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Low preoperative skeletal muscle density is predictive for negative postoperative outcomes in older women with ovarian cancer

Vera van der Zanden [a,*,1], Neeltje J. van Soolingen [b,1], Alain R. Viddeleer [c], Johannes W. Trum [b], Frédéric Amant [b,d], Marian J.E. Mourits [e], Johanneke E.A. Portielje [f], Frederiek van den Bos [f], Cornelis D. de Kroon [g], Marjolein J. Kagie [h], Stanley A. Oei [i], Astrid Baalbergen [j], Anne-Marie L.D. van Haaften-de Jong [k], Danny Houtsma [l], Barbara C. van Munster [a,*], Esteban T.D. Souwer [f]

[a] University Medical Center Groningen, University of Groningen, Department of Internal Medicine, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands
[b] The Netherlands Cancer Institute, Department of Gynecologic Oncology, Center for Gynecologic Oncology Amsterdam, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands
[c] University Medical Center Groningen, University of Groningen, Department of Radiology, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands
[d] KU Leuven, Department of Oncology, Herestraat 49, 3000 Leuven, Belgium
[e] University Medical Center Groningen, University of Groningen, Department of Gynecological Oncology, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands
[f] Leiden University Medical Center, Leiden University, Department of Medical Oncology, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands
[g] Leiden University Medical Center, Leiden University, Department of Obstetrics and Gynecology, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands
[h] Haaglanden Medical Center, Department of Obstetrics and Gynecology, Lijnbaan 32, 2512 VA, The Hague, the Netherlands
[i] Haaglanden Medical Center, Department of Radiology, Lijnbaan 32, 2512 VA, The Hague, the Netherlands
[j] Reinier de Graaf Group, Department of Obstetrics and Gynecology, Reinier de Graafweg 5, 2625 AD, Delft, the Netherlands
[k] Haga Medical Center, Department of Obstetrics and Gynecology, Els Borst-Eilersplein 275, 2545 AA, The Hague, the Netherlands
[l] Haga Medical Center, Department of Medical Oncology, Els Borst-Eilersplein 275, 2545 AA, The Hague, the Netherlands

HIGHLIGHTS

- Low preoperative skeletal muscle density measured on an abdominal CT scan is associated with worse postoperative outcomes.
- Preoperative low skeletal muscle mass is associated with infectious complications, but not with other outcomes.
- Preoperative low skeletal muscle density is of added value to functional impairment in predicting surgical complications.
- Low skeletal muscle quality and functional impairment can be seen as markers for sarcopenia.

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ABSTRACT

Objective. To determine the predictive value of lumbar skeletal muscle mass and density for postoperative outcomes in older women with advanced stage ovarian cancer.

Methods. A multicenter, retrospective cohort study was performed in women ≥ 70 years old receiving surgery for primary, advanced stage ovarian cancer. Skeletal muscle mass and density were assessed in axial CT slices on level L3. Low skeletal muscle mass was defined as skeletal muscle index < 38.50 cm^2/m^2. Low skeletal muscle density was defined as one standard deviation below the mean (muscle attenuation < 22.55 Hounsfield Units). The primary outcome was any postoperative complication ≤ 30 days after surgery. Secondary outcomes included severe complications, infections, delirium, prolonged hospital stay, discharge destination, discontinuation of adjuvant chemotherapy and mortality.

Results. In analysis of 213 patients, preoperative low skeletal muscle density was associated with postoperative complications ≤ 30 days after surgery (Odds Ratio (OR) 2.83; 95% Confidence Interval (CI) 1.41–5.67), severe complications (OR 3.01; 95%CI 1.09–8.33), infectious complications (OR 2.79; 95%CI 1.30–5.99) and discharge to a care facility (OR 3.04; 95%CI 1.16–7.93). Preoperative low skeletal muscle mass was only associated with infectious complications (OR 2.32; 95%CI 1.09–4.92). In a multivariable model, low skeletal muscle density was of added predictive value for postoperative complications (OR 2.57; 95%CI 1.21–5.45) to the strongest existing predictor functional impairment (KATZ-ADL ≥ 2).

