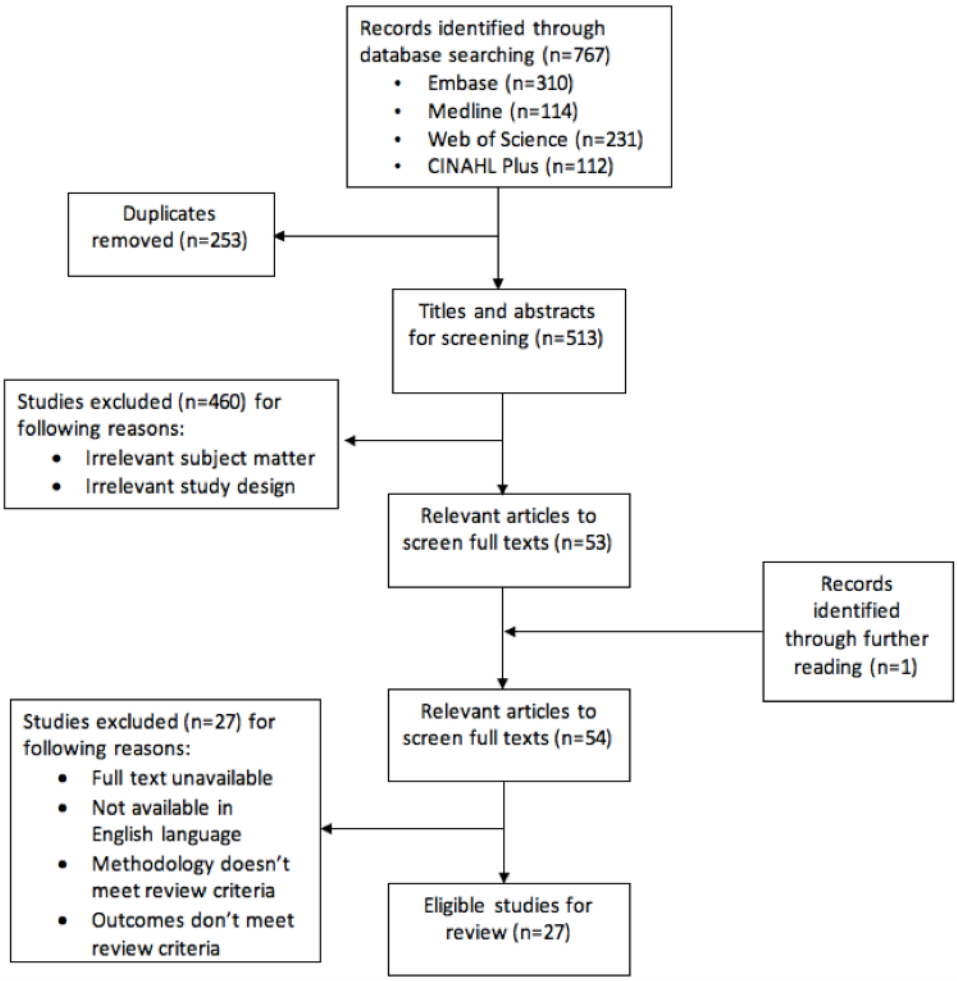


Figure 2. Forest plot of univariable results for pre-treatment sarcopenia (using seven different sarcopenia assessments: SMI, SMD, PA, PV, PI, IMAT, SMA) and overall survival in ovarian cancer patients. The forest plot showed a pooled significant negative effect of sarcopenia on overall survival (HR:1.40, 1.20-1.64, P<0.0001). Abbreviations: CI – confidence intervals, HR – hazard ratio, IMAT – intramuscular adipose tissue index, OS – overall survival, PA – psoas area, PI – psoas index, PV, psoas volume, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

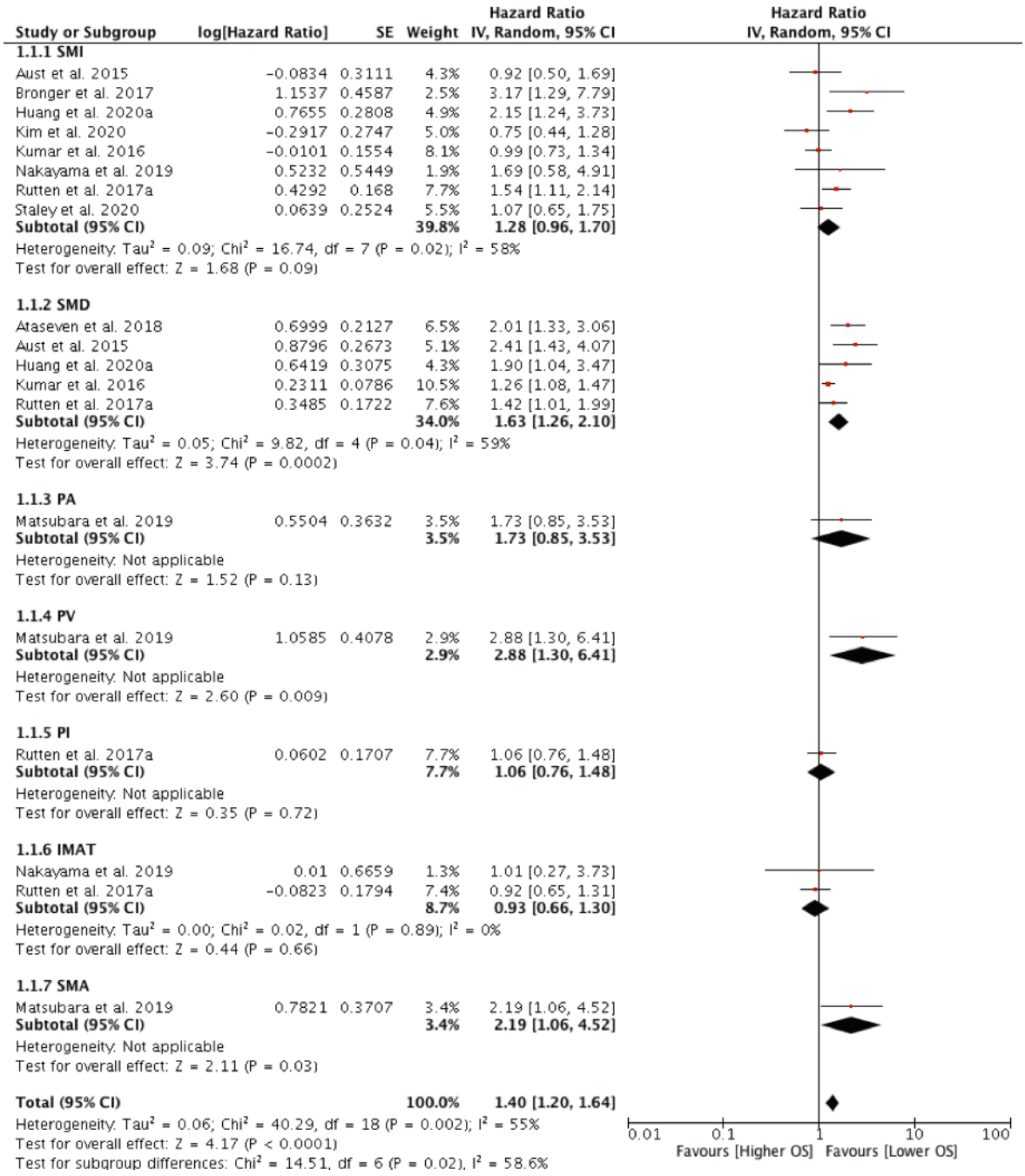


Figure 3. Forest plot of univariable results for pre-treatment sarcopenia (using five sarcopenia assessments: SMI, SMD, PI, SMG, SMI+SMD) and overall survival in endometrial cancer patients. The forest plot showed a pooled negative effect of sarcopenia on overall survival (HR:1.42, 0.97-2.10, P=0.07). Abbreviations: CI – confidence intervals, HR – hazard ratio, OS – overall survival, PI – psoas index, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index.

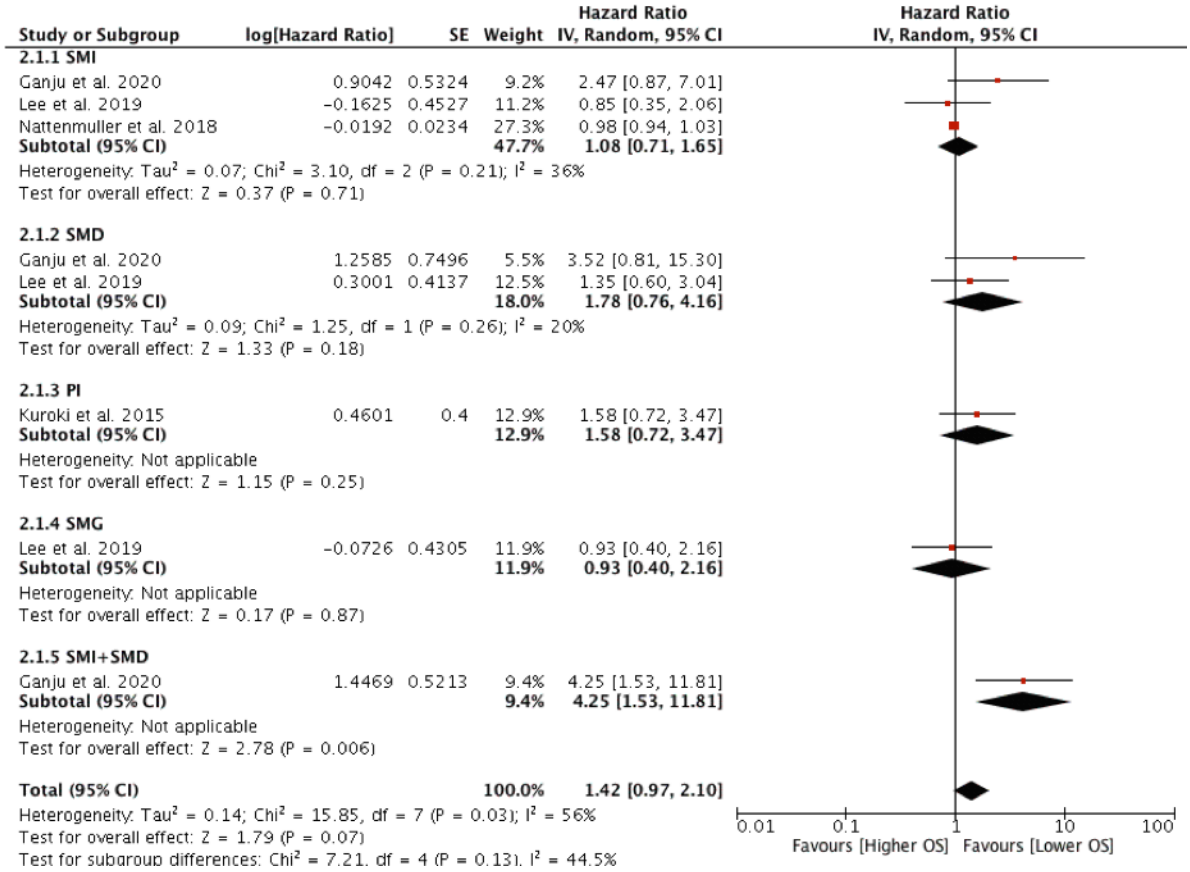


Figure 4. Forest plot of univariable results for pre-treatment sarcopenia (using five sarcopenia assessments: SMI, SMD, PI, PA, SMA) and overall survival in cervical cancer patients. The forest plot showed a pooled negative effect of sarcopenia on overall survival (HR:1.10, 0.93-1.31, P=0.28). Abbreviations: CI – confidence intervals, HR – hazard ratio, OS – overall survival, PA – psoas area, PI – psoas index, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

