Abstract. – OBJECTIVE: The aim of this study was to examine the association of sarcopenia and low muscle attenuation with survival and other clinical outcomes in patients with ovarian cancer.

MATERIALS AND METHODS: Systematic search was done in PubMed, EMBASE and Scopus databases for observational studies that documented the link between sarcopenia and outcomes of interest in patients with ovarian cancer, with long-term survival as a primary outcome. Other outcomes included risk of recurrence, progression-free survival and complications. Pooled effect sizes were reported as hazards ratio (HR), relative risk ratio (RR) or weighted mean difference (WMD). Random effects model was used for the analysis.

RESULTS: Twenty-two studies were selected, of which all, except one, were retrospective in design. Low skeletal muscle index (SMI, indicating muscle mass) (HR 1.30, 95% CI: 1.07, 1.58) and low muscle quality (HR 1.24, 95% CI: 1.03, 1.49) were associated with poor long-term survival, but not with the risk of recurrence and progression-free survival. Both low skeletal muscle index (SMI) (RR 1.49, 95% CI: 1.13, 1.98) and low muscle quality (RR 1.99, 95% CI: 1.04, 3.79) were associated with increased risk of complications.

CONCLUSIONS: Both low skeletal muscle mass and low muscle quality showed significant association with poor long-term survival and an increased risk of complications. However, they do not have a significant association with the risk of recurrence and progression-free survival. There is a need for more prospective studies to confirm these associations.

Key Words: Ovarian cancer, Muscle mass, Skeletal muscle index, Muscle quality, Muscle attenuation, Survival, Complications, Progression free survival, Meta-analysis.

Introduction

Ovarian cancer (OC) is associated with a high mortality risk mainly due to the asymptomatic growth, emergence of symptoms at an advanced stage and lack of validated and reliable screening methods. This cancer accounts for nearly 2,40,000 new cases globally and 1,50,000 deaths annually. There has been a substantial advancement in the staging procedures and management of OC. However, this advancement had only minimal effect on the long-term survival rates (10-15 years of follow-up) of cancer patients. While the 5-year survival rates of the OC patients improved, studies suggest that it is related to the improved disease control and does not reflect the improvement in the chances for cure. Several factors influencing the prognosis of ovarian cancer include, but are not limited to, age at diagnosis, stage of the tumor, residual tumor volume and histology. Studies have shown that malnutrition and abnormal body composition could also adversely affect the prognostic outcomes. A recent study showed that around 70% of the patients with ovarian cancer are malnourished. Involuntary weight loss and sarcopenia are important components of cancer cachexia. Sarcopenia is a progressive and generalized loss of skeletal muscle mass, muscle strength and overall physical performance, and is associated with poor tolerance to chemotherapeutic drugs, increased risk of post-operative complications and a reduced survival in different cancers.

In the case of ovarian cancer, establishing a diagnosis of cachexia is particularly challenging as the weight loss is often masked by accompanying ascites. Therefore, measuring skeletal mass instead...
of body weight is considered to be more reliable. There are several techniques to measure muscle mass/quantity, including bioelectrical impedance analysis (BIA), dual-energy absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI)\textsuperscript{14,21,22}. Of them, MRI and CT are considered the golden standard\textsuperscript{14,21,22}. An additional advantage of CT is that it may be used to measure skeletal muscle mass in patients that have a condition that requires several CT-based examinations, which is often a case in OC patients. Sarcopenia is diagnosed using two commonly used indices: skeletal muscle index (SMI) and skeletal muscle radiation attenuation (SMRA). SMI indicates muscle mass quantity and is calculated as the total muscle area on the CT scan adjusted for height\textsuperscript{23-25}. SMRA is a measure of muscle quality (muscle fat content) and can be used as a surrogate marker of physical function\textsuperscript{23-25}.

There have been attempts in the form of reviews and meta-analysis to summarize the association between SMI and SMRA in OC patients with survival and complications\textsuperscript{26-29}. A meta-analysis by Ubachs et al\textsuperscript{26} that included eight studies found that low skeletal muscle index (Hazards ratio, HR 1.17) and low muscle attenuation (indicating increased muscle lipid content) (HR 1.13) was linked to higher risk of mortality. However, the quality of the included studies was low. Meta-analysis by McSherry et al\textsuperscript{27} included findings from six studies and found that sarcopenia did not correlate significantly with 3-year or 5-year survival. However, low muscle attenuation was associated with the increased risk of mortality at 3 and 5 years of follow-up. Damay et al\textsuperscript{28} included four studies in their review and found that sarcopenia was not associated with overall survival in OC patients that were treated with chemotherapy. Meta-analysis by Rinninella et al\textsuperscript{29} included 6 studies and found that low skeletal muscle index did not correlate with the overall survival. At the same time, they found a strong association of low skeletal muscle radiodensity with the lower overall survival. An extensive systematic search revealed that a substantial number of potentially relevant studies were not included in the previous reviews. Moreover, previous reviews\textsuperscript{26-29} did not look at outcomes based on the tumor stage, histologic type and mode of management. The aim of our study was to address the limitations of the previous reviews and provide the most updated evidence on the association of sarcopenia and low muscle attenuation with survival, complications and other clinical outcomes.

**Materials and Methods**

**Formulating the Search Strategy and Databases Searched**

A detailed search strategy was designed for systematic search for eligible studies in three databases i.e., PubMed, EMBASE and Scopus. The search strategy used consisted of the following terms: (sarcopenia OR skeletal muscle index OR SMI OR skeletal muscle radiation attenuation OR SMRA OR cachexia OR muscle depletion OR muscle wasting OR muscle loss OR muscle strength OR muscle atrophy OR depleted muscle OR skeletal muscle OR muscle attenuation) AND (ovarian cancer OR ovarian tumour OR ovarian carcinoma OR ovarian malignancy OR Ovarian neoplasm OR ovarian adenocarcinoma) AND (survival OR mortality OR complications OR clinical outcome OR prognosis OR recurrence free survival OR event free survival OR treatment outcome). The electronic search aimed at identifying English language studies published until 30th September 2022. The review was registered in PROSPERO (registration number CRD42022366180) and followed the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines\textsuperscript{30}.