* Corresponding authors at: University Medical Center Groningen, Department of Internal Medicine, HPC AA43, Postbus 30.001, 9700 RB Groningen, the Netherlands.
E-mail addresses: v.van.der.zanden@umcg.nl (V. van der Zanden), b.c.van.munster@umcg.nl (B.C. van Munster).
[1] These authors share a co-first authorship

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Conclusion. Low skeletal muscle density, as a proxy of muscle quality, is associated with poor postoperative outcomes in older patients with advanced stage ovarian cancer. These findings can contribute to postoperative risk assessment and clinical decision making.

1. Introduction

In the Western world, ovarian cancer is the most lethal gynecological malignancy and is ranked as the fifth leading cause of cancer death among women. [1] The incidence of gynecological cancer in older women is increasing. Currently, 47% of all new ovarian cancers are detected in patients aged 70 years and older [2] and most are diagnosed at an advanced stage. Primary treatment of ovarian carcinoma consists of abdominal surgery and multi-agent chemotherapy. Women with advanced stage ovarian cancer receive either primary cytoreductive surgery followed by six cycles of platinum and taxane based chemotherapy, or three cycles of neoadjuvant chemotherapy (NACT), followed by interval cytoreductive surgery and three cycles of adjuvant chemotherapy. [3] Clinicians have difficulty deciding whether older patients with comorbidity benefit from extensive surgery, [4] and older patients are less frequently treated in compliance with clinical guidelines than younger patients. [5] Better data are required to select patients who benefit from standard care and patients that need adjusted treatment.

Sarcopenia is often seen in patients with cancer (11–74% of all adults) and even more often in older patients with cancer. [6] Several definitions are used to determine sarcopenia. In Europe, consensus is achieved on the following definition by the European Working Group on Sarcopenia in Older People (EWGSOP): (1) Low muscle strength combined with (2) low muscle quantity or quality and/or (3) low physical performance. [7] Low muscle quantity (measured as skeletal muscle mass on a computed tomography (CT) scan) and quality (measured as skeletal muscle density on a CT scan) are thus hallmarks of sarcopenia. [7] In older patients with cancer, sarcopenia is associated with negative health outcomes such as postoperative complications, lower treatment tolerability, functional impairment and lower overall survival. [6] Therefore, skeletal muscle mass and density might be predictors for poor postoperative outcomes and could be helpful in selecting patients who might benefit from an adjusted treatment strategy.

Studies on skeletal muscle mass and density in an older population with ovarian cancer are lacking, while skeletal muscle mass and density are known to decline with age and are more likely to show strong associations with surgical outcomes in older patients. [6] As an abdominal CT scan is performed as part of the routine preoperative work up for patients with (suspected) ovarian cancer, assessment of skeletal muscle mass and density will take no extra effort from the patient and could be well implemented in clinical practice. The aim of this study was to determine the predictive value of skeletal muscle mass and density for postoperative outcomes in an older population of patients with advanced stage ovarian cancer.

2. Methods

2.1. Study design and setting

This multicenter, retrospective cohort study was performed in six hospitals in the Netherlands: University Medical Center Groningen (UMCG); The Netherlands Cancer Institute (NKI), Amsterdam; Leiden University Medical Center (LUMC); Haaglanden Medical Center (HMC), The Hague; Reinier de Graaf (RDG), Delft; and Haga Hospital (Haga), The Hague.

2.2. Participants

We included women aged 70 years and older who were treated surgically for primary, advanced stage (International Federation of Gynecology and Obstetrics (FIGO) stage III and IV [3]) ovarian cancer of any grade and of whom at least one preoperative CT scan was available for analysis. Patients receiving synchronous oncological surgery for another malignancy or receiving non-elective surgery were excluded.

In NKI, LUMC, HMC, RDG and Haga, patients were selected from the prospectively registered Dutch Gynecological Oncology Audit (DGOA) database. [8] In these hospitals, patients receiving surgery between January 2014 and January 2017 were included. Patients and data from UMCG were retrieved from the local oncology database (OncoLifeS) [9]. Inclusion was limited to patients who consented to participate in OncoLifeS from January 2016 (the start of the OncoLifeS) to August 2019. Clinical data was retrieved from the hospital specific DGOA data sets or OncoLifeS and was complemented with information from the electronic medical records.