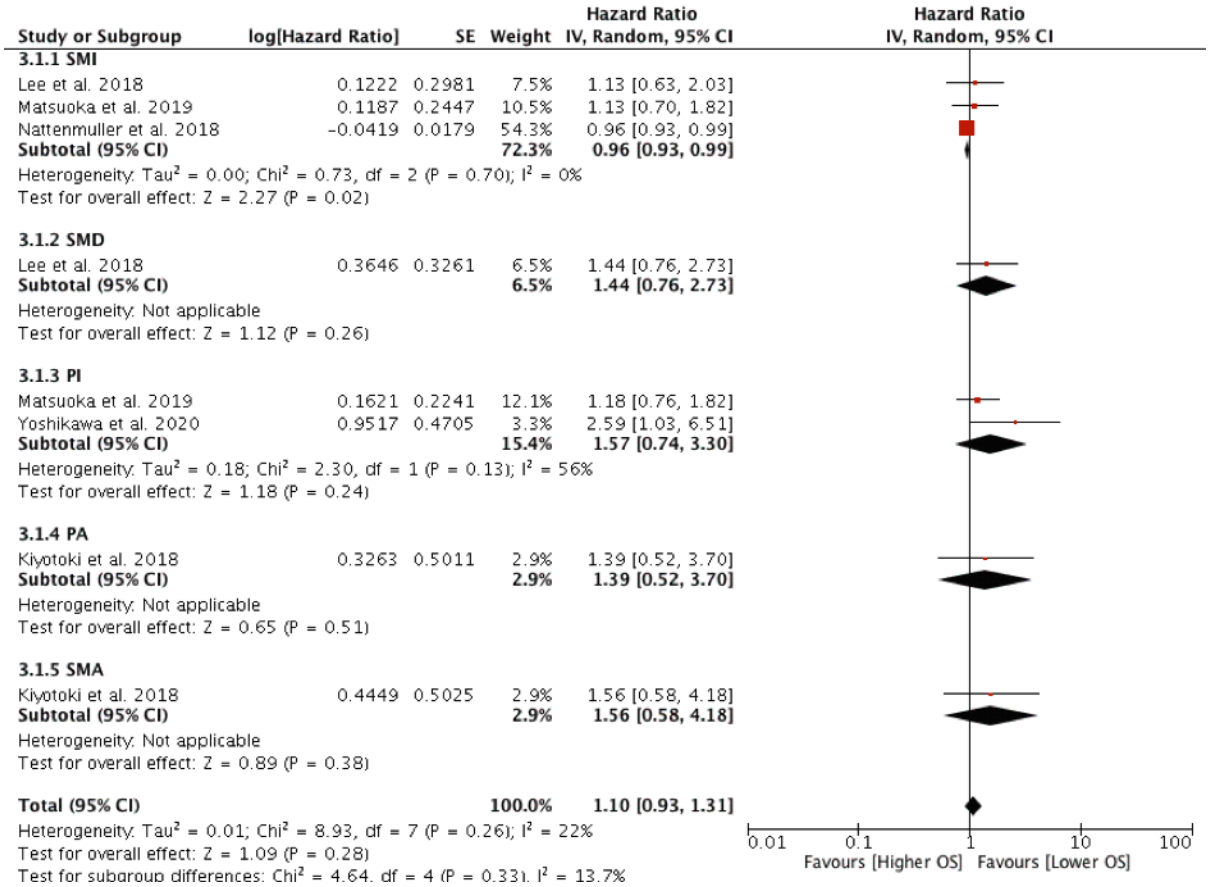


Figure 5. Forest plot of univariable results for pre-treatment sarcopenia (using six sarcopenia assessments: SMI, SMD, PA, PV, IMAT, SMA) and progression free survival in ovarian cancer patients. The forest plot showed a pooled significant negative effect of sarcopenia on overall survival (HR:1.28, 1.11-1.46, P=0.0005). Abbreviations: CI – confidence intervals, HR – hazard ratio, IMAT – intramuscular adipose tissue index, PFS – progression free survival, PA – psoas area, PV – psoas volume, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

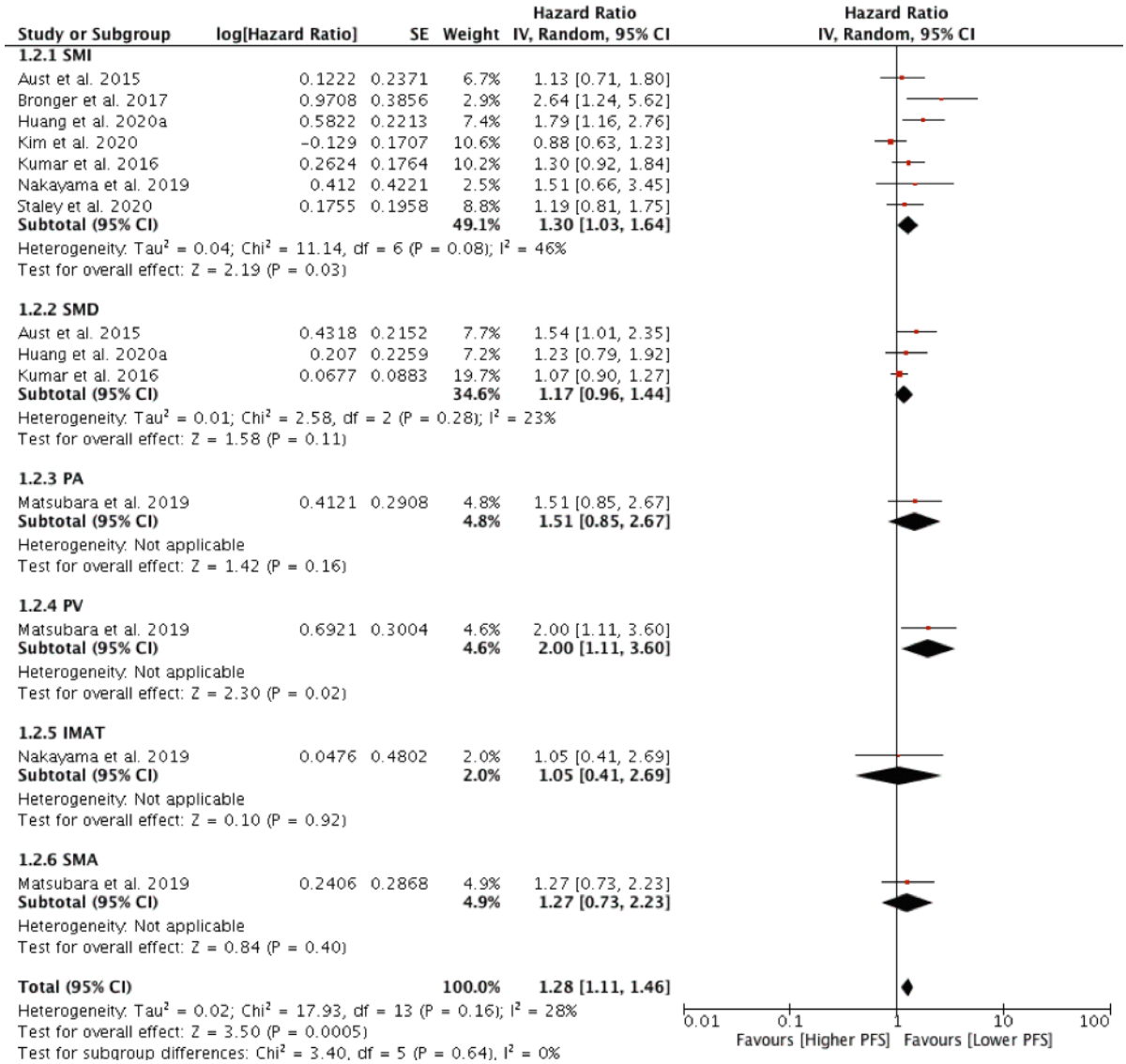


Figure 6. Forest plot of univariable results for pre-treatment sarcopenia (using four sarcopenia assessments: SMI, SMD, PI, SMG) and progression free survival in endometrial cancer patients. The forest plot showed a pooled significant negative effect of sarcopenia on overall survival (HR:1.51, 1.03-2.20, P=0.03). Abbreviations: CI – confidence intervals, HR – hazard ratio, PFS – progression free survival, PI – psoas index, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index.

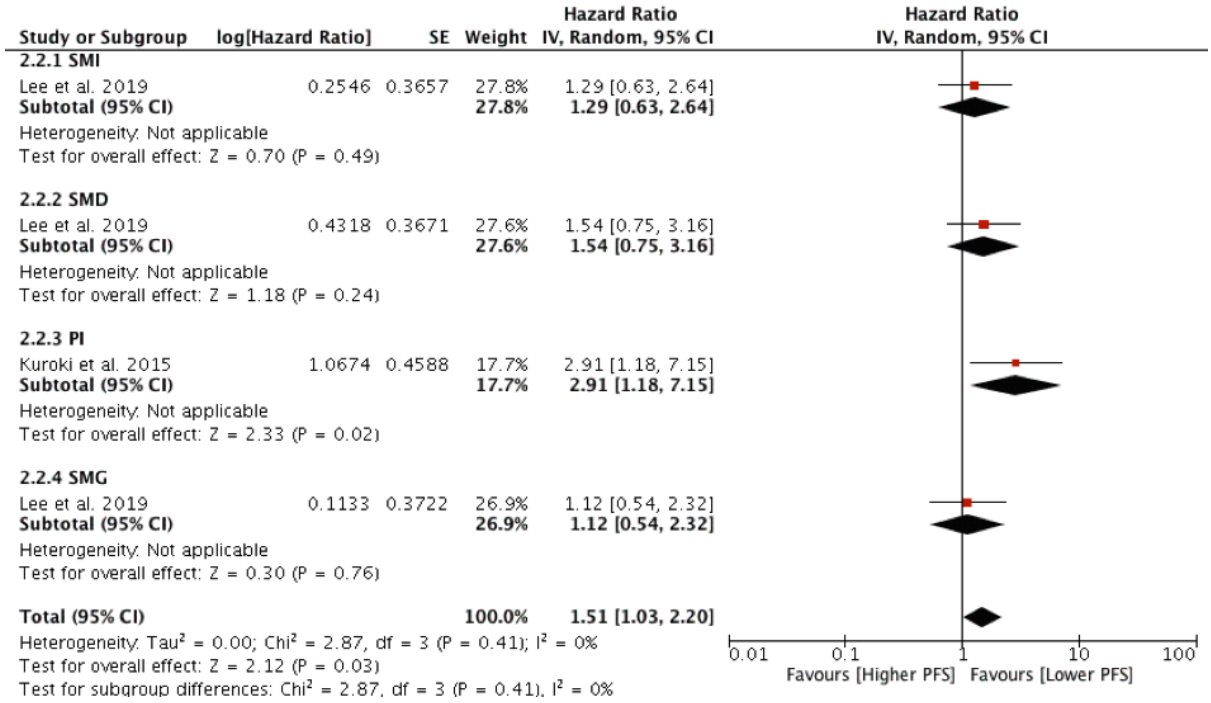
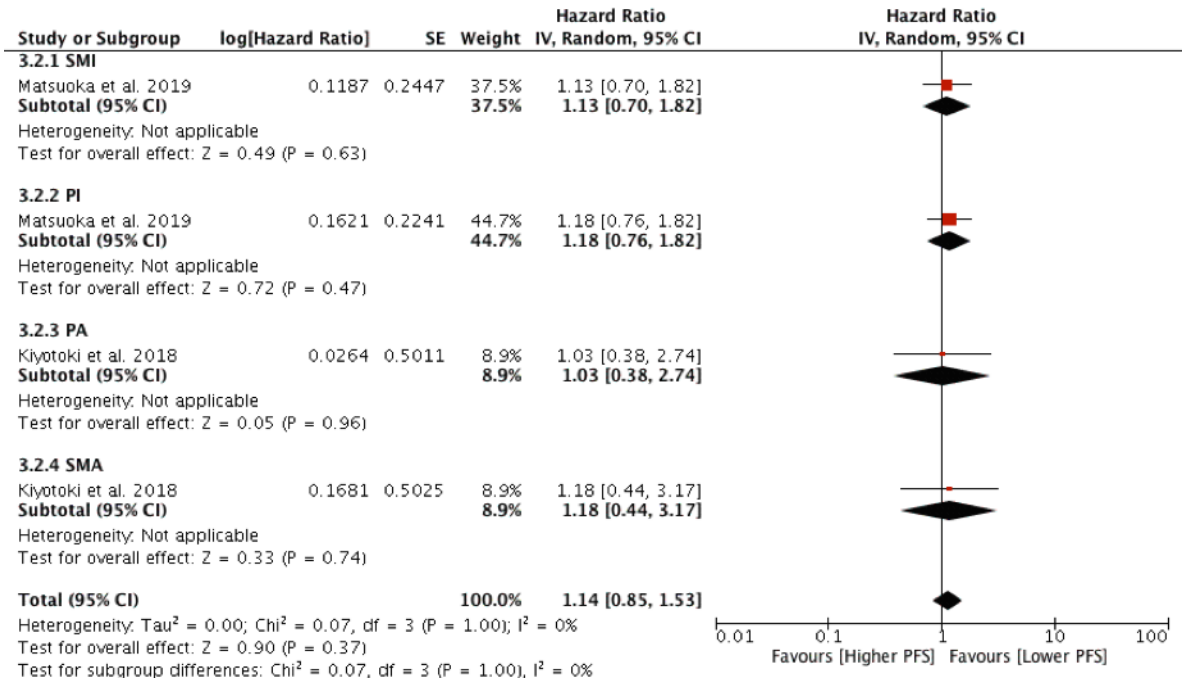


Figure 7. Forest plot of univariable results for pre-treatment sarcopenia (using four sarcopenia assessments: SMI, PI, PA, SMA) and progression free survival in cervical cancer patients. The forest plot showed a pooled negative effect of sarcopenia on overall survival (HR:1.14, 0.85-1.53, P=0.37). Abbreviations: CI – confidence intervals, HR – hazard ratio, PFS – progression free survival, PA – psoas area, PI – psoas index, SMA – skeletal muscle area, SMI – skeletal muscle index.