**Study Selection and Data Extraction**

Only observational (prospective or retrospective cohort, case-control or cross-sectional) studies that had documented the association between sarcopenia, measured in terms of either SMI or SMRA, or both, in patients with ovarian cancer and with long-term survival as the primary outcome of interest were considered for inclusion. Secondary outcomes included risk of complications and other post-operative outcomes.

Titles and abstracts were independently screened by two authors to identify eligible studies that were then subjected to the full text review. The data from a final set of eligible studies was extracted using a pre-tested sheet that was comprised of variables related to study identifier, design, characteristics of participants, sample size and key outcome effects. Any disagreements or discrepancies were resolved by discussions or by referring to a third review author.

**Statistical Analysis**

Data analysis was done using STATA 16 software (College Station, TX, USA). Pooled effect sizes were reported either as hazards ratio (HR) or relative risk (RR) for categorical outcomes and as
weighted mean difference (WMD) for continuous outcomes. The included studies seemed to differ in the baseline characteristics of their subjects, tumor characteristics such as stage and histologic type, cut-offs used to define sarcopenia, management provided, duration of follow-up and study setting. Since these differences could create substantial heterogeneity, random effects model was selected a priori for the analysis, and the Restricted Maximum Likelihood Method (REML) was used for all outcomes of interest. Publication bias was assessed using Egger’s test\textsuperscript{31}. Assessment of the risk of bias was done using the Newcastle-Ottawa Scale\textsuperscript{32}. A \( p \)-value lower than 0.05 was used to denote statistical significance.

Subgroup analysis was conducted based on the type of study design (retrospective and prospective), stage of tumor (I/II, exclusively III/IV and predominantly III/IV), histologic grade (exclusively serous and predominantly serous) and mode of management [Primary debulking surgery (PDS); primary debulking surgery and adjuvant chemotherapy (PDS+AC); interval cytoreductive surgery (ICRS) and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy]. The term “predominantly” has been used to denote studies wherein, not all, but majority of the subjects had stage III/IV (i.e., predominantly III/IV) or serous histology (i.e., predominantly serous histologic type).

**Results**

**Selection of Suitable Studies and Their Characteristics**

Systematic search in the three databases resulted in the identification of 503 studies. After removal of the duplicates, titles and abstracts of 441 remaining studies were reviewed, and 397 studies were excluded, leaving 44 studies. Another 22 studies were excluded after full text review. Eventually, 22 studies were included in this meta-analysis\textsuperscript{33-54}. Figure 1 shows the process of study selection. Out of the 22 studies, nearly all (n=21) were retrospective, and one study\textsuperscript{37}.
was prospective. Five studies were conducted in Netherlands, four in Japan and three in USA. Two studies each were done in Germany, Switzerland, Belgium, and Austria. There were 15 studies where the patients had stage III/IV cancer, 6 studies where the patients had predominantly stage III/IV cancer and only one study had patients with stage I/II cancer (Table I). Based on the histological data, six studies had patients with serous ovarian cancer, 11 studies with predominant serous, 4 studies did not report the histologic type and one study had predominant non-serous type of ovarian cancer. Patients in 8 studies were managed with primary debulking surgery and adjuvant chemotherapy, 7 studies reported management through primary debulking surgery alone and in 4 studies, interval cytoreductive surgery was conducted. The quality assessment indicated that the studies were of good quality. The scores ranged from 7 to 9 (9 as a maximal score) (Table I).

**Overall Survival**

**Based on skeletal muscle mass index (SMI)**

We found a comparatively lower chance of long-term survival among patients with low SMI (HR 1.30, 95% CI: 1.07, 1.58; N=15, \(I^2=47.4\%\)), compared to those with normal and/or higher SMI (Figure 2). There was evidence of publication bias on Egger’s test (\(p\)-value=0.001). Findings of the subgroup analysis are presented in Table II. Higher risk of mortality was observed when pooling together studies with patients with advanced stage tumor (exclusively stage III/IV: HR 1.19, 95% CI: 1.01, 1.41; N=11, \(I^2=32.0\%\); predominantly stage III/IV: HR 1.94, 95% CI: 1.00, 3.75; N=3, \(I^2=36.0\%\)), serous histology (exclusively serous histologic type: HR 1.29, 95% CI: 0.90, 1.84; N=5, \(I^2=47.1\%\); predominantly serous histologic type: HR 1.55, 95% CI: 1.07, 2.24; N=7, \(I^2=64.5\%\)) and management with primary debulking surgery (HR 1.84, 95% CI: 1.01, 3.43; N=5, \(I^2=67\%\)) or primary debulking surgery and adjuvant chemotherapy (HR 1.26, 95% CI: 1.00, 1.62; N=6, \(I^2=40.3\%\)).

**Based on skeletal muscle quality**

Among patients with low muscle attenuation, there was lower chance of long-term survival (HR 1.24, 95% CI: 1.03, 1.49; N=5, \(I^2=36.9\%\)), compared to those with high muscle attenuation (Figure 3). Egger’s test (\(p\)-value=0.156) showed no publication bias. Higher risk of mortality was observed when pooling together studies with subjects with advanced stage tumor (exclusively stage III/IV: HR 1.12, 95% CI: 1.06, 1.19; N=4, \(I^2=0.0\%\); predominantly stage III/IV: HR 2.25, 95% CI: 1.09, 4.65; N=1), serous histology (predominantly serous histologic type: HR 1.12, 95% CI: 1.05, 1.19; N=2, \(I^2=0.0\%\) ) and management with primary debulking surgery (HR 1.42, 95% CI: 1.01, 1.98; N=1) or primary debulking surgery and adjuvant chemotherapy (HR 1.27, 95% CI: 0.96, 1.70; N=3, \(I^2=53.9\%\)) (Table III).