2.3. Procedures and data assessment

2.3.1. Baseline characteristics

The following baseline data were collected: Demographics (age; living situation); Body Mass Index (BMI); polypharmacy (defined as daily use of five or more medicaments); comorbidity (using the Charlson Comorbidity Index [10] with a cut-off of ≥ 2, highest quartile); history of abdominal surgery; American Society of Anesthesiologists (ASA) score [11] and WHO performance status [12]. At admission, a standardized questionnaire on risk assessment was taken by a nurse as part of standard care and included: fall risk (defined as any fall incident in the last six months. [13]), use of a walking aid, risk for malnutrition (defined as a Short Nutritional Assessment Questionnaire (SNAQ) score ≥ 2 [14] or Malnutrition Universal Screening Tool (MUST) score ≥ 1 [15]), the six-item Katz Index of Independence in Activities of Daily Living (KATZ-ADL) [16] to assess functional impairment (using a cut-off score of ≥ 2 for dependency [13]), patient reported and hetero-anamnestic pre-existing memory problems, and history of confusion during illness or hospital admission.

Concerning oncological disease and treatment, we collected tumor characteristics (histology, grade and FIGO stage); type of surgery (cytoreductive surgery or other surgery); timing of cytoreductive surgery (primary or interval); result of cytoreductive surgery (no macroscopic residual disease, ≤ 1 cm residual disease or > 1 cm residual disease); performance of bowel surgery; intraoperative blood loss > 1000 cc; intraoperative injury (including lesions of the bowel, bladder, ureters or major blood vessels); initial chemotherapy strategy; and preoperative involvement of a geriatrician.

2.3.2. Skeletal muscle mass and density assessment

CT was used to assess skeletal muscle mass and density. Contrast enhanced CT scans were performed as part of routine preoperative clinical care. If more preoperative scans were available (often the case for patients treated with NACT, for whom routine CT scans were performed before the start of NACT and after ≥ 2 cycles of NACT), the scan closest to surgery was selected. Of every patient the transversal slice on the level of the midpoint of the third lumbar vertebra (L3) in the portal venous contrast phase of the preoperative CT scan was extracted. On level L3 the following abdominal muscles are visible: *Musculi (M.) psoas, M. erector spinae, M. quadratus lumborum, M. transversus abdominis, M. obliquus externus* and *internus abdominis*, and the *M. rectus abdominis*. In the selected slice, a board-certified radiologist with extensive experience, blinded for all outcomes, manually outlined the muscles. Within these contours, muscle voxels were defined by radiodensity ranging from −29 to +150 Hounsfield Units (HU). [17] Skeletal muscle index (SMI) was calculated by dividing the total muscle surface area on level L3 by the square of the length of the patient (cm^2/m^2). Skeletal muscle density was defined as the mean Muscle Attenuation (MA) in HU of the muscle voxels in this slice. All CT scan measurements were performed using in-house developed analysis software (SarcoMeas version 0.60). [18]

Low skeletal muscle mass was defined as a SMI < 38.50 cm^2/m^2 based on recommendations of a systematic review and meta-analysis of eight studies on sarcopenia and survival in ovarian cancer, performed in patients with a mean age between 55 and 68 years. It proposes to use tertiles, quartiles, or a relatively low cut-off (< 38.50 cm^2/m^2), since cut-offs between 38.50 and 38.73 cm^2/m^2 were more probable to report a prognostic effect. [19]

Low skeletal muscle density, which indicates augmented fat infiltration within muscle, is a proxy for low muscle quality. [20] Martin et al. suggested to use BMI-dependent cut-off points (BMI < 25 kg/m^2: < 41 HU and BMI ≥ 25 kg/m^2: < 33 HU) for MA based on a cohort of patients with lung or gastro-intestinal cancer. [21] However, this has not been assessed in a population of patients with ovarian cancer. Ascites, often present in patients with ovarian cancer, influences BMI. Therefore we could not extrapolate these BMI-dependent cut-off points directly to our population. Previous studies in gynecological oncological patients used data driven cut-off points. [19] In our study, low skeletal muscle density was therefore defined by the lowest quartile of the MA or, if normally distributed, one standard deviation (SD) below the mean.

2.3.3. Outcome measurements

Our primary outcome measure was any postoperative complication within 30 days of surgery. Intraoperative complications (intraoperative blood loss, technical problems or injuries) were not considered as postoperative complication.