Supplementary information

Appendix 1. Inclusion criteria

	Inclusion Criteria
Study design	Observational (prospective and retrospective)
Population	Female adults with diagnosed primary or secondary gynaecology malignancy undergoing cancer treatment. This includes: • Ovarian treated with debulking surgery, with/without chemotherapy • Cervical treated with either chemoradiotherapy, radiotherapy and/or surgery • Endometrial treated with surgery and/or chemotherapy, radiotherapy, chemoradiotherapy
Index (Prognostic) Factor	Muscle measurements from CT to define sarcopenia prior to treatment including: • Skeletal muscle index/density/mass • Psoas muscle index/density/mass
Outcomes	Prognostic risk of sarcopenia in cancer survival (hazard ratio, mean/median): • Overall survival (or 1/3/5-year survival rates) • Progression free survival • Complications • Length of hospital stay • Change in sarcopenia assessments over treatment and effect on survival outcomes
Timing	• Pre-treatment assessment within 2 months of treatment • Survival must be measured after a minimum of 12 months post-treatment
Setting	Single or multiple medical institution(s) where the patient medical records are collected during a particular time period

Appendix 2. Search strategy

Embase Ovid

1. Exp sarcopenia/
2. (Sarcopen* OR Malnutrition OR Muscle loss OR Muscle wasting OR Muscle depletion OR Muscle reduction OR Muscle strength OR Muscle mass OR skeletal muscle attenuation OR Skeletal muscle OR Body composition)
3. ((Muscle OR muscular) adj3 (Loss* OR waste* OR wastage* OR depletion* OR reduction* or low))
4. 1 OR 2 OR 3
5. Exp female genital tract cancer/
6. Exp ovary cancer/
7. Exp uterine cervix cancer/
8. Exp endometrium cancer/
9. Uterine cervix adenocarcinoma/
10. Ovary adenocarcinoma/
11. Endometrium carcinoma/
12. ((Gynae* OR Gyne* OR Ovar* OR Endometr* OR Cervi* OR female genital*) adj3 (Cancer* OR Tumo?r* OR Oncolog* OR Carci* OR Malignan* OR Neoplasm* OR onco* OR adenocarcinoma*))
13. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. 4 AND 13
15. Exp prognosis/
16. Survival/
17. Overall survival/
18. Exp cancer survival/
19. Treatment outcome

20. Mortality/
21. Survival rate/
22. Survival predictor/
23. (Prognos* OR Predict* OR Survival OR Outcome* OR Mortality OR Disease progression)
24. 15 OR 16 OR 17 18 OR 19 OR 20 OR 21 OR 22 OR 23
25. 14 AND 24

Medline Ovid

1. Exp sarcopenia/
2. (Sarcopen* OR Malnutrition OR Muscle loss OR Muscle wasting OR Muscle depletion OR Muscle reduction OR Muscle strength OR Muscle mass OR Skeletal muscle attenuation OR Skeletal muscle OR Body composition)
3. ((Muscle OR muscular) adj3 (Loss* OR waste* OR wastage* OR depletion* OR reduction* or low))
4. 1 OR 2 OR 3
5. Genital neoplasms, Female/
6. Exp uterine neoplasms/
7. Ovarian neoplasms/
8. Carcinoma, ovarian epithelial/
9. Carcinoma, endometrioid/
10. ((Gynae* OR Gyne* OR Ovar* OR Endometr* OR Cervi* OR Female genital*) adj3 (Cancer* OR Tumo?r* OR Carci* OR Malignan* OR Neoplasm* OR Onco* OR Adenocarcinoma*)
11. 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. 4 AND 11
13. Prognosis/
14. Treatment outcome/
15. Mortality/
16. Survival/
17. Survival rate/
18. (Prognos* OR Predict* OR Survival OR Outcome* OR Mortality OR Disease progression)
19. 13 OR 14 OR 15 16 OR 17 OR 18
20. 19 AND 20

Web of Science

1. (Sarcopen* OR Malnutrition OR “Muscle loss” OR “Muscle wasting” OR “Muscle depletion” OR “Muscle reduction” OR “Muscle strength” OR “Muscle mass” OR “skeletal muscle attenuation” OR “Skeletal muscle” OR “Body composition”)
2. ((Muscle OR muscular) NEAR/3 (Loss* OR waste* OR wastage* OR depletion* OR reduction* or low))
3. 1 OR 2
4. ((Gynae* OR Gyne* OR Ovar* OR Endometr* OR Cervi* OR “female genital*”) NEAR/3 (Cancer* OR Tumo$r* OR Carci* OR Malignan* OR Neoplasm* OR Adenocarcinoma* OR Onco*)
5. 3 AND 4
6. (Prognos* OR Predict* OR Survival OR Outcome* OR Mortality OR “Disease progression”)
7. 5 AND 6

CINAHL Plus

1. (MH “Sarcopenia”)
2. (Sarcopen* OR Malnutrition OR “Muscle loss” OR “Muscle wasting” OR “Muscle depletion” OR “Muscle reduction” OR “Muscle strength” OR “Muscle mass” OR “Skeletal muscle attenuation” OR “Skeletal muscle” OR “Body composition”)
3. ((Muscle OR muscular) N3 (Loss* OR waste* OR wastage* OR depletion* OR reduction* or low))
4. 1 OR 2 OR 3
5. (MH “Genital neoplasms, female”)
6. (MH “Ovarian neoplasms”)

7. (MH “Carcinoma, ovarian epithelial”)
8. (MH “Uterine neoplasms+”)
9. (MH “Adenocarcinoma in situ, cervix”)
10. ((Gynae* OR Gyne* OR Ovar* OR Endometr* OR Cervi* OR “Female genital”) N3 (Cancer* OR Tumo#r* OR Carci* OR Malignan* OR Neoplasm* OR Onco* OR Adenocarcinoma*))
11. 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. 4 AND 11
13. (MH “Prognosis”)
14. (MH “Treatment outcomes”)
15. (MH “Survival”)
16. (MH “Mortality”)
17. (MH “Predictive validity”)
18. (Prognos* OR Predict* OR Survival OR Outcome* OR Mortality OR “Disease progression”)
19. 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. 19 AND 20

Appendix 3. Trivella (77) calculator for recovering survival analysis data.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1		where	O	N	Rp	Rn	p	Φ−1	se=1/rootV	ln(HR)	ln(LCl)	ln(UCl)	HR	LCl	UCl	p/2	ln(HR)(p/2)	ln(LCl)(p/2)	ln(UCl)(p/2)	HR (p/2)	LCl (p/2)	UCl (p/2)
2	Nakayama SMI-OS	1	15	94	32	62	0.337	0.9601097	0.544893203	0.5231573	-0.544833	1.5911479	1.69	0.58	4.91	-0.96011	-0.52315726	-1.59114793	0.54483342	0.59	0.2	1.72
3	Nakayama IMAC -OS	1	13	94	21	73	0.988	0.0150403	0.665863333	0.0100148	-1.295077	1.3151069	1.01	0.27	3.73	-0.01504	-0.01001481	-1.31510694	1.29507732	0.99	0.27	3.65
4	Nakayama SMI - PFS	1	25	94	32	62	0.329	0.9761301	0.42207246	0.4119976	-0.415264	1.2392597	1.51	0.66	3.45	-0.97613	-0.41199763	-1.23925965	0.41526439	0.66	0.29	1.51
5	Nakayama IMAC - PFS	1	25	94	21	73	0.921	0.0991741	0.480160878	0.0476195	-0.893496	0.9887349	1.05	0.41	2.69	-0.099174	-0.04761955	-0.98873487	0.89349577	0.95	0.37	2.44
6	Ataseven MA-OS	2	133	323	68	255	0.001	3.2905267	0.21269249	0.6998703	0.282993	1.1167476	2.01	1.33	3.05	-3.290527	-0.69987032	-1.1167476	-0.282993	0.5	0.33	0.75
7	Staley SMI - OS	1	65	201	119	82	0.8	0.2533471	0.252382346	0.0639403	-0.430729	0.5586097	1.07	0.65	1.75	-0.253347	-0.06394034	-0.55860973	0.43072906	0.94	0.57	1.54
8	Staley SMI - PFS	1	108	201	119	82	0.37	0.8964734	0.195795981	0.1755259	-0.208234	0.559286	1.19	0.81	1.75	-0.896473	-0.17552588	-0.559286	0.20823424	0.84	0.57	1.23
9	Kuroki PI-OS	1	25	122	61	61	0.25	1.1503494	0.4	0.4601398	-0.32386	1.2441398	1.58	0.72	3.47	-1.150349	-0.46013975	-1.24413975	0.32386025	0.63	0.29	1.38
10	Kuroki PI-PFS	1	19	122	61	61	0.02	2.3263479	0.458831468	1.0674016	0.1680919	1.9667113	2.91	1.18	7.15	-2.326348	-1.06740161	-1.96671129	-0.1680919	0.34	0.14	0.85
11	Kiyotoki PA-OS	2	16	60	32	28	0.515	0.651072	0.501114829	0.3262618	-0.655923	1.3084469	1.39	0.52	3.7	-0.651072	-0.32626184	-1.30844691	0.65592322	0.72	0.27	1.93
12	Kiyotoki SMA-OS	2	16	60	33	27	0.376	0.8852904	0.502518908	0.4448752	-0.540062	1.4298122	1.56	0.58	4.18	-0.88529	-0.44487519	-1.42981225	0.54006187	0.64	0.24	1.72
13	Kiyotoki PA-PFS	1	16	60	32	28	0.958	0.0526635	0.501114829	0.0263905	-0.955795	1.0085755	1.03	0.38	2.74	-0.052664	-0.02639047	-1.00857554	0.95579459	0.97	0.36	2.6
14	Kiyotoki SMA-PFS	1	16	60	33	27	0.738	0.334503	0.502518908	0.1680941	-0.816843	1.1530312	1.18	0.44	3.17	-0.334503	-0.1680941	-1.15303116	0.81684296	0.85	0.32	2.26
15	Rodrigues SMI - 1YS	2	49	208	104	104	0.01	2.5758293	0.285714286	0.7359512	0.1759512	1.2959512	2.09	1.19	3.65	-2.575829	-0.73595123	-1.29595123	-0.1759512	0.48	0.27	0.84

Appendix 4. Factors adjusted for in multivariable analysis in each included study.

Study	*Factors adjusted for in multivariable analysis:*
Ataseven et al. (41)	***NR***
Aust et al. (29)	***NR***
Bronger et al. (42)	***Age, FIGO stage, and postsurgical tumour burden.***
Conrad et al. (43)	***NR***
De Paula et al. (44)	***SMI: age, histological subtype, staging, comorbidities systemic arterial hypertension and diabetes mellitus and body mass index.*** ***LRMSI/HRSMI: age, race, staging, comorbidities systemic arterial hypertension and diabetes mellitus and body mass index and low SMI.***
Ganju et al. (31)	***NR***
Gillen et al. (45)	***Age, stage, and residual disease.***
Huang et al. (30)	***Stage, residual disease after PDS, and malignant ascites.***
Huang et al. (46)	***FIGO stage, PDS outcome, and malignant ascites.***
Kim et al. (47)	***Age, FIGO stage, serum CA-125 levels, primary treatment strategy, residual tumour size after surgery, and BMI.***
Kiyotoki et al. (48)	***"known prognostic factors".***
Kumar et al. (49)	***NR***
Kuroki et al. (50)	***Race, BMI, lymphocyte count, and histology.***
Lee et al. (32)	***FIGO stage, pathology and treatment.***
Lee et al. (51)	***OS: histological grade and type, and cervical stromal involvement.*** ***PFS: age, histological grade and type, and cervical stromal involvement.*** ***Longitudinal: histological grade and type, and cervical stromal involvement).***
Lee et al. (52)	***NR***
Matsubara et al. (53)	***"known prognostic factors"***
Matsuoka et al. (54)	***N/A***

Nakayama et al. (35)	***N/A***
Nattenmuller et al. (55)	***Model 1: age, SMI, IMFA and VAT*** ***Model 2: BMI, age, VAT, SAT, VAT/SAT, IMA and SMI***
Rodrigues and Chaves, (56)	***Age, histologic type, staging, comorbidities (e.g. systemic arterial hypertension and diabetes mellitus), type of cancer treatment, and fat mass index (kg/m^2).***
Rutten et al. (57)	***NR***
Rutten et al. (58)	***Age, tumour stage, and surgical outcome.***
Rutten et al. (59)	***NR***
Sanchez et al. (60)	***NR***
Staley et al. (61)	***N/A***
Yoshikawa et al. (62)	***NR***

Abbreviations: BMI – body mass index, CA – cancer antigen, FIGO - International Federation of Gynaecology and Obstetrics, IMA – intramuscular adipose, IMFA – intramuscular fat area, L/H-RSMI – low/high-radiodensity skeletal muscle index, NR – not reported, OS – overall survival, PDS – primary debulking surgery, PFS – progression free survival, SAT – subcutaneous adipose tissue, SMI – skeletal muscle index, VAT – visceral adipose tissue.

Appendix 5. Level and software used for sarcopenia assessments from computed tomography (CT) scan.