**Risk of Recurrence and Progression Free Survival (PFS)**

**Based on SMI**

Patients with low and normal SMI had similar risk of recurrence (HR 1.08, 95% CI: 0.36, 1.37; N=3, \(I^2=73.0\%\)) and progression free survival (PFS) (HR 1.15, 95% CI: 0.95, 1.40; N=7, \(I^2=40.8\%\)) (Figure 4-5). For both these outcomes, there was no indication of publication bias on Egger’s test (\(p\)=0.20 for recurrence and \(p\)=0.34 for PFS). Lower PFS was observed when studies with predominantly serous histology (HR 1.25, 95% CI: 1.02, 1.54; N=2, \(I^2=0.0\%\)) and those managed with primary debulking surgery and adjuvant chemotherapy (HR 1.36, 95% CI: 1.03, 1.80; N=3, \(I^2=21.3\%\)) were pooled together (Table II).

**Based on skeletal muscle quality**

Compared to patients with normal or high SMI, those with low SMI had a similar risk of progression free survival (PFS) (HR 1.22, 95% CI: 0.69, 2.16; N=1). There were no studies that reported the risk of recurrence based on muscle quality. Findings of the subgroup analysis are presented in Table III.

**Complications**

**Based on skeletal muscle mass index (SMI)**

We found a higher risk of complications among patients with low SMI (RR 1.49, 95% CI: 1.13,
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design and country</th>
<th>Stage (FIGO)</th>
<th>Predominant histologic type</th>
<th>Definition of sarcopenia</th>
<th>Mode of management</th>
<th>Measurement site</th>
<th>Samples size/ follow-up time</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chae et al33 (2021)</td>
<td>Retrospective South Korea</td>
<td>I/II</td>
<td>Serous (majority; 42%)</td>
<td>Skeletal mass index (SMI) ≤38.7 cm²/m²</td>
<td>Primary surgery or debulking surgery after neoadjuvant chemotherapy (in around 9%)</td>
<td>CT based 3rd lumbar level</td>
<td>82 (17 sarcopenic; 65 non-sarcopenic) Median-42 months</td>
<td>Survival: HR 21.9 (95% CI: 2.0, 199.9) Recurrence: HR 2.68 (95% CI: 1.20, 5.98) Length of hospital stay (LOS) (mean, SD): 17 (2.83) vs. 12 (8.0)</td>
</tr>
<tr>
<td>Kim et al34 (2020)</td>
<td>Retrospective South Korea</td>
<td>III/IV</td>
<td>Serous</td>
<td>Skeletal mass index (SMI) &lt;39.0 cm²/m²</td>
<td>Primary debulking surgery (75%) or neoadjuvant chemotherapy (25%)</td>
<td>CT based 3rd lumbar level</td>
<td>179 (76 sarcopenic; 103 non-sarcopenic) Median-43 months</td>
<td>Survival: HR 0.87 (95% CI: 0.49, 1.55) Recurrence: HR 1.08 (95% CI: 0.93, 1.26) Progression free survival: HR 1.29 (95% CI: 0.91, 1.84)</td>
</tr>
<tr>
<td>Mercan et al35 (2021)</td>
<td>Retrospective Turkey</td>
<td>IIIc</td>
<td>Serous</td>
<td>Total psoas index (TPI, cm²/m²): &lt;4 for 20-39 years; &lt; 2.88 for 40-49 years; &lt;2.43 for 50-59 years; &lt;2.20 for 60-69 years age; &lt;1.48 for 70-89 years</td>
<td>Cytoreduction surgery and hyperthermic intraperitoneal chemotherapy</td>
<td>CT based 3rd lumbar level (psoas muscle area measured)</td>
<td>40 (11 sarcopenic; 29 non-sarcopenic)</td>
<td>In-hospital mortality: RR 1.32 (95% CI: 0.13, 13.1) Overall complication: RR 5.27 (95% CI: 1.12, 24.8) Cardiac complication: RR 1.32 (95% CI: 0.28, 6.20) Pulmonary complication: RR 2.11 (95% CI: 1.14, 3.92) Infective complication: RR 3.16 (95% CI: 1.21, 8.28) Wound complication: RR 2.64 (95% CI: 0.62, 11.2) Acute renal failure: RR 1.76 (95% CI: 0.34, 9.14) Blood loss (&gt;1000 ccc) RR 1.32 (95% CI: 0.28, 6.20)</td>
</tr>
<tr>
<td>Nakayama et al36 (2019)</td>
<td>Retrospective Japan</td>
<td>III/IV (50% subject)</td>
<td>Serous (48%); endometroid (22%)</td>
<td>Skeletal mass index (SMI) &lt;30.88 cm²/m² (muscle mass) Intramuscular adipose tissue content (IMAC) &gt; -0.229 (high IMAC indicated poor muscle quality)</td>
<td>Primary debulking surgery and adjuvant combination chemotherapy</td>
<td>CT based 3rd lumbar level</td>
<td>94 (62 with low SMI; 32 with normal SMI) (21 with high IMAC and 73 with low IMAC)</td>
<td>Based on SMI Overall complication: RR 1.45 (95% CI: 0.57, 3.65) Length of hospital stay (LOS) (mean, SD): 18 (10.3) vs. 17.4 (8.7) Based on IMAC (for muscle quality) Overall complication: RR 0.41 (95% CI: 0.10, 1.63) Length of hospital stay (LOS) (mean, SD): 18 (10.3) vs. 17.4 (8.7) No significant difference in terms of overall survival (OS) and disease-free survival (DFS) based on skeletal muscle mass and muscle quality</td>
</tr>
</tbody>
</table>