Secondary outcome measures comprised: severe complications (defined as Clavien-Dindo classification ≥ grade 3, [22] in patients with multiple complications the highest grade complication was included in this analysis); infectious complications; postoperative delirium; extended length of hospital stay (> 14 days); discharge to a care facility without living there preoperatively (as indicator of functional decline); readmission within 30 days after discharge; unintentional discontinuation of adjuvant chemotherapy; and mortality (30-day, 6-months and 12-months mortality calculated from the date of surgery to date of death). Information on mortality was retrieved through linkage with the Dutch Personal Records Database or, if linkage was not available, extracted from the electronic medical records. If follow-up duration was shorter than 30 days, 6 months or 12 months, these patients were not included in the respective 30-day, 6-months or 12-months mortality analysis.

2.4. Statistical analysis

Baseline differences between groups with and without low skeletal muscle mass or density were compared using a Fisher's exact test for binominal variables, a Fisher-Freeman-Halton exact test for nominal or ordinal data, an unpaired *t*-test for normally distributed continuous variables or a Mann-Whitney *U* test for not normally distributed continuous variables. Univariable logistic regression analysis was used to determine the predictive value of low skeletal muscle mass and low skeletal muscle density on the outcome measurements.

Because of the low frequency of the secondary outcomes, multivariable logistic regression analysis was performed only on our primary outcome measure 'any postoperative complication'. Multivariable analysis was only performed if univariable regression analysis of skeletal muscle mass or density demonstrated an association with postoperative complications. To investigate whether skeletal muscle mass or density are of added value as a predictor for postoperative complications, we first built a model with pre-existing relevant preoperative predictors only. Candidate predictors identified from previous research in patients with ovarian cancer were: age, BMI, polypharmacy, ASA classification, comorbidity, functional impairment, and FIGO stage. [23–26] Other predictors we hypothesized that could be relevant were: preoperative living situation, fall risk, pre-existing memory problems, history of confusion during illness, malnutrition, use of a walking aid, tumor grade and bowel surgery performed (as indicator of surgical complexity).

To build the final model, we selected the variables that were associated with postoperative complications with a *p*-value of < 0.20 in univariable analysis and added them to the model in order of statistical significance (hierarchical entry). Factors were kept in the model if they significantly improved the model based on a significant change in the step Chi-square statistic. After this model was built, we added skeletal muscle mass or skeletal muscle density as potential predictor to assess if it significantly improved the predictive value of the model. We assessed whether the new model improved using the step Chi-square statistic. A statistically significant step Chi-square statistic demonstrated that the model with skeletal muscle mass/density performed better than the model without skeletal muscle mass/density. Only patients with complete data for all included variables were included in the multivariable analysis.

Level of statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23.0.

2.5. Ethical approval

The study was undertaken in compliance with the Helsinki Declaration and Good Clinical Practice Guidelines. The Medical Research Ethics Committee confirmed that the study was not subject to the Dutch Medical Research Involving Human Subjects Act. Approval was obtained from the OncoLifeS Scientific Board of UMCG and all participating centers individually.

3. Results

3.1. Participants and baseline data

Two hundred-seventeen patients met the inclusion criteria, of whom 213 were included in the final analysis. For two patients no preoperative CT scan was available, one patient had simultaneous surgery for another malignancy and one patient underwent non-elective surgery.

Table 1 shows the baseline characteristics of all included patients distributed by skeletal muscle density. Supplemental material 1 (S1) shows the baseline characteristics of all included patients divided by skeletal mass. In the whole cohort, median age at surgery was 75.9 years (range 70–89). Six percent of patients had pre-existing memory problems ($n = 10$) and 4% ($n = 7$) had a history of confusion during illness or hospital admission (missing $n = 32$). For 81% of patients fall risk was available, 26 of these patients (15%) were known to be at risk for falls. For 84% of patients a KATZ-ADL score was available, 15 of these patients (8%) were known with functional impairment. For 55% of patients a SNAQ or MUST score was available, 41 of these patients (35%) were at risk for malnutrition. Use of a walking aid was known for 84% of the patients, of whom 27 patients (15%) actually used walking support. Most patients lived at home without professional help before surgery ($n =$ 177, 84%) and 69 patients (32%) had polypharmacy. As compared to patients with normal skeletal muscle density, patients with low skeletal muscle density had a higher BMI, more polypharmacy, a higher ASA classification and more often lived in a care facility.