Study	*Level*	*HU Range*	*Software or Manual*
Ataseven et al. (41)	***L3***	***-29-150***	***SliceOmatic***
Aust et al. (29)	***L3***	***-29-150***	***SliceOmatic***
Bronger et al. (42)	***L3***	***-29-150***	***OsiriX***
Conrad et al. (43)	***L4***	***NR***	***NR***
De Paula et al. (44)	***L3***	***-29-150***	***SliceOmatic***
Ganju et al. (31)	***L3***	***-20-150***	***NR***
Gillen et al. (45)	***L3***	***-30-110***	***NR***
Huang et al. (30)	***L3***	***-29-150***	***Varian Eclipse***
Huang et al. (46)	***L3***	***-29-150***	***Varian Eclipse***
Kim et al. (47)	***L3***	***-29-150***	***AsanJ-Morphometry***
Kiyotoki et al. (48)	***L3***	***-29-150***	***Synapse Vincent***
Kumar et al. (49)	***L3***	***-29-150***	***SliceOmatic***
Kuroki et al. (50)	***L3***	***NR***	***Manual***
Lee et al. (32)	***L3***	***-29-150***	***Varian Eclipse***
Lee et al. (51)	***L3***	***-29-150***	***Varian Eclipse***
Lee et al. (52)	***L3***	***-29-150***	***Varian Eclipse***
Matsubara et al. (53)	***L3***	***-29-150***	***Synapse Vincent***
Matsuoka et al. (54)	***L3***	***-29-150***	***Synapse Vincent***
Nakayama et al. (35)	***L3***	***-29-150***	***NR***
Nattenmuller et al. (55)	***L3/4***	***-20-150***	***Syngo Volume Tool***
Rodrigues and Chaves, (56)	***L3***	***-29-150***	***SliceOmatic***
Rutten et al. (57)	***L3***	***-30-150***	***SliceOmatic***
Rutten et al. (58)	***L3***	***-29-150***	***SliceOmatic***
Rutten et al. (59)	***L3***	***-29-150***	***SliceOmatic***

Sanchez et al. (60)	***L3***	***-29-150***	***SliceOmatic***
Staley et al. (61)	***L3***	***-29-150***	***SliceOmatic***
Yoshikawa et al. (62)	***L3***	***NR***	***Manual***

Abbreviations: HU – Hounsfield units, L3/4 – third/fourth lumbar, NR – not reported.

Appendix 6. Sarcopenia cut-off points from each study and where they were determined from.

Study	*Sarcopenia cut offs used*	*Cut offs determined from*
Ataseven et al. (41)	***SMI <38.5 cm^2/m^2***	***Prado et al. (36)***
	SMI <39.0 cm^2/m^2	***Kumar et al. (49)***
	SMI <41.0 cm^2/m^2	***Martin et al. (63)***
	SMD <32 HU	***Martingale residuals method***
Aust et al. (29)	***SMI <41.0 cm^2/m^2***	***Martin et al. (63)***
	SMD <39.0 HU	***Multivariable fractional polynomials (FP) method***
	SMI <41 + SMD <39	***Martin et al. (63) + Multivariable FP method***
Bronger et al. (42)	***SMI <38.5 cm^2/m^2***	***Prado et al. (36)***
Conrad et al. (43)	***CMI <2.8 cm^2/m^2***	***Cohort mean***
De Paula et al. (44)	***SMI <38.9 cm^2/m^2***	***Mourtzakis et al. (64)***
Ganju et al. (31)	***SMI <41.0 cm^2/m^2***	***Martin et al. (63)***
	SMD <41.0 HU + BMI <25	***Martin et al. (63)***
	SMD <33.0 HU + BMI >25	***Martin et al. (63)***
	SMD <37.0 HU	***Calculated for review***
	SMI <41.0 + SMD <37.0	***Martin et al. (63) + calculated for review***
Gillen et al. (45)	***PA <15.0 cm^2***	***Cohort median***
Huang et al. (30)	***SMI <39.1 cm^2/m^2***	***Lowest tertile***
	SMD <35.5 HU	***Lowest tertile***
Huang et al. (46)	***SMI <39.2 cm^2/m^2***	***Lowest tertile***
	SMD <35.5 HU	***Lowest tertile***
Kim et al. (47)	***SMI <39.0 cm^2/m^2***	***Fearon et al. (65)***

Kiyotoki et al. (48)	*SMA <90.29 cm^2*	*Cohort mean*
	PA <10.07 cm^2	*Cohort mean*
Kumar et al. (49)	*SMI <39.0 cm^2/m^2*	*Fearon et al. (65), Prado et al. (36)*
	SMI <39.0 cm^2/m^2 + BMI >25	*Tan et al. (75)*
Kuroki et al. (50)	*PI <4.33 cm^2/m^2*	*Cohort median*
	PI <4.33 + BMI >30	*n/a*
Lee et al. (32)	*SMI <41.0 cm^2/m^2*	*Martin et al. (63)*
	SMD <41.0 HU + BMI<25	*Martin et al. (63)*
	SMD <33.0 HU + BMI>25	*Martin et al. (63)*
	SMD <37.0 HU	*Calculated for review*
Lee et al. (51)	*SMI <39.3 cm^2/m^2*	*Lowest tertile*
	SMD <35.1 HU	*Lowest tertile*
	SMG <1408.1	*Lowest tertile*
Lee et al. (52)	*SMI <36.3 cm^2/m^2*	*Lowest tertile*
	SMD <30.7 HU	*Lowest tertile*
Matsubara et al. (53)	*SMA <92.92 cm^2*	*Cohort median*
	PA <9.96 cm^2	*Cohort median*
	PV <195.6 cm^3	*Cohort median*
Matsuoka et al. (54)	*SMI <36.55 cm^2/m^2*	*Receiver operator curve analysis*
	PI <3.9 cm^2/m^2	*Receiver operator curve analysis*
Nakayama et al. (35)	*SMI <30.88 cm^2/m^2*	*Hojan et al. (75)*
	IMAC >-0.511	*Cohort median*
Nattenmuller et al. (55)	*SMI <41.0 cm^2/m^2*	*Martin et al. (63)*
Rodrigues and Chaves, (56)	*SMI <42.4 cm^2/m^2*	*Cohort median*
	SMD <30.0 HU	*Cohort median*
Rutten et al. (57)	*SMI <38.73 cm^2/m^2*	*Optimum stratification*

	SMD <33.67 HU	***Lowest tertile***
	IMAT <3.51 cm^2/m^2	***Highest tertile***
	PI <4.65 cm^2/m^2	***Lowest tertile***
Rutten et al. (58)	***NR***	***NR***
Rutten et al. (59)	***SMI <41.5 cm^2/m^2***	***Cohort median***
Sanchez et al. (60)	***SMI <38.5 cm^2/m^2***	***Prado et al. (36)***
Staley et al. (61)	***SMI <41.0 cm^2/m^2***	***Martin et al. (63)***
Yoshikawa et al. (62)	***PI <3.72 cm^2/m^2***	***Receiver operator curve analysis***

Abbreviations: BMI – body mass index, CMI – central muscle index, IMAC - intramuscular adipose tissue content, IMAT – intramuscular adipose tissue index, NR – not reported, PA – psoas muscle area, PI – psoas muscle index, PV – psoas muscle volume, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index.

Appendix 7. The mean and range of pre-treatment sarcopenia prevalence using the three most frequently used assessments: SMI, SMD and PI.

Assessment	Mean (range) prevalence of sarcopenia overall (%)	Mean (range) prevalence of sarcopenia in OC (%)	Mean (range) prevalence of sarcopenia in EC (%)	Mean (range) prevalence of sarcopenia in CC (%)
SMI (cm^2/m^2)	38.0 (11.0 – 66.0)	38.3 (11.0-66.0)	37.5 (25.8 – 50.0)	33.5 (33.1 – 34.2)
SMD (HU)	39.3 (21.0 – 80.0)	30.0 (21.1-35.0)	56.8 (33.6 – 80.0)	33.1 (n/a)
PI (cm^2/m^2)	53.7 (50.0-57.5)	n/a	50.0 (n/a)	57.5 (n/a)

Abbreviations: CC – cervical cancer, EC – endometrial cancer, n/a – not applicable (used when there was not enough data to calculate a mean or range), OC – ovarian cancer, PI – psoas index, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

Appendix 8. Survival outcome definitions from each study.

Study	*Outcome definitions*
Ataseven et al. (41)	***OS was calculated in days from the date of surgery to the date of last follow-up or death.***

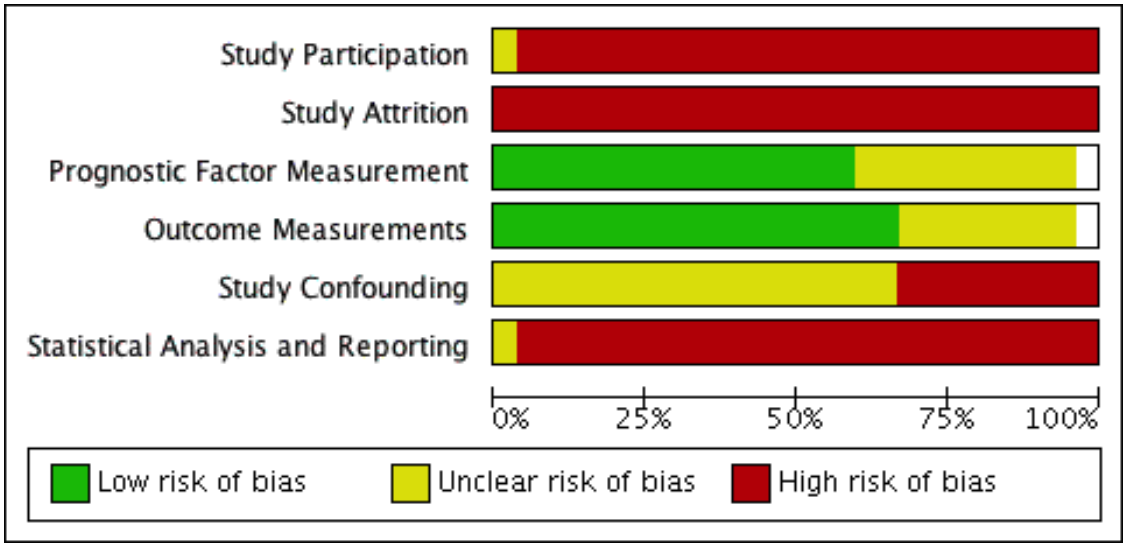
	OS was defined as the time interval between diagnosis and tumour associated death.
Aust et al. (29)	***PFS as the time between diagnosis and disease progression or death.*** ***Overall observation time was the time interval between diagnosis and last contact or date of death. Patients without recurrence, disease progression or non-cancer related death were censored at the time of last follow-up visit.***
Bronger et al. (42)	***Progression was stated if it was verifiably documented by imaging techniques.***
Conrad et al. (43)	***PFS was defined as the length of time in months from treatment initiation to recurrence or progression of disease.*** ***OS was defined as the length of time in months from diagnosis to death, and patients alive at the last contact were considered right-censored for survival analysis.***
De Paula et al. (44)	***One-year survival was estimated from Kaplan Meier. Those who remained alive within 365 days based on the date of primary cancer treatment were censored.***
Ganju et al. (31)	***Progression was calculated as time from surgery until radiographic or clinical progression. If no radiographic or clinical progression was identified, these patients were analysed as censored using time from surgery to last recorded contact.***
Gillen et al. (45)	***OS and PFS were estimated from Kaplan Meier.***
Huang et al. (30)	***PFS was measured from the date of diagnosis until dis- ease progression, death, or last follow-up visit.*** ***OS was measured from the date of diagnosis until death of any cause or last follow-up visit.***
Huang et al. (46)	***OS was defined as the time from the date of surgery to the date of death from any cause.*** ***PFS was defined as the time from the date of surgery to the date of disease recurrence, progression, or death from any cause.***
Kim et al. (47)	***OS was defined as the time interval between the date of diagnosis and the date of cancer-related death or the end of the study.***

	PFS as the time interval between the start date of primary treatment and the date of image-confirmed disease progression, which was assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Kiyotoki et al. (48)	***OS and PFS were estimated from Kaplan Meier.***
Kumar et al. (49)	***Duration of follow-up was calculated from the date of the surgery to the date of death or last follow-up.***
	Time to recurrence was defined as the time from date of surgery to physical or radiographic evidence of disease recurrence.
Kuroki et al. (50)	***RFS was the time from surgery to physical or radiographic evidence of disease recurrence or date of last contact if no recurrence occurred. Patients alive without disease recurrence were censored at the date of last contact.***
	OS was defined as the time between date of surgery and the date of death or the date at last follow-up.
Lee et al. (32)	***Survival was measured from the date of treatment to the date of death or last follow-up.***
Lee et al. (51)	***OS was defined as the time from the date of diagnosis to that of death from any cause***
	PFS was defined as the time from the date of diagnosis to that of disease recurrence, progression, or death from any cause.
	RFS was defined as the time from diagnosis to recurrence or death from any cause.
Lee et al. (52)	***Distant failure was defined as recurrence in non-regional lymph nodes (mediastinal or supraclavicular region) or visceral metastasis. Pelvic failure was defined as recurrence in the cervix, adjacent pelvic organs (e.g., parametrium, bladder, and vagina), or PLNs. Failure was recorded on the basis of clinical examination and imaging findings with pathology proven where possible.***
	This lead to use of DRFS.
Matsubara et al. (53)	***OS and PFS were estimated from Kaplan Meier.***