Continued
# Table I (Continued). Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Study design and country</th>
<th>Stage (FIGO)</th>
<th>Predominant histologic type</th>
<th>Definition of sarcopenia</th>
<th>Mode of management</th>
<th>Measurement site</th>
<th>Samples size/ follow-up time</th>
<th>Key outcomes [Sarcopenic vs. normal]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ubachs et al37 (2020)</td>
<td>Prospective Netherlands</td>
<td>III</td>
<td>Serous (90%)</td>
<td>Skeletal mass index (SMI) decreases of &gt;2% in 100 days</td>
<td>Intravenous chemotherapy (3 cycles) followed by interval cytoreduction surgery</td>
<td>CT based 3rd lumbar level</td>
<td>212 (138 sarcopenic; 74 non-sarcopenic)</td>
<td>Survival: HR 1.41 (95% CI: 0.79, 2.51) Recurrence-free survival: HR 0.83 (95% CI: 0.52, 1.34) Recurrence: HR 0.95 (95% CI: 0.84, 1.07) Overall complications*: RR 2.47 (95% CI: 1.33, 4.59) *included pulmonary embolism, Peripheral neuropathy, thrombocytopenia, infections, renal insufficiency etc.</td>
</tr>
<tr>
<td>Yoshikawa et al (2021)</td>
<td>Retrospective Japan</td>
<td>III/IV</td>
<td>Serous (40%); clear cell (22%); endometrioid (15%)</td>
<td>Psoas muscle index (PMI) &lt;5.4 cm²/m²</td>
<td>Primary debulking surgery (57%); chemotherapy (43%)</td>
<td>CT based 5th lumbar level</td>
<td>72 (36 sarcopenic; 36 non-sarcopenic)</td>
<td>Survival: HR 3.87 (95% CI: 1.37, 12.1) Complications (includes ascites. Pulmonary embolism, deep vein thrombosis): RR 3.00 (95% CI: 1.56, 5.77)</td>
</tr>
<tr>
<td>Van der Zanden et al40 (2021)</td>
<td>Retrospective Netherlands</td>
<td>III/IV</td>
<td>Serous (94%)</td>
<td>Skeletal mass index (SMI) &lt;38.50 cm²/m² (muscle mass) Low skeletal muscle density: Mean muscle attenuation (MA) &lt;22.55 HU</td>
<td>Primary cytoreductive surgery (27%); Interval cytoreductive surgery (73%)</td>
<td>CT based 3rd lumbar level</td>
<td>213 (41 sarcopenic; 172 non-sarcopenic)</td>
<td>Survival: HR 1.73 (95% CI: 0.98, 3.03) Complications: RR 1.38 (95% CI: 0.92, 2.06) Infections: RR 2.00 (95% CI: 1.06, 3.77) Skeletal muscle quality Survival: HR 0.99 (95% CI: 0.52, 1.89) Complications: RR 2.57 (95% CI: 1.21, 5.45) Infections: RR 2.18 (95% CI: 1.26, 3.76) Blood loss (&gt;1,000 cc): RR 1.39 (95% CI: 0.83, 2.37)</td>
</tr>
<tr>
<td>Del Grande et al40 (2021)</td>
<td>Retrospective Italy</td>
<td>III/IV</td>
<td>Serous</td>
<td>Skeletal mass index (SMI) &lt;41.0 cm²/m²</td>
<td>Chemotherapy with or without debulking surgery</td>
<td>CT based 3rd lumbar level</td>
<td>69 (20 sarcopenic; 49 non-sarcopenic)</td>
<td>Survival (5-year): HR 0.95 (95% CI: 0.63, 1.44) Progression free survival (5-year): HR 0.91 (95% CI: 0.72, 1.16) Complications (related to toxicity of chemotherapy): RR 1.00 (0.62, 1.38)</td>
</tr>
</tbody>
</table>