The majority of patients was diagnosed with FIGO stage IIIC (63%) or IV (28%) disease. Most patients had a poorly differentiated tumor (89%)

Table 1
Characteristics of all Included Patients Grouped by Skeletal Muscle Density.

Patient/treatment characteristics ($n = 213$)	Patient group*		
	Low Muscle Density† ($n = 41$)	Normal Muscle Density ($n = 172$)	p-value
Age in years (median; IQR)	77.0 (74.3–79.5)	75.8 (73.4–78.3)	0.10
Living situation ($n = 210$)			**0.047**
Independent at home	31 (75.6)	146 (86.4)	
At home with help	7 (17.1)	21 (12.4)	
Care facility	3 (7.3)	2 (1.2)	
Charlson Comorbidity Index ≥ 2‡	11 (26.8)	50 (29.1)	0.85
History of abdominal surgery	26 (63.4)	92 (53.5)	0.30
Body Mass Index (median; IQR)	27.3 (24.4–30.1)	23.7 (21.4–26.2)	**<0.001**
Polypharmacy§	27 (65.9)	42 (24.4)	**<0.001**
ASA classification‖ ($n = 211$)			**0.01**
1	2 (4.9)	31 (18.2)	
2	26 (63.4)	113 (66.5)	
3	13 (31.7)	26 (15.3)	
Fall risk ($n = 173$)	5 (14.3)	21 (15.2)	1.00
KATZ-ADL ≥ 2 ($n = 178$)	6 (16.2)	9 (6.4)	0.09
Risk for malnutrition ($n = 117$)	8 (29.6)	33 (36.7)	0.65
History of confusion during illness or hospital admission ($n = 181$)	2 (5.3)	5 (3.5)	0.64
Pre-existing memory problems ($n = 181$)	3 (7.3)	7 (4.1)	0.44
Walking aid (n = 178)	7 (19.4)	20 (14.1)	0.44
WHO performance status¶ ($n = 168$)			0.69
0	23 (79.3)	96 (69.1)	
1	3 (10.3)	24 (17.3)	
2	2 (6.9)	15 (10.8)	
3	1 (3.4)	4 (2.9)	
FIGO stage			0.29
IIIA	0 (0.0)	4 (2.3)	
IIIB	1 (2.4)	14 (8.1)	
IIIC	31 (75.6)	103 (59.9)	
IV	9 (22.0)	51 (29.7)	
Tumor grade ($n = 195$)			0.81
Well differentiated	2 (5.4)	8 (5.1)	
Moderately differentiated	1 (2.7)	8 (5.1)	
Poorly differentiated	33 (89.2)	140 (88.6)	
Undifferentiated	1 (2.7)	2 (1.3)	
Involvement of geriatrician preoperatively	7 (17.1)	15 (8.7)	0.15
Skeletal muscle mass (median; IQR)	36.0 (33.2–39.8)	37.8 (35.5–41.3)	**0.008**
Skeletal muscle density (mean; SD)	18.1 (3.6)	34.6 (6.5)	**<0.001**
Type of cytoreductive surgery (n = 210)			1.00
Primary cytoreductive surgery	11 (26.8)	45 (26.6)	
Interval cytoreductive surgery	30 (73.2)	124 (73.4)	
Bowel surgery (n = 210)	13 (31.7)	19 (11.2)	**0.003**
Intraoperative blood loss > 1000 cc	13 (31.7)	39 (22.7)	0.23
Intraoperative injury	2 (4.9)	6 (3.5)	0.65
Results of cytoreductive surgery (=210)			0.10
No residual disease	19 (46.3)	73 (43.2)	
≤ 1 cm residual disease	18 (43.9)	55 (32.5)	
> 1 cm residual disease	4 (9.8)	41 (24.3)	
Strategy of (neo)adjuvant chemotherapy (n = 210)			0.76
Neoadjuvant & adjuvant	30 (75.0)	124 (72.9)	
Adjuvant only	10 (25.0)	40 (23.5)	
No chemotherapy	0 (0.0)	6 (3.5)	