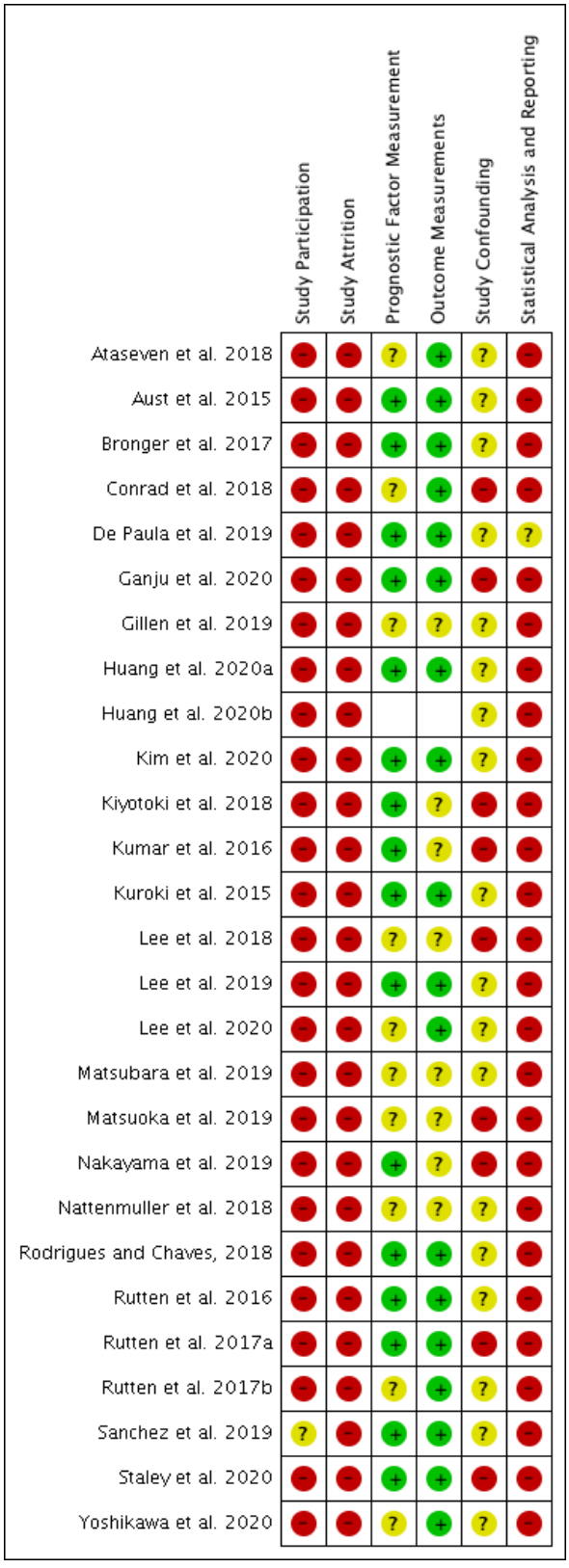
Matsuoka et al. (54)	*NR*
Nakayama et al. (35)	*OS and PFS were estimated from Kaplan Meier.*
Nattenmuller et al. (55)	*OS and PFS were estimated from Kaplan Meier.*
Rodrigues and Chaves, (56)	*One-year survival was estimated by Kaplan Meier. Those who remained alive within 365 days based on the date of first cancer treatment were censored.*
Rutten et al. (57)	*OS was calculated as the time between surgery and death of any cause. Survivors were censored at a fixed date no sooner than six months after inclusion of the last patient.*
Rutten et al. (58)	*OS was defined as the period of time between the initial CT and a patient's death from any cause as reported in national registries. Patients who were still alive at the time of analysis were censored at a fixed date.*
Rutten et al. (59)	*OS was computed from the date of the initial CT scan up to the date of death from any cause.* *For patients who were still alive at the time of analysis, a fixed date was set for data collection, and all patients were censored at this date, which was at least 6 months after the last included subject was diagnosed.*
Sanchez et al. (60)	*A recurrence curve was measured from date of diagnosis to the date of progression or last follow-up visit.* *A survival curve was measured from the date of diagnosis to the date of death or last follow-up visit.*
Staley et al. (61)	*PFS was defined as the time of date of pathologic diagnosis until date of confirmed recurrence.* *OS was defined as date of pathologic diagnosis until date of death.*
Yoshikawa et al. (62)	*OS was defined as the time from primary treatment initiation to death for any reason, was the main outcome analysed.* *The diagnosis of recurrence was based on CT images.* *The follow-up time was defined as the time interval between the beginning of primary treatment and the last date of follow-up or death.*

Abbreviations: CT – computed tomography, DRFS – disease recurrence free survival, OS – overall survival, PFS – progression free survival, RFS – recurrence free survival.

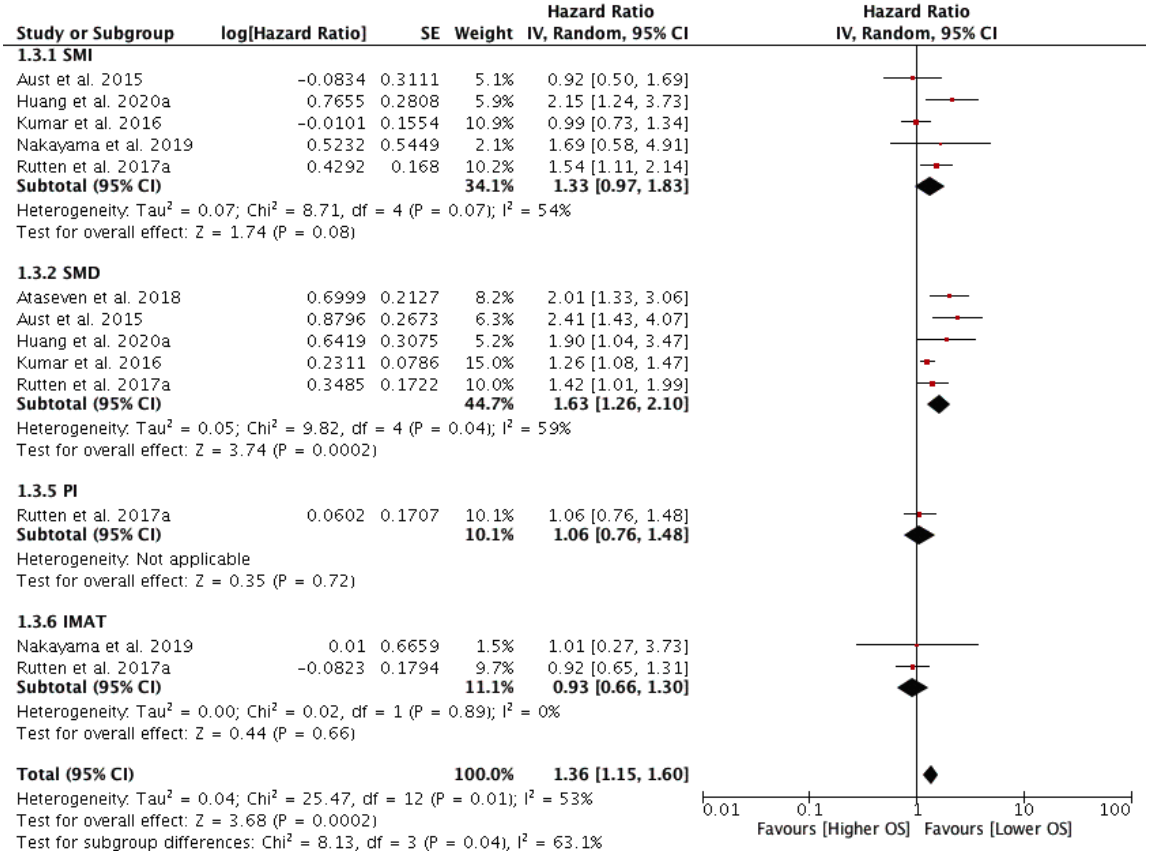
Appendix 9. Risk of bias graph: the authors' judgements about each risk of bias item from the QUIPS checklist presented as percentages across all included studies.



Appendix 10. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

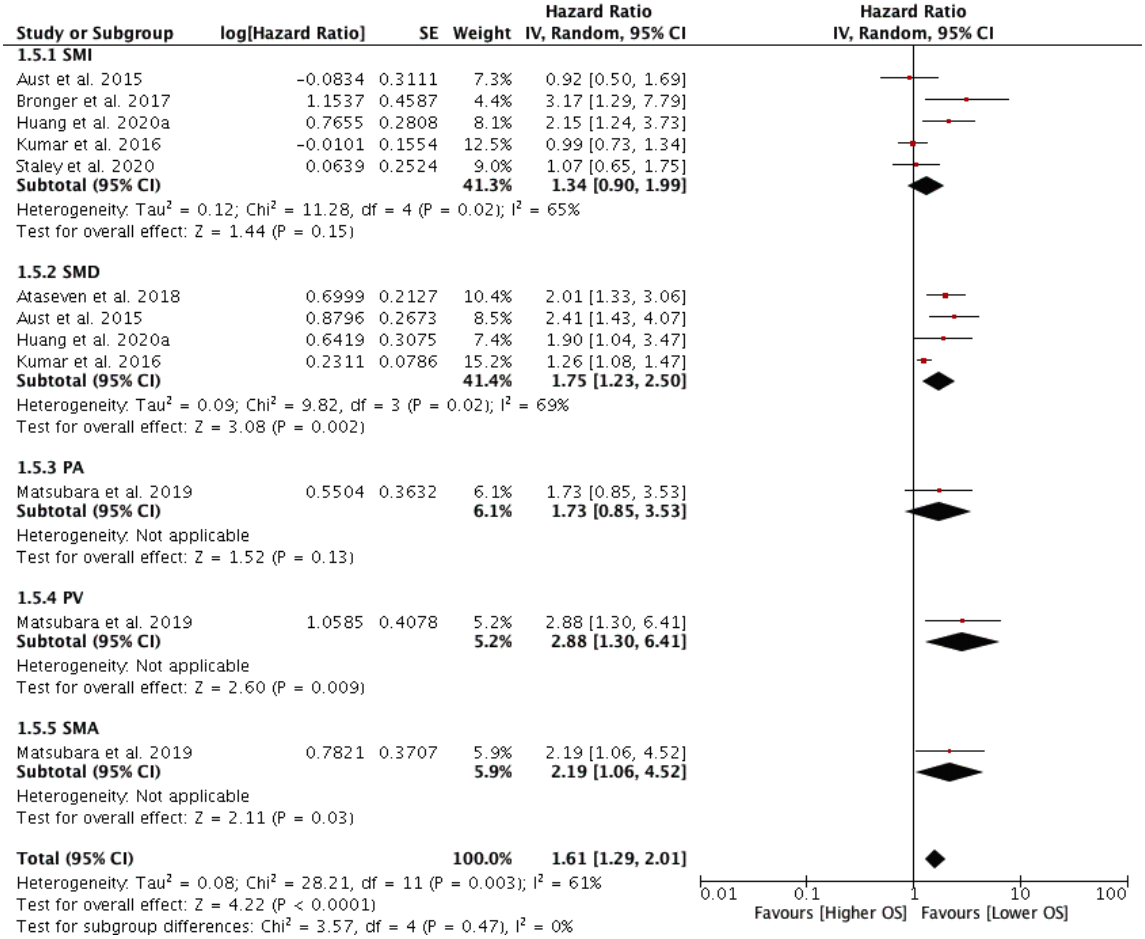


Appendix 11. Forest plot of univariable results for pre-treatment sarcopenia measured <60 days before treatment and overall survival in ovarian cancer patients.