*Continued*
Table 1 (Continued). Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Study design and country</th>
<th>Stage (FIGO)</th>
<th>Predominant histologic type</th>
<th>Definition of sarcopenia</th>
<th>Mode of management</th>
<th>Measurement site</th>
<th>Samples size/ follow-up time</th>
<th>Key outcomes (Sarcopenic vs. normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heus et al (2021)</td>
<td>Retrospective Netherlands</td>
<td>III/IV</td>
<td>Not provided</td>
<td>Based on skeletal mass index (SMI); cut-off not provided</td>
<td>Primary or interval debulking surgery; interval debulking in 76%</td>
<td>CT based L3-L4 level</td>
<td>298</td>
<td>Overall complication*: RR 0.99 (95% CI: 0.98, 1.01) includes sepsis, wound infection, ileus, pneumonia, urinary tract infection, thrombotic events</td>
</tr>
<tr>
<td>Huang et al (2020)</td>
<td>Retrospective Taiwan</td>
<td>III</td>
<td>Majority with serous carcinoma</td>
<td>Skeletal mass index (SMI) &lt;39.2 cm²/m²</td>
<td>Primary debulking surgery and adjuvant platinum-based chemotherapy</td>
<td>CT based L3-iliac crest</td>
<td>139 (47 sarcopenic; 92 non-sarcopenic)</td>
<td>Survival (5-year): HR 1.26 (95% CI: 1.00, 1.57) Progression free survival (5-year): HR 1.25 (95% CI: 1.00, 1.57)</td>
</tr>
<tr>
<td>Wang et al (2022)</td>
<td>Retrospective China</td>
<td>III/IV</td>
<td>Not provided</td>
<td>Based on skeletal muscle density (SMD); cut-off not provided</td>
<td>Primary debulking surgery and adjuvant platinum-based chemotherapy</td>
<td>CT based 3rd lumbar level</td>
<td>57 (26 sarcopenic; 31 non-sarcopenic)</td>
<td>SMD was not associated with overall survival (3-year and 5-year) (p&gt;0.05)</td>
</tr>
<tr>
<td>Aust et al (2015)</td>
<td>Retrospective Austria</td>
<td>III/IV</td>
<td>Non-serous (70%) Serous (30%)</td>
<td>Skeletal mass index (SMI) &lt;41.0 cm²/m² Skeletal muscle density (SMD) &lt;39 HU</td>
<td>Debulking followed by platinum-based chemotherapy</td>
<td>CT based 3rd lumbar level</td>
<td>140 (49 sarcopenic; 91 non-sarcopenic)</td>
<td>Survival: HR 1.23 (95% CI: 0.61, 2.48) Recurrence-free survival: HR 1.31 (95% CI: 0.76, 2.26) Skeletal muscle quality Survival: HR 2.25 (95% CI: 1.09, 4.65) Recurrence-free survival: HR 1.22 (95% CI: 0.69, 2.17)</td>
</tr>
<tr>
<td>Rutten et al (2016)</td>
<td>Retrospective Netherland</td>
<td>III/IV</td>
<td>Not provided</td>
<td>Skeletal mass index (SMI) &lt;41.5 cm²/m²</td>
<td>Neoadjuvant chemotherapy and interval debulking</td>
<td>CT based 3rd lumbar level</td>
<td>62 (34 sarcopenic; 28 non-sarcopenic)</td>
<td>Survival: HR 0.89 (95% CI: 0.56, 1.41)</td>
</tr>
<tr>
<td>Kumar et al (2016)</td>
<td>Retrospective USA</td>
<td>III/IV</td>
<td>Serous (84%)</td>
<td>Skeletal mass index (SMI) &lt;39 cm²/m² Skeletal muscle density (SMD) &lt;36.4 HU</td>
<td>Primary debulking surgery followed by adjuvant chemotherapy</td>
<td>CT based 3rd lumbar level</td>
<td>296 (132 sarcopenic; 164 non-sarcopenic)</td>
<td>Survival: HR 0.99 (95% CI: 0.73, 1.36) Skeletal muscle quality Survival: HR 1.11 (95% CI: 1.04, 1.18)</td>
</tr>
</tbody>
</table>

Continued
### Table 1 (Continued). Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author [year of publication]</th>
<th>Study design and country</th>
<th>Stage (FIGO)</th>
<th>Predominant histologic type</th>
<th>Definition of sarcopenia</th>
<th>Mode of management</th>
<th>Measurement site</th>
<th>Samples size/ follow-up</th>
<th>Key outcomes [Sarcopenic vs. normal]</th>
</tr>
</thead>
</table>
| Bronger et al (2017)        | Retrospective Germany    | III/IV       | Serous                      | Skeletal mass index (SMI) <38.5 cm²/m² | Primary debulking surgery followed by adjuvant chemotherapy | CT based 3rd lumbar level | 105 (12 sarcopenic; 93 non-sarcopenic) | Median follow-up of 117 weeks | Survival: HR 2.89 (95% CI: 1.11, 7.54)  
Progression-free survival: HR 2.52 (95% CI: 1.10, 5.81) |
| Rutten et al (2017)         | Retrospective Netherland | III/IV (90%) | Not provided                | Skeletal mass index (SMI) ≤38.73 cm²/m², Skeletal muscle density (SMD) <36.0 HU | Primary debulking surgery (72%); primary debulking surgery with interval debulking surgery (28%) | CT based 3rd lumbar level | 216 (70 sarcopenic; 146 non-sarcopenic) | Follow-up for >5 years | Survival: HR 1.36 (95% CI: 0.97, 1.92)  
Mortality (30-day): RR 0.83 (95% CI: 0.17, 4.19)  
Complications: RR 1.13 (95% CI: 0.56, 2.29)  
Length of hospital stay (LOS) (mean, SD): 15.3 (1.6) vs. 13.6 (0.9)  
Skeletal muscle quality  
Survival: HR 1.42 (95% CI: 1.01, 1.98)  
Complications: RR 2.32 (95% CI: 1.17, 4.60) |
| Conrad et al (2018)         | Retrospective USA        | III/IV       | Serous (majority; 75%)      | Core muscle index (CMI) <2.8 cm²/m² | Primary cytoreductive surgery followed by platinum- and taxane-based adjuvant chemotherapy | CT based 4th lumbar level | 102 (55 sarcopenic; 47 non-sarcopenic) | Median follow-up of 26 months | Complications: RR 1.21 (95% CI: 0.82, 1.76)  
Length of hospital stay (LOS) (mean, SD): 8 (2.1) vs. 10 (1.3) |
| Silva de Paula et al (2018) | Retrospective Brazil     | III/IV (76%) | Serous (67%)                | Skeletal mass index (SMI) ≤38.9 cm²/m², Skeletal muscle quality (Low-radiodensity skeletal muscle index, LRSMI)-quartiles | Primary debulking surgery | CT based 3rd lumbar level | 89 (23 sarcopenic; 66 non-sarcopenic) |                      | Survival: mortality (within 30 days): RR 2.97 (95% CI: 1.04, 8.48)  
Complications: RR 3.11 (95% CI: 1.23, 7.89)  
Skeletal muscle quality  
Mortality (within 30 days): RR 1.15 (95% CI: 0.40, 3.32)  
Complications: RR 3.15 (95% CI: 1.22, 8.12) |