IQR = inter quartile range; SD = standard deviation; ASA = American Society of Anesthesiologists; KATZ-ADL = Six-item Katz Index of Independence in Activities of Daily Living; FIGO = International Federation of Gynecology and Obstetrics.
Boldface data are statistically significant. If a variable has missing values, the number presented behind a variable represents the number of patients included in this analysis.
* Number (valid %) of patients, unless indicated otherwise.
† Low skeletal muscle density is defined as a mean Muscle Attenuation (MA) < 22.55 HU.
‡ High Charlson Comorbidity Index was defined as a score ≥ 2.
§ Polypharmacy was defined as the daily use of ≥ 5 different medicaments.
‖ The ASA classification (measured before surgery) ranges for 1 to 6, with higher scores indicating a worse physiological status and a higher operative risk. [11].
¶ The WHO/ECOG performance status (measured before surgery) ranges from 0 to 4, with higher scores indicating a worse level of functioning. [12].

and serous carcinoma was the most common histological subtype ($n = 191$, 94%). Tumor characteristics were equally distributed between patients with normal and decreased skeletal muscle density or mass.

Cytoreductive surgery was performed in 210 patients (99%). For 154 patients (73%) the initial chemotherapeutic strategy consisted of neoadjuvant and adjuvant chemotherapy, for 50 patients (24%) it comprised adjuvant chemotherapy alone. Patients with low muscle density underwent bowel surgery more often (32% vs 11%). Other treatment variables did not differ between patients with low and normal skeletal muscle density or mass.

Seventy-two patients (34%) had one or more complication within 30 days after surgery. Fifty-three patients (25%) had one complication, 13 patients (6%) had two complications, four patients (2%) had three complications and two patients (1%) had four complications. Eighteen patients (9%) had a severe complication. Postoperative complications were: infections ($n = 41$, 19%) (consisting of local infections (urinary tract infections/phlebitis) ($n = 16$), sepsis (n = 7, including anastomotic leakage ($n = 2$) and bowel perforations (n = 2)), abscesses ($n = 5$), pneumonia (n = 3), wound infections (n = 5), and other infections (n = 5)); cardiac complications ($n = 18$, 9%); ileus ($n = 13$, 6%);

kidney or liver dysfunction (n = 3, 1%); urinary retention (n = 4, 2%); postoperative hemorrhage or hematomas ($n = 6$, 3%); wound dehiscence (n = 6, 3%) or fascial dehiscence (Platzbauch) (n = 5, 2%); thromboembolic problems (n = 1, 1%); or other complications (n = 2, 1%).

3.2. Low skeletal muscle density and mass

Median time between CT scan and surgery was 32 days (IQR 22–46 days). Skeletal muscle density followed a normal distribution in our study population. Therefore, our cut-off point for low skeletal muscle density, defined as one standard deviation (8.89 HU) below the mean (31.44 HU), was set at < 22.55 HU. Low skeletal muscle density was found in 41 participants (19%). Preoperative low skeletal muscle mass (i.e. a skeletal muscle index (SMI) < 38.50 cm^2/m^2 [19]) was present in 123 (58%) participants.

3.3. Outcomes

3.3.1. Skeletal muscle density

Table 2 shows descriptive statistics of all outcome variables stratified by preoperative skeletal muscle density. In univariable analysis, preoperative low skeletal muscle density was significantly associated with having any postoperative complication within 30 days after surgery (Odds Ratio (OR) 2.83; 95% Confidence Interval (CI) 1.41–5.67). It was also associated with severe complications (OR 3.01; 95%CI 1.09–8.33), infectious complications (OR 2.79; 95%CI 1.30–5.99) and functional decline (discharge to a care facility without living there preoperatively) (OR 3.04; 95%CI 1.16–7.93).

3.3.2. Skeletal muscle mass

Supplemental material 2 (S2) shows descriptive statistics of all outcome variables stratified by preoperative skeletal muscle mass. Univariable analysis showed no significant association of low skeletal muscle mass with postoperative complications within 30 days after surgery (OR 1.61; 95%CI 0.89–2.89). When we performed a sensitivity analysis with a cut-off at the lowest quartile (< 35.02 cm^2/m^2) or with SMI as continuous variable, this conclusion sustained (OR 1.40; 95%CI 0.74–2.67 and OR 0.98; 95%CI 0.93–1.04, respectively). Therefore, low skeletal muscle mass was not included in the multivariable regression analysis.

Low