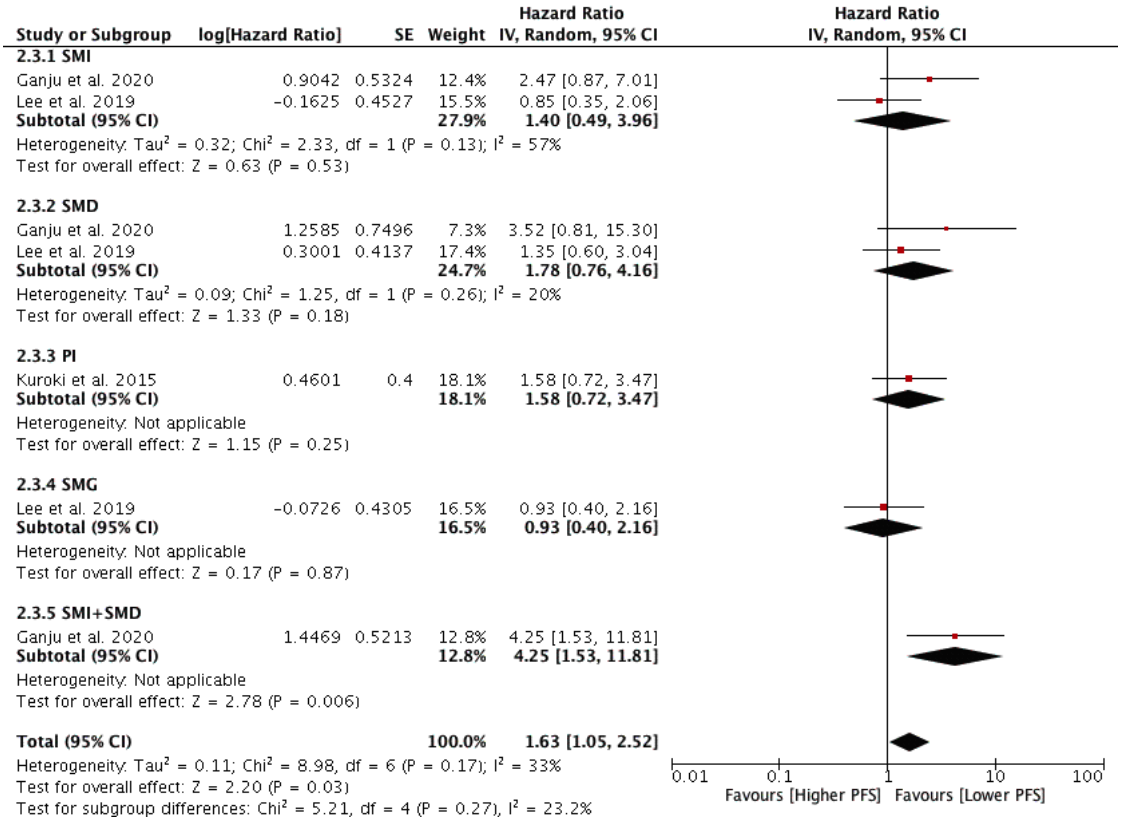
Abbreviations: CI – confidence interval, OS – overall survival, PI- psoas index, SMD – skeletal muscle density, SMI – skeletal muscle index.

Appendix 12. Forest plot of univariable results for pre-treatment sarcopenia and overall survival in epithelial ovarian cancer patients.



Abbreviations: CI – confidence interval, OS – overall survival, PA – psoas area, PI- psoas index, PV – psoas volume, SMA – skeletal muscle area, SMD – skeletal muscle density, SMI – skeletal muscle index.

Appendix 13. Forest plot of univariable results for pre-treatment sarcopenia measured <60 days before treatment and overall survival in endometrial cancer patients.



Abbreviations: CI – confidence interval, PFS – progression free survival, PI - psoas index, SMD – skeletal muscle density, SMG – skeletal muscle gauge, SMI – skeletal muscle index.

Appendix 14. Narrative reporting of multivariable analysis results from cox-proportional hazard regression analysis for pre-treatment sarcopenia (using four sarcopenia assessments: SMI, SMD, PV, SMA) and overall survival in ovarian cancer patients.

Study	Adjusted Result	Comments
SMI		
Aust et al. (29)	HR:1.23, 0.61-2.48, P=0.565	Adjusted results indicated low SMI was not an independent predictor of lower OS.
Bronger et al. (42)	HR:2.89, 1.11-7.54, P=0.031	Adjusted results indicated low SMI was an independent predictor of lower OS.
Huang et al. (30)*	HR:1.08, 1.03-1.12, P=0.001	Adjusted results indicated low SMI was an independent predictor of lower OS.
Huang et al. (46)*	HR:1.01, 1.03-1.11, P=0.002	Adjusted results indicated low SMI was an independent predictor of lower OS.
Kim et al. (47)	HR:0.87, 0.49-1.55, P=0.636	Adjusted results indicated low SMI was not an independent predictor for lower OS.
Rutten et al. (57)	HR:1.36, 0.97-1.92, P=0.076	Adjusted results indicated low SMI was not an independent predictor of lower OS.
SMD		
Ataseven et al. (41)	HR:1.79, 1.22-2.62, P=0.003	Adjusted results indicated low SMD was an independent predictor of lower OS.
Aust et al. (29)	HR:2.25, 1.09-4.65, P=0.028	Adjusted results indicated low SMD was an independent predictor of lower OS.
Huang et al. (30)*	HR:1.05, 1.01-1.10, P=0.04	Adjusted results indicated low SMD was an independent predictor of lower OS.
Huang et al.	HR:1.05, 1.01-1.10, P=0.01	Adjusted results indicated low SMD was

(46)*		an independent predictor for OS.
Kumar et al. (49)	HR:1.23, 1.05-1.43, P=0.009	Adjusted results indicated low SMD was an independent predictor for OS.
PV		
Matsubara et al. (53)	HR:0.98, 0.37-2.62, P=0.969	Adjusted results indicated low PV was not an independent predictor for lower OS.
SMA		
Matsubara et al. (53)	HR:2.11, 0.77-5.80, P=0.15	Adjusted results indicated low SMA was not an independent predictor for lower OS.

Abbreviations: CI – confidence intervals, HR – hazard ratio, PV – psoas volume, OS – overall survival, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

Studies marked with an Asterisk (*) contain some of the same population.

Appendix 15. Narrative reporting of multivariable analysis results from cox-proportional hazard regression analysis for pre-treatment sarcopenia (using six sarcopenia assessments: SMI, SMD, PI, PA, SMG, SMI+SMD) and overall survival in endometrial cancer patients.

Study	Adjusted Result	Comments
SMI		
Lee et al. (51)	HR:0.63, 0.23-1.72, P=0.37 (model A) HR:0.67, 0.27-1.70, P=0.40 (model B)	Adjusted results indicated low SMI was not an independent predictor of lower OS.
SMD		
Lee et al. (51)	HR:1.18, 0.48-2.86, P=0.72 (model A) HR:1.33, 0.54-3.28, P=0.54 (model B)	Adjusted results indicated low SMD was not an independent predictor of lower OS.
PI		
Kuroki et al. (50)	HR:1.98, 0.81-4.86, P=0.13	Adjusted results indicated low PI was not an independent predictor of lower OS.
PA		
Gillen et al. (45)	HR:1.83, 0.34-1.72, P=0.09	Adjusted results indicated low PA was not an independent predictor of lower OS.
SMG		
Lee et al. (51)	HR:0.73, 0.29-1.79, P=0.49	Adjusted results indicated low SMG was not an independent predictor of lower OS.
SMI+SMD		
Ganju et al. (31)	HR:3.02, 1.04-8.74, P=0.04	Adjusted results indicated low SMI+SMD was an independent predictor of low OS.

Abbreviations: CI – confidence intervals, HR – hazard ratio, PI – psoas index, PV – psoas volume, OS – overall survival, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index.

Appendix 16. Narrative reporting of multivariable analysis results for cox-proportional hazard regression analysis for pre-treatment sarcopenia (using one sarcopenia assessment: SMI) and overall survival in ovarian, endometrial and cervical cancer patients.

Study	Adjusted Result	Comments
SMI		
Nattenmuller et al. (55)	HR:1.04, 0.93-1.15, P=0.510 (model 1) HR:0.987, 0.94-1.03, P=0.530 (model 2)	Adjusted results indicated low SMI was not an independent predictor of low OS.

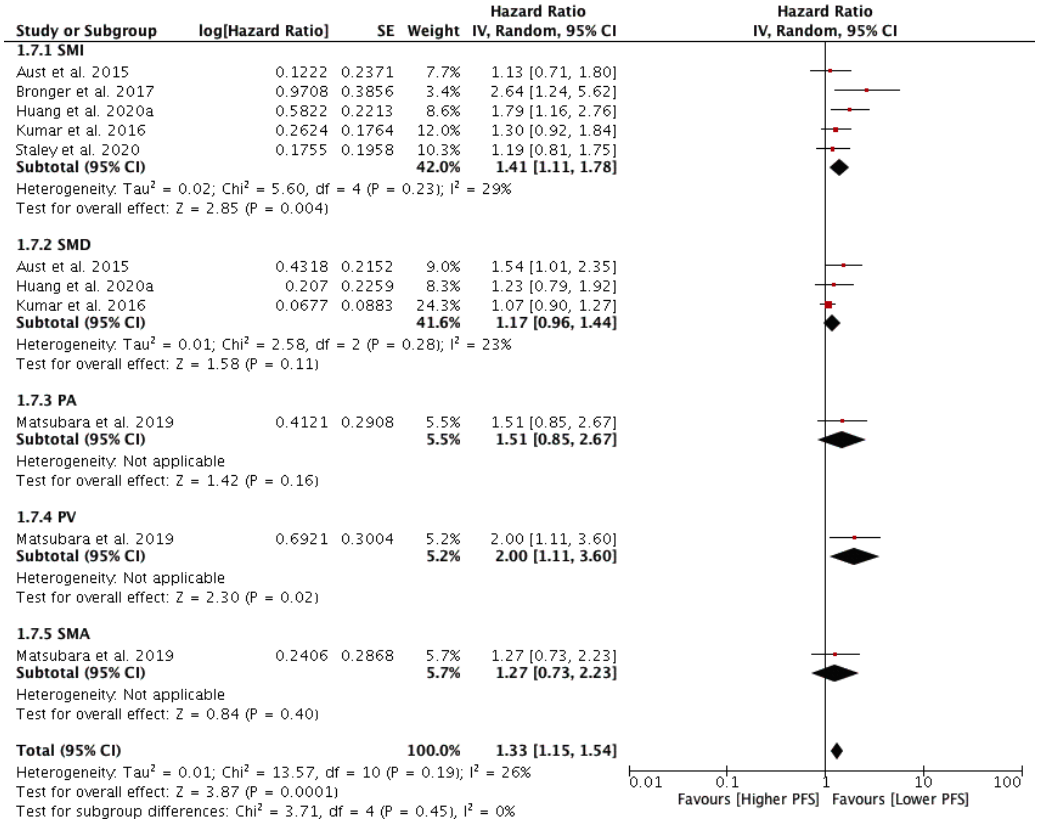
Abbreviations: CI – confidence intervals, HR – hazard ratio, OS – overall survival, SMI – skeletal muscle index.

Appendix 17. Narrative reporting of multivariable analysis results from cox-proportional hazard regression analysis for pre-treatment sarcopenia (using one sarcopenia assessment: PI) and overall survival in cervical cancer patients.

Study	Adjusted Result	Comments
PI		
Yoshikawa et al. (62)	HR:4.55, 1.36-1.82, P=0.014	Adjusted results indicated low PI was an independent predictor of lower OS.

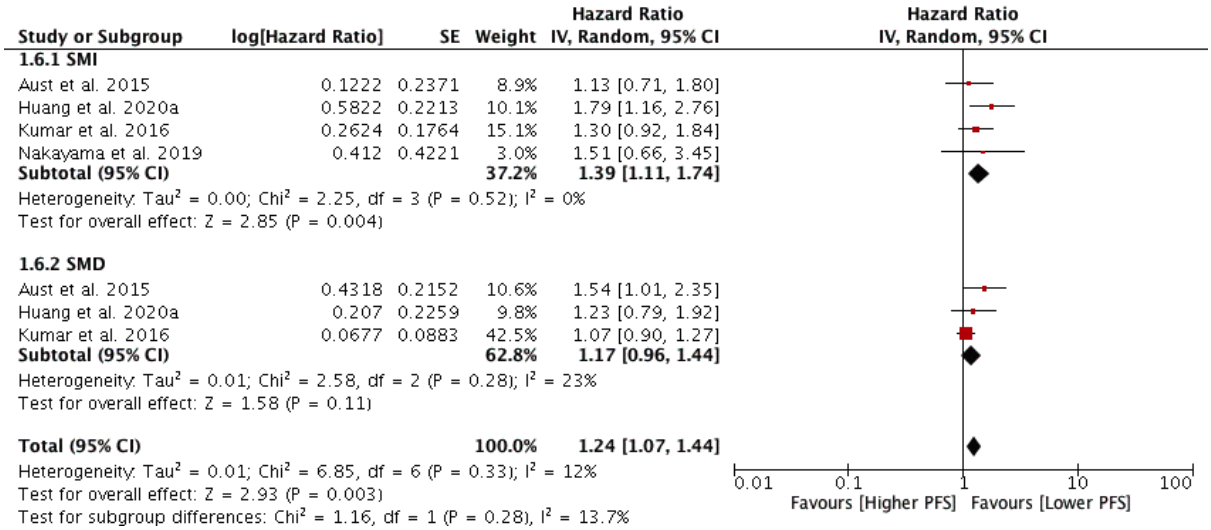
Abbreviations: CI – confidence intervals, HR – hazard ratio, OS – overall survival, PI – psoas index.

Appendix 18. Forest plot of univariable results for pre-treatment sarcopenia and progression free survival in epithelial ovarian cancer patients.