Continued
Table 1 (Continued). Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Study design and country</th>
<th>Stage (FIGO)</th>
<th>Predominant histologic type</th>
<th>Definition of sarcopenia</th>
<th>Mode of management</th>
<th>Measurement site</th>
<th>Samples size/ follow-up time</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataseven et al (2018)</td>
<td>Retrospective Germany</td>
<td>III/IV</td>
<td>Serous (87%)</td>
<td>Skeletal mass index (SMI) $&lt;$41 cm$^2$/m$^2$ Skeletal muscle density (SMD) $&lt;$32 HU</td>
<td>Primary debulking surgery; post-operative chemotherapy for all</td>
<td>CT based 3rd lumbar level</td>
<td>323 (68 sarcopenic; 255 non-sarcopenic)</td>
<td>Median follow-up of 40 months Survival: HR 1.14 (95% CI: 0.88, 1.48) Skeletal muscle density (SMD) $&lt;$32 HU Survival: HR 1.32 (95% CI: 1.22, 2.62)</td>
</tr>
<tr>
<td>Staley et al (2020)</td>
<td>Retrospective USA</td>
<td>III/IV</td>
<td>Serous (74%)</td>
<td>Skeletal mass index (SMI) $\leq$41 cm$^2$/m$^2$</td>
<td>Platinum and taxane based chemotherapy</td>
<td>CT based 3rd lumbar level</td>
<td>201 (119 sarcopenic; 82 non-sarcopenic)</td>
<td>Median follow-up of $&gt;$24 months The median overall survival (in months) was similar in sarcopenic and non-sarcopenic groups (28.5 vs. 26.7) The median overall progression free survival (in months) was similar in sarcopenic and non-sarcopenic groups (14.9 vs. 13.1)</td>
</tr>
<tr>
<td>Yoshino et al (2020)</td>
<td>Retrospective Japan</td>
<td>III/IV</td>
<td>Serous (85%)</td>
<td>Skeletal mass index (SMI) $&lt;$39 cm$^2$/m$^2$</td>
<td>Induction chemotherapy followed by primary debulking surgery</td>
<td>CT based 3rd lumbar level</td>
<td>60 (41 sarcopenic; 19 non-sarcopenic)</td>
<td>Survival: HR 3.17 (95% CI: 1.18, 9.06)</td>
</tr>
<tr>
<td>Matsubara et al (2019)</td>
<td>Retrospective Japan</td>
<td>III/IV</td>
<td>Serous (majority; 43%)</td>
<td>Skeletal mass area (SMA) $&lt;$92.92 cm$^2$</td>
<td>Primary debulking surgery or interval debulking surgery with or without neoadjuvant chemotherapy (in 34%)</td>
<td>CT based 3rd lumbar level</td>
<td>92 (24 sarcopenic; 68 non-sarcopenic)</td>
<td>Range of follow-up: 1-144 months Progression free survival: HR 1.27 (95% CI: 0.73, 2.23)</td>
</tr>
</tbody>
</table>

Continued
Figure 2. Long-term survival in those with low skeletal muscle index (SMI), indicating low muscle mass, compared to those with normal and/or high SMI.

Figure 3. Long term survival in those with low muscle attenuation, indicating low muscle quality, compared to those with normal and/or high muscle attenuation.
Table II. Details of included studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Overall survival HR (95% CI)</th>
<th>Progression free survival HR (95% CI)</th>
<th>Complications RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>1.30 (1.06, 1.60) (N=14; I2=50.6%)</td>
<td>1.20 (1.00, 1.47) (N=6; I2=40.4%)</td>
<td>1.39 (1.06, 1.82) (N=9; I2=68.9%)</td>
</tr>
<tr>
<td>Prospective</td>
<td>1.41 (0.79, 2.51) (N=1)</td>
<td>0.83 (0.52, 1.33) (N=1)</td>
<td>2.47 (1.33, 4.59) (N=1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Overall survival HR (95% CI)</th>
<th>Progression free survival HR (95% CI)</th>
<th>Complications RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>21.9 (2.0, 199.9) (N=1)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>III/IV</td>
<td>1.19 (1.01, 1.41) (N=11; I2=32.0%)</td>
<td>1.14 (0.89, 1.45) (N=5; I2=58.4%)</td>
<td>1.25 (0.98, 1.61) (N=7; I2=63.9%)</td>
</tr>
<tr>
<td>Predominantly III/IV</td>
<td>1.94 (1.00, 3.75) (N=3; I2=36.0%)</td>
<td>1.29 (0.87, 1.91) (N=2; I2=0.0%)</td>
<td>2.53 (1.59, 4.01) (N=3; I2=0.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Overall survival HR (95% CI)</th>
<th>Progression free survival HR (95% CI)</th>
<th>Complications RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>1.29 (0.90, 1.84) (N=5; I2=47.1%)</td>
<td>1.11 (0.80, 1.55) (N=4; I2=61.8%)</td>
<td>1.61 (0.98, 2.63) (N=4; I2=65.7%)</td>
</tr>
<tr>
<td>Predominantly serous</td>
<td>1.55 (1.07, 2.24) (N=7; I2=64.5%)</td>
<td>1.25 (1.02, 1.54) (N=2; I2=0.0%)</td>
<td>1.91 (1.11, 3.28) (N=4; I2=60.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Overall survival HR (95% CI)</th>
<th>Progression free survival HR (95% CI)</th>
<th>Complications RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDS</td>
<td>1.84 (1.01, 3.43) (N=5; I2=67%)</td>
<td>1.28 (0.95, 1.73) (N=2; I2=0.0%)</td>
<td>1.97 (1.17, 3.34) (N=4; I2=43.7%)</td>
</tr>
<tr>
<td>PDS+AC</td>
<td>1.26 (1.00, 1.62) (N=6; I2=40.3%)</td>
<td>1.36 (1.03, 1.80) (N=3; I2=21.3%)</td>
<td>1.21 (0.82, 1.76) (N=1)</td>
</tr>
<tr>
<td>ICRS</td>
<td>1.26 (0.84, 1.89) (N=3; I2=42.9%)</td>
<td>0.83 (0.52, 1.34) (N=1)</td>
<td>1.38 (0.86, 2.21) (N=3; I2=81.8%)</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>0.95 (0.63, 1.44) (N=1)</td>
<td>0.91 (0.72, 1.16) (N=1)</td>
<td>1.00 (0.62, 1.38) (N=1)</td>
</tr>
<tr>
<td>CRS+HIPEC</td>
<td>----</td>
<td>----</td>
<td>5.27 (1.12, 24.8) (N=1)</td>
</tr>
</tbody>
</table>