Abbreviations: CI – confidence interval, PFS – progression free survival, PA – psoas area, PI - psoas index, PV – psoas volume, SMA – skeletal muscle area, SMD – skeletal muscle density, SMI – skeletal muscle index.

Appendix 19. Forest plot of univariable results for pre-treatment sarcopenia measured <60 days before treatment and progression free survival in ovarian cancer patients.



Abbreviations: CI – confidence interval, PFS – progression free survival, SMD – skeletal muscle density, SMI – skeletal muscle index.

Appendix 20. Narrative reporting of multivariable analysis results from cox-proportional hazard regression analysis for pre-treatment sarcopenia (using three sarcopenia assessments: SMI, SMD, PV) and progression free survival in ovarian cancer patients.

Study	Adjusted Result	Comments
SMI		
Aust et al. (29)	HR:1.31, 0.76-2.26, P=0.336	Adjusted results indicated low SMI was not an independent predictor of lower PFS.
Bronger et al. (42)	HR:2.52, 1.10-5.81, P=0.03	Adjusted results indicated low SMI was an independent predictor of lower PFS.
Huang et al. (30)*	HR:1.04, 1.01-1.08, P=0.008	Adjusted results indicated low SMI was an independent predictor of lower PFS.
Huang et al. (46)*	HR:1.03, 1.01-1.06, P=0.04	Adjusted results indicated low SMI was an independent predictor of lower PFS.
Kim et al. (47)	HR:1.29, 0.91-1.84, P=0.157	Adjusted results indicated low SMI was not an independent predictor of lower PFS.
SMD		
Aust et al. (29)	HR:1.22, 0.69-2.17, P=0.5	Adjusted results indicated low SMD was not an independent predictor of lower PFS.
Huang et al. (30)*	HR:1.02, 0.98-1.05, P=0.3	Adjusted results indicated low SMD was not an independent predictor of lower PFS.
Huang et al. (46)*	HR:1.04, 1.01-1.09, P=0.03	Adjusted results indicated low SMD was an independent predictor of lower PFS.
PV		
Matsubara et al. (53)	HR:0.82, 0.40-1.65, P=0.576	Adjusted results indicated low PV was not an independent predictor of lower PFS.

Abbreviations: CI – confidence intervals, HR – hazard ratio, PFS – progression free survival, PV – psoas volume, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

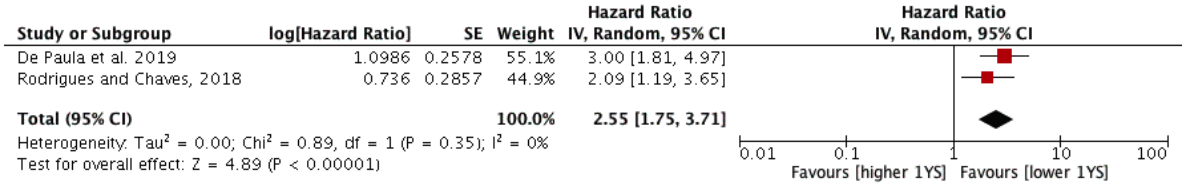
Studies marked with an Asterisk (*) contain some of the same population.

Appendix 21. Narrative reporting of multivariable analysis results from cox-proportional hazard regression analysis for pre-treatment sarcopenia (using four sarcopenia assessments: SMI, SMD, PA, SMG) and progression free survival in endometrial cancer patients.

Study	Adjusted Result	Comments
SMI		
Lee et al. (51)	HR:0.61, 0.25-1.48, P=0.28 (model A) HR:0.57, 0.29-1.52, P=0.33 (model B)	Adjusted results indicated low SMI was not an independent predictor of lower PFS.
SMD		
Lee et al. (51)	HR:1.19, 0.54-2.64, P=0.67 (model A) HR:1.19, 0.54-2.65, P=0.66 (model B)	Adjusted results indicated low SMD was not an independent predictor of lower PFS.
PA		
Gillen et al. (45)	HR:1.09, 0.53-2.27, P=0.81	Adjusted results indicated low PA was not an independent predictor of lower PFS.
SMG		
Lee et al. (51)	HR:0.63, 0.28-1.42, P=0.27	Adjusted results indicated low SMG was not an independent predictor of lower PFS.

Abbreviations: CI – confidence intervals, HR – hazard ratio, PFS – progression free survival, PA – psoas area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index.

Appendix 22. Forest plot of univariable results for pre-treatment sarcopenia (using SMI) and 1-year survival in endometrial cancer patients. The forest plot showed a negative effect of



sarcopenia on overall survival (HR:2.55, 1.75-3.71, P=<0.00001).

Abbreviations: CI – confidence intervals, HR – hazard ratio, SMI – skeletal muscle index, 1YS – 1-year survival.

Appendix 23. The 5-year overall survival and progression-free survival rates of pre-treatment sarcopenic (using three sarcopenia assessments: SMI, SMD, SMG) and non-sarcopenic patients from five studies on gynaecology cancer patients.

Study	Cancer Type	Sarcopenia Assessment	Sarcopenic 5YS rate % (n)	Non-sarcopenic 5YS rate % (n)	Sarcopenic 5Y-PFS rate % (n) or median months (range)	Non-sarcopenic 5Y-PFS rate % (n) or median months (range)
Huang et al. (30)*	OC	SMI SMD SMG	52.5 (12/50)[a] 48.9 (10/48)[b] 44.9 (10/49)[c]	64.2 (27/97)[a] 65.0 (29/99)[b] 67.9 (29/98)[c]	20.6 (4/50)[e] 22.9 (4/48)[f] 27.3 (5/49)	40.8 (16/97)[e] 37.7 (16/99)[f] 36.3 (20/98)
Huang et al. (46)*	OC	SMI SMD	54.7 (NR) 48.4 (NR)[d]	63.2 (NR) 65.7 (NR)[d]	22.3 (NR)[g] 21.8 (NR)	38.5 (NR)[g] 37.7 (NR)
Kim et	OC	SMI	64.1 (55/76)	59.3 (67/103)	18.3 (15.5-	18.7 (14.2-

al. (47)					21.1)	23.2)
Lee et al. (51)	EC	SMD	76.7 (21/44)	81.3 (31/87)	70.5 (20/44)	80.7 (31/87)
Lee et al. (32)	CC	SMI SMD	82.6 (67/127) 80.9 (91/154)	83.0 (64/118) 86.1 (40/91)	NR	NR

Abbreviations: CC – cervical cancer, EC – endometrial cancer, NR – not reported, OC – ovarian cancer, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index, 5Y-PFS – 5 year progression free survival, 5YS – 5 year survival.

Studies marked with an asterisk (*) contain some of the same population.

Values in the same row with the same superscript were statistically significant using K-M analysis ($p<0.05$).

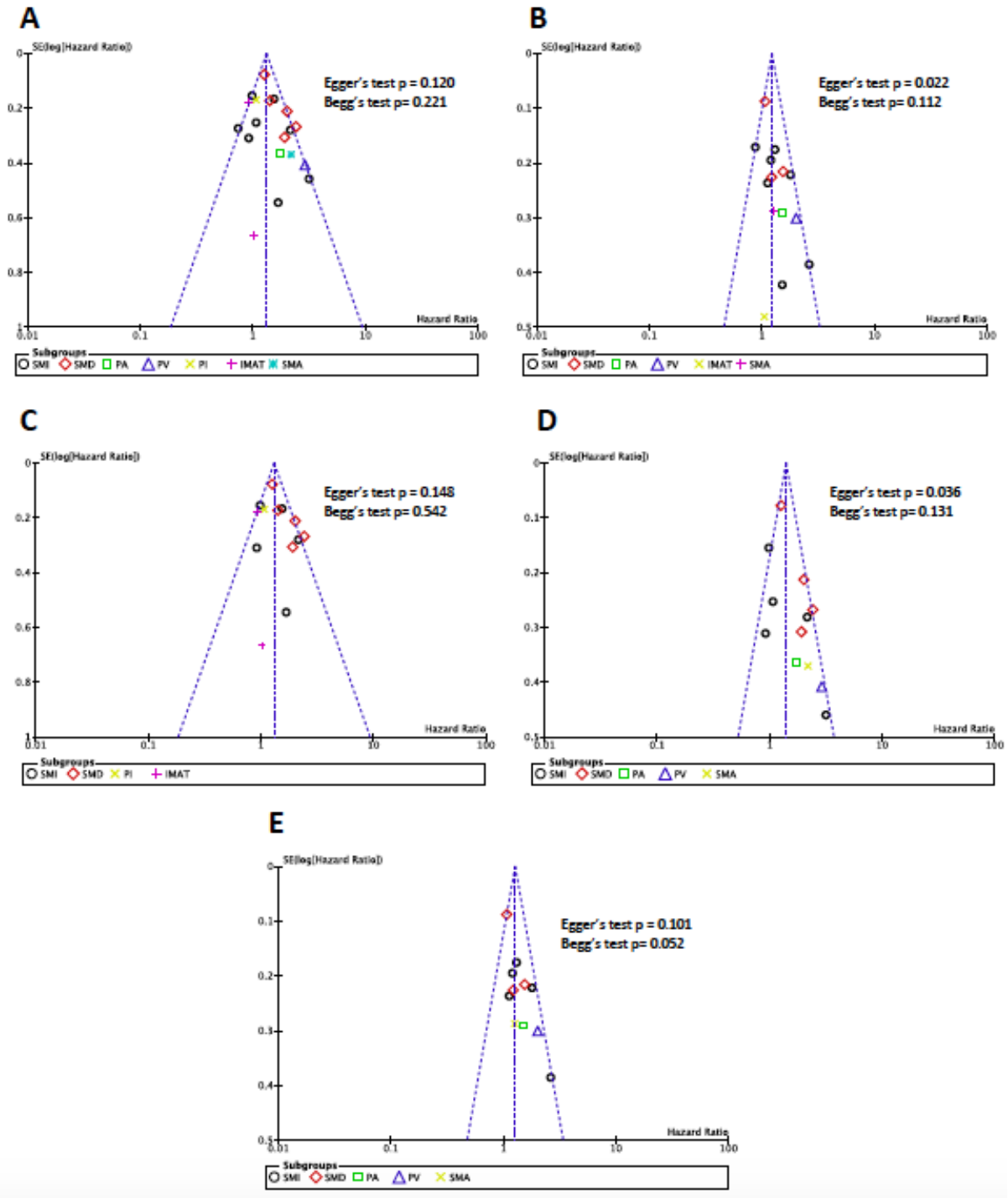
Appendix 24. Characteristics and main findings of longitudinal analysis in nine studies.

Study	Sample size	Cancer site	Duration between pre- and post-treatment CT scan (days)	Mean change in sarcopenia assessment	Outcomes measured	Main findings
Bronger et al. (42)	43	EOC	Median = 30	-1.4% SMI per 100 days -1.4% SMD per 100 days	OS	Change in SMI or SMD was not associated with OS.
Huang et al. (46)	139	EOC	Median = 182	-1.8% SMI per 180 days -1.7% SMD per 180 days	OS, PFS, 5YS, 5Y-PFS	SMI change, not SMD change, was independently associated with OS and PFS.
Kiyotoki et al. (48)	60	CC	NR	51.6% >5% loss of SMA 53.3% >5% loss of PA	OS, PFS	PA loss >15% was an independent predictor of OS and PFS.
Lee et al. (32)*	245	CC	Median = 146	-0.6% SMI per 150 days -2.9% SMD per 105 days	OS, 5YS	SMI loss >10% was an independent prognostic factor for reduced OS.
Lee et al. (51)	131	EC	NR	-0.2% SMI per 210 days -2.1% SMD per 210 days -2.2% SMG per 210 days	OS, PFS, 5YS, 5Y-PFS	SMD and SMG loss were independent prognostic factors for poorer OS and PFS.
Lee et al. (52)*	278	CC	Median = 143	-1.0% SMI per 150 days -2.9% SMD per 150 days	3Y-DRFS	SMI loss >5% was an independent prognostic factor for worse DRFS.
Rutten et al. (59)**	123	OC	NR	-5.2% SMA per 100 days +5.6% IMAT per 100 days	OS	Loss of SMA was an independent prognostic factor for lower OS.
Rutten et al. (58)**	150	OC	Median = 82.4	-5.8% SMA per 100 days +1.4% PA per 100 days	OS	Loss of SMA was an independent prognostic factor for lower OS.
Sanchez et al. (60)	55	CC	Mean = 122	-5.5% SMI per 200 days	OS, DR	SMI loss >10% had a significantly higher risk of tumour recurrence and a tendency towards reduced OS.

Abbreviations: CC – cervical cancer, DR – disease recurrence, DRFS – disease recurrence free survival, EC – endometrial cancer, EOC – epithelial ovarian cancer, IMAT – intramuscular adipose tissue, NR – not reported, OC – ovarian cancer, OS – overall survival, PA – psoas muscle area, PFS – progression free survival, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index, 5Y-PFS – 5-year progression free survival, 5YS – 5-year survival.

Studies marked with the same number of Asterisks (*) are studies where some of the same population has been used.