PDS- Primary debulking surgery; PDS+AC- primary debulking surgery and adjuvant chemotherapy; ICRS- interval cytoreductive surgery; CRS+HIPEC- cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.
Impact of sarcopenia and low muscle attenuation on outcomes of ovarian cancer

**Table III.** Details of included studies.

<table>
<thead>
<tr>
<th>Sarcopenia based on skeletal muscle quality</th>
<th>Overall survival HR (95% CI)</th>
<th>Progression free survival HR (95% CI)</th>
<th>Complications RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>1.24 (1.03, 1.49) (N=5; I2=36.9%)</td>
<td>1.22 (0.69, 2.16) (N=1)</td>
<td>1.99 (1.04, 3.79) (N=4; I2=52.4%)</td>
</tr>
<tr>
<td>Prospective</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>III/IV</td>
<td>1.12 (1.06, 1.19) (N=4; I2=0.0%)</td>
<td>----</td>
<td>2.43 (1.46, 4.03) (N=2; I2=0.0%)</td>
</tr>
<tr>
<td>Predominantly III/IV</td>
<td>2.25 (1.09, 4.65) (N=1)</td>
<td>1.22 (0.69, 2.16) (N=1)</td>
<td>1.22 (0.17, 8.92) (N=2; I2=82.2%)</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>0.99 (0.52, 1.89) (N=1)</td>
<td>----</td>
<td>2.57 (1.21, 5.45) (N=1)</td>
</tr>
<tr>
<td>Predominantly serous</td>
<td>1.12 (1.05, 1.19) (N=2; I2=0.0%)</td>
<td>----</td>
<td>1.22 (0.17, 8.92) (N=2; I2=82.2%)</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDS</td>
<td>1.42 (1.01, 1.98) (N=1)</td>
<td>----</td>
<td>1.67 (0.63, 4.44) (N=3; I2=66.8%)</td>
</tr>
<tr>
<td>PDS+AC</td>
<td>1.27 (0.96, 1.70) (N=3; I2=53.9%)</td>
<td>1.22 (0.69, 2.16) (N=1)</td>
<td>----</td>
</tr>
<tr>
<td>CRS</td>
<td>0.99 (0.52, 1.89) (N=1)</td>
<td>----</td>
<td>2.57 (1.21, 5.45) (N=1)</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>CRS+HIPEC</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

PDS- Primary debulking surgery; PDS+AC- primary debulking surgery and adjuvant chemotherapy; ICRS- interval cytoreductive surgery; CRS+HIPEC- cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.
Figure 4. Risk of recurrence in those with low skeletal muscle index (SMI), indicating low muscle mass, compared to those with normal and/or high SMI.

Figure 5. Progression free survival (PFS) in those with low skeletal muscle index (SMI), indicating low muscle mass, compared to those with normal and/or high SMI.
Impact of sarcopenia and low muscle attenuation on outcomes of ovarian cancer

1.98; N=10, $I^2=73.6\%$), compared to those with normal and/or higher SMI (Figure 6). Publication bias was detected on Egger’s test ($p$-value=0.003). Findings of the subgroup analysis are presented in Table II. Higher risk of complications was observed when studies with patients with advanced stage tumor $^{35-41,48-50}$, serous histology $^{35-40,49,50}$ and management with primary debulking surgery $^{36,38,48,50}$ were pooled together.

Among patients with low muscle attenuation, there was a higher risk of complications (RR 1.99, 95% CI: 1.04, 3.79; N=4, $I^2=52.4\%$), compared to those with high muscle attenuation (Figure 7). No publication bias was evident on Egger’s test ($p$-value=0.229). Higher risk of complications was observed when studies with patients with advanced stage tumor (Stage III/IV) $^{39,48}$ (RR 2.43, 95% CI: 1.46, 4.03; N=2, $I^2=0.0\%$), were pooled together (Table III).

For both SMI and muscle quality, the commonly reported complications were pulmonary embolism, peripheral neuropathy, infections, wound complications, sepsis, renal insufficiency, thrombotic events, chemotherapy related toxicity, urinary tract infections, pneumonia etc. (Table I).

**Miscellaneous Outcomes**

The length of hospital stay (in days) between low and normal/high SMI patients was similar (WMD 1.23, 95% CI: -1.53, 3.99; N=4, $I^2=97\%$) (data not visually presented as forest plot). The risk of having blood loss >1,000 cc was statistically not significant between low and normal/high SMI (RR 1.32, 95% CI: 0.28, 6.21) as well as between low and high muscle attenuation groups (RR 1.39, 95% CI: 0.82, 2.35)$^{35,39}$.

**Discussion**

We conducted the review to understand and document the association of sarcopenia and low muscle attenuation with survival, complications, and other clinical outcomes in patients with ovarian cancer. Our findings indicate that low muscle mass and quality correlate with poor survival and high risk of complications but have no association with risk of recurrence and recurrence-free survival. These findings are in concurrence with previous meta-analysis$^{26}$. Ubachs et al$^{26}$ in their review found that low skeletal muscle index and low muscle attenuation was associated with higher risk of mortality. Further, low skeletal muscle index was associated with
increased risk of surgical complications. Another review by McSharry et al\textsuperscript{27} found that normal muscle attenuation, but not skeletal muscle index, was associated with improved 3-year and 5-year survival. Together, these findings\textsuperscript{26,27} suggest that low muscle mass and/or quality may be associated with poor survival and increased risk of complications.

A causal relationship between low muscle mass/muscle quality and survival and/or complications is not likely. Many of the studies included in our review had patients in advanced stage of the disease\textsuperscript{34,35,37,39-41,45-47,51,53}. It is well documented\textsuperscript{55} that cachexia is a common occurrence in advanced tumor and could be reflected as low muscle mass and/or quality. The poor survival and increased risk of complications may be due to the advanced stage of the tumor itself. Researchers\textsuperscript{56} have looked at other nutritional indices in patients with cancer to understand whether these indices could predict survival and other clinical outcomes. A recent meta-analysis\textsuperscript{57} looked at the prognostic value of PNI (a nutritional index; prognostic nutritional index), which considers serum albumin and total lymphocyte count and found that patients with low PNI had shorter overall survival and progression-free survival. Another widely used nutritional index is the controlling nutritional status score (CONUT)\textsuperscript{58}. Studies\textsuperscript{59,60} have shown that CONUT score is an independent prognostic marker for survival in OC patients.

Another potential area of interest is to understand how the objective nutritional indices perform against the markers of sarcopenia in patients with advanced tumor. Retrospective study by Une et al\textsuperscript{61}, including 200 subjects with advanced urothelial carcinoma, found that both sarcopenia and high CONUT score were not significantly correlated but were independent prognostic factors for overall survival. The authors\textsuperscript{61} also found that the prognostic accuracy of the models improved upon adding both CONUT score and sarcopenia. Zheng et al\textsuperscript{62} conducted their study among gastric cancer patients undergoing radical gastrectomy and found that use of skeletal muscle index had better prognostic value, when compared to use to CONUT score. Skeletal muscle index is considered a relatively stable parameter, whereas nutritional indices are affected by factors other than nutrition, such as body fluid volume (which could be affected by dehydration or fluid overload) and presence of inflammation\textsuperscript{63,64}.

It may appear that CT based assessment of muscle mass and quality may be better than nutritional indices (which are prone to fluctuations) in terms of their prognostic value for the long-term survival. Further studies are required to test this theory.

Interestingly, our meta-analysis showed that low SMI and muscle quality correlated with poor long-term survival. However, they did not have significant association with the risk of recurrence and progression-free survival. These results might suggest that the reduced survival may not be directly related to sarcopenia but rather, to increased risk of life-threatening complications (such as infections,
Impact of sarcopenia and low muscle attenuation on outcomes of ovarian cancer

Sepsis, thrombotic events, renal insufficiency etc.) and toxicity associated with chemotherapy. Therefore, future methodologically robust studies are needed to explore the effect of interventions aimed at improving nutritional status on long-term survival in patients with ovarian cancer. The findings have considerable implications for nursing care of ovarian cancer patients with sarcopenia. Patients with low muscle mass and/or quality may require enhanced nutritional and rehabilitative care. Trained nursing personnel could not only provide excellent patient care but could also periodically assess the nutritional and clinical status of such patients. They could also provide support to the treating physicians during nutrition support therapy. Additionally, nursing personnel could provide timely assessment of the appropriate nutrition needs and early recognition of complications.

Limitations

Our study has some limitations. Firstly, it included only retrospective studies and therefore, it is possible that some of the important confounders have not been adjusted for. Secondly, through our analysis, we could only explore the associations but could not comment on the causality i.e., we cannot conclusively ascertain whether low SMI or low muscle quality led to poor survival. It is possible that low SMI/muscle quality could be due to advanced tumor-induced cachexia and that advanced tumor stage could have led to increased risk of mortality. Thirdly, for some of the outcomes, there was considerable heterogeneity, and this could be due to the methodological differences among the studies. The included studies used different cut-offs for defining sarcopenia i.e., low SMI and muscle quality, the management modality differed among the studies and even the choice and frequency of adjuvant chemotherapy varied. The duration of follow-up also varied among the studies. While these differences are largely unavoidable, it is important to consider these differences. Fourthly, the number of studies exploring the impact of the skeletal muscle mass on the outcomes of interest outnumbered the studies with skeletal muscle quality. Future studies should also attempt to focus on muscle quality along with muscle mass. Finally, in our meta-analysis we considered the exposures as a binary entity based on cut-offs used in the individual studies e.g., low or high/normal SMI or low and high muscle attenuation and did not consider the association with outcomes of interest based on each unit change in SMI and/or muscle attenuation. We specifically did not conduct this unit change-based analysis as we thought, in terms of the clinical applicability, identifying “at-risk” patients based on cut-offs is more pragmatic.

Conclusions

Both low skeletal muscle mass and low muscle quality are significantly associated with poor long-term survival and an increased risk of complications. However, they do not have significant association with risk of recurrence and progression-free survival. Variability in CT-based cut-offs to define low SMI and/or muscle quality reduces the external validity of the findings but at the same time, calls for efforts to come up with harmonized standard cut-offs that could be used in clinical practices.

Authors’ Contributions

HG conceived and designed the study, PW and HX collected data and performed data analysis, HG wrote the draft of this manuscript. DS edited the manuscript.

Funding

None.

Conflict of Interests

The authors declare that there is no conflict of interests.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

ORCID ID

H.-P. Ge, 0009-0002-0135-8410
D.-F. Song, 0009-0005-6362-8852
P. Wu, 0009-0008-3951-7695
H.-F. Xu, 0009-0001-1937-4622

References


Impact of sarcopenia and low muscle attenuation on outcomes of ovarian cancer