Appendix 25. Funnel plots with Egger's and Begg's tests to determine publication bias in 5 meta-analyses where effect sizes were more than 10. **A** = Pre-treatment sarcopenia and overall survival in ovarian cancer (corresponding forest plot shown in figure 2). **B** = Pre-treatment sarcopenia and progression free survival in ovarian cancer (corresponding forest plot shown in figure 3). **C** = Pre-treatment sarcopenia measured <60 days before treatment and overall survival in ovarian cancer (corresponding forest plot shown in appendix 11). **D** = Pre-treatment sarcopenia and overall survival in epithelial ovarian cancer (corresponding forest plot shown in appendix 12). **E** = Pre-treatment sarcopenia and progression free survival in epithelial ovarian cancer (corresponding forest plot shown in appendix 14).



Appendix 26. Summary of main findings.

Outcome	Main Findings
Overall Survival	Overall • Pre-treatment sarcopenia had an overall negative effect on OS in meta-analysis of univariate results. • Pre-treatment sarcopenia was not a unanimous independent prognostic factor for OS. Ovarian • Pre-treatment sarcopenia had a statistically significant overall negative effect on OS in meta-analysis of univariate results. • Low SMD had the largest, statistically significant, negative effect on OS in subgroup meta-analysis of univariate results. • Low SMD was an independent prognostic factor for OS in five studies and low SMI was an independent prognostic factor in three. Endometrial • Pre-treatment sarcopenia had an overall negative effect on OS in meta-analysis of univariate results. • Low SMI and SMD combined had the largest, statistically significant, negative effect in subgroup meta-analysis of univariate results. • Low SMI and SMD combined was an independent prognostic factor for OS in one study. Cervical • Pre-treatment sarcopenia had an overall negative effect on OS in meta-analysis of univariate results. • Low PI had the largest negative effect in subgroup meta-analysis of univariate results. • Low PI was an independent prognostic factor in one study.
Progression Free Survival	Overall • Pre-treatment sarcopenia had an overall negative effect on PFS in meta-analysis of univariate results. • Pre-treatment sarcopenia was not a unanimous independent prognostic factor for PFS. Ovarian • Pre-treatment sarcopenia had a statistically significant overall negative effect on PFS in meta-analysis of univariate results. • Low SMI had the largest, statistically significant, negative effect on PFS in subgroup meta-analysis of univariate results. • Three studies showed low SMI was an independent prognostic factor and one study found SMD was an independent prognostic factor for PFS. Endometrial • Pre-treatment sarcopenia had an overall, statistically significant, negative effect on PFS in meta-analysis of univariate results. • None of the studies that carried out multivariable analysis found pre-treatment sarcopenia was an independent prognostic factor for PFS. Cervical • Pre-treatment sarcopenia had an overall negative effect on PFS in meta-analysis of univariate results.
1 Year Survival	Endometrial Pre-treatment low SMI had a strong, statistically significant, negative effect on 1YS in meta-analysis of univariate results.
3 Year Survival	Endometrial • The 3YS rate was lower in the sarcopenic compared to non-sarcopenic group in one study. Cervical

	The 3YS rate was lower in the sarcopenic compared to non-sarcopenic group in one study.
5 Year Survival	Overall The 5YS and 5Y-PFS rates were mostly lower in sarcopenic compared to non-sarcopenic patients.
Complications and Length of Stay	Overall Pre-treatment sarcopenia did not have significant effects on these outcomes.
Change in Sarcopenia over Treatment and Effect on Survival	Overall • Loss of muscle mass and quality had negative effects on survival outcomes. Ovarian • One study found loss of SMI, not SMD, was an independent prognostic factor for lower OS and PFS. • Loss of SMA was an independent prognostic factor for lower OS in two studies. • One study found no association between muscle change and outcome. Endometrial • SMD and SMG loss were independent prognostic factors for lower OS and PFS in one study. Cervical • Muscle mass loss was an independent prognostic factor in all four studies. One study assessed SMD loss and found no significant association with outcomes.

Abbreviations: OS – overall survival, PI – psoas muscle index, PFS – progression free survival, SMA – skeletal muscle area, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMG – skeletal muscle gauge, SMI – skeletal muscle index, 5Y-PFS – 5-year progression free survival, 5/3/1YS – 5/3/1-year survival.

Appendix 27. Mean and range cut-off points for sarcopenia using the three most frequently used assessments in this review: SMI, SMD and PI.

Assessment	Mean (range) cut-off overall	Mean (range) cut-off in OC	Mean (range) cut-off in EC	Mean (range) cut-off in CC
SMI (cm^2/m^2)	39.03 (30.88-42.4)	38.9 (30.88 – 41.0)	40.51 (38.9 – 42.4)	38.6 (36.3 – 41.0)
SMD (HU)	34.12 (30.0-41.0)	35.1 (32.0– 35.5)	34.0 (30.0 – 37.0)	30.7 (n/a)
PI (cm^2/m^2)	4.15 (3.72-4.65)	4.65 (n/a)	4.33 (n/a)	3.81 (3.72 – 3.9)

Abbreviations: CC – cervical cancer, EC – endometrial cancer, n/a – not applicable (used when there was not enough data to calculate a mean or range), OC – ovarian cancer, PI – psoas index, SMD – skeletal muscle density (includes measures of muscle attenuation (MA)), SMI – skeletal muscle index.

Appendix 28. Timing of pre-treatment sarcopenia assessment used for sensitivity analysis.

Timing	*Studies*
"Baseline"	***Bronger et al. (42)***
	Kim et al. (47)
	Staley et al. (61)
<1 month before treatment	***Aust et al. (29)***
	De Paula et al. (44)
	Ganju et al. (31)
	Huang et al. (30)
	Huang et al. (46)
	Kiyotoki et al. (48)
	Kumar et al. (49)
	Lee et al. (32)
	Nakayama et al. (35)
	Rodrigues and Chaves (56)
	Sanchez et al. (60)
<60 days before treatment	***Ataseven et al. (41)***
	Kuroki et al. (50)
	Rutten et al. (57)
"Prior to treatment" – no more indication of timing	***Conrad et al. (43)***
	Gillen et al. (45)
	Lee et al. (32)
	Lee et al. (52)
	Matsubara et al. (53)
	Matsuoka et al. (54)
	Nattenmuller et al. (55)
	Rutten et al. (58)
	Rutten et al. (59)
	Yoshikawa et al. (62)

Appendix 29. List of the 27 excluded studies during screening of 54 studies.

ARAKAKI, Y., SHIMOJI, Y., NAKASONE, T., TAIRA, Y., NAKAMOTO, T., OOYAMA, T., KUDAKA, W. & AOKI, Y. 2019. SARCOPENIA IS REALLY PROGNOSTIC FACTOR OF OUTCOME IN PATIENTS WITH CERVICAL CANCER WITH CONCURRENT CHEMORADIOTHERAPY? *International Journal of Gynecological Cancer,* 29**,** A196-A196.

AREDES, M. A., GARCEZ, M. R. & CHAVES, G. V. 2018. Influence of chemoradiotherapy on nutritional status, functional capacity, quality of life and toxicity of treatment for patients with cervical cancer. *Nutrition & Dietetics,* 75**,** 263-270.

ATASEVEN, B., GONZALEZ LUENGO, T., ALESINA, P. F., TRAUT, A., PRADER, S., KOCH, J. A., HEITZ, F., WALTERING, K., HARTER, P., DU BOIS, A. & HEIKAUS, S. 2018. Impact of quantitative body composition on survival in patients with epithelial ovarian cancer undergoing primary debulking surgery. *Geburtshilfe und Frauenheilkunde. Conference,* 78.

BRUNO, K. D. A., DE PAULA, N. S., AREDES, M. A. & CHAVES, G. V. 2017. MON-P087: High-Radiodensity Skeletal Index as Predictor of Early Mortality in Ovarian Adenocarcinoma. *Clinical Nutrition,* 36**,** S211-S212.

CONRAD, L. B., AWDEH, H., ACOSTA-TORRES, S., CONRAD, S. A., BAILEY, A. A. & LEA, J. S. 2016. Defining sarcopenia in advanced ovarian cancer patients. *Obstetrics and Gynecology,* 127 (Supplement 1)**,** 135S.

CONRAD, L. B., AWDEH, H., BAILEY, A. A., MILLER, D. & LEA, J. S. 2016. Core muscle index is prognostic of survival in advanced ovarian cancers. *Gynecologic Oncology,* 143 (1)**,** 206-207.

CONRAD, L. B., SCHMIDT, S., BAILEY, A. A., CARLSON, M., KEHOE, S., RICHARDSON, D., MILLER, D. S. & LEA, J. S. 2017. Patients with sarcopenia benefit from neoadjuvant chemotherapy in advanced ovarian cancer. *Gynecologic Oncology,* 147 (1)**,** 226.

DE PAULA, N. S., BRUNO, K. A., AREDES, M. A. & CHAVES, G. V. 2017. SUN-P097: High-Radiodensity Skeletal Muscle Index is the Best Predictor of Major Surgical Complications in Gynecologic Cancer. *Clinical Nutrition,* 36**,** S90-S90.

DE PAULA, N. S., BRUNO, K. D., AREDES, M. A. & CHAVES, G. V. 2018. Sarcopenia and Skeletal Muscle Quality as Predictors of Postoperative Complication and Early Mortality in Gynecologic Cancer. *International Journal of Gynecological Cancer,* 28**,** 412-420.

DE PAULA, N. S. & CHAVES, G. V. 2018. Skeletal muscle radiodensity and overall survival in endometrial cancer patients...European Society for Clinical Nutrition and Metabolism (ESPEN) 40th Congress, September 1-4, 2018, Madrid, Spain. *Clinical Nutrition,* 37**,** S82-S83.

FADADU, P. P., MCGREE, M. E., WEAVER, A. L., MOYNAGH, M. R., LANGSTRAAT, C. L., CLIBY, W. A. & KUMAR, A. 2020. Sarcopenia in advanced ovarian cancer: comparing neoadjuvant chemotherapy patients to primary cytoreductive surgery patients. *Gynecologic Oncology,* 156 (3)**,** e16-e17.

FLORES-CISNEROS, L., FERNANDEZ-LOAIZA, M., CETINA-PEREZ, L., CASTILLO-MARTINEZ, L., JIMENEZ-LIMA, R., GONZALEZ-ISLAS, D., LUVIAN-MORALES, J., SANCHEZ-LOPEZ, M., CASTRO-EGUILUZ, D. & ALARCON-BARRIOS, S. 2019. Body Composition Changes Evaluated by Bioelectrical Impedance in Women with Cervical Cancer under Chemoradiotherapy Treatment. *Clinical Nutrition,* 38 (Supplement 1)**,** S100.

GANJU, R. G., TENNAPEL, M. J., CHEN, A. M. & HOOVER, A. 2017. Prognostic significance of sarcopenia for patients treated by surgery and radiation for uterine cancer. *International Journal of Radiation Oncology Biology Physics,* 99 (2 Supplement 1)**,** E292.

GIL, K. M., FRASURE, H. E., HOPKINS, M. P., JENISON, E. L. & VON GRUENIGEN, V. E. 2006. Body weight and composition changes in ovarian cancer patients during adjuvant chemotherapy. *Gynecologic Oncology,* 103**,** 247-252.

INCI, G., MULLER, K., RICHTER, R., WOOPEN, H. & SEHOULI, J. 2020. Effects of sarcopenia and malnutrition on morbidity and mortality in gynecologic cancer surgery: Results of a prospective cohort study in 237 patients. *Journal of Cachexia, Sarcopenia and Muscle,* 11 (1)**,** 319.

KUMAR, A., DEJONG, S. R., MCGREE, M., WEAVER, A. L., CLIBY, B. A. & LANGSTRAAT, C. L. 2017. A novel frailty index is associated with sarcopenia and independently predicts survival in advanced ovarian cancer. *Gynecologic Oncology,* 145 (Supplement 1)**,** 65-66.

KUMAR, A., MOYNAGH, M., CLIBY, B. A., MCGREE, M., YOUNG, P., BAKKUM-GAMEZ, J. N., LANGSTRAAT, C. L., DOWDY, S. C., JATOI, A. & MARIANI, A. 2015. Sarcopenia as a predictor of surgical morbidity in advanced ovarian cancer patients. *Gynecologic Oncology,* 137**,** 53-53.

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RODRIGUES, C. S. & CHAVES, G. V. 2017. PT05.2: High-Radiodensity Skeletal Muscle Index: A Better Indicator of Poor Prognosis than Skeletal Muscle Index in Endometrial Cancer Patients. *Clinical Nutrition,* 36**,** S39-S39.

SCALETTA, G., QUAGLIOZZI, L., ERGASTI, R., MELE, M. C., RINNINELLA, E., CINTONI, M., GASBARRINI, A., MANFREDI, R., DEZIO, M., SCAMBIA, G. & FAGOTTI, A. 2019. Preoperative nutritional status assessed by CT scan in patients with newly-diagnosed advanced ovarian cancer: A prospective study. *International Journal of Gynecological Cancer,* 29 (Supplement 3)**,** A137.

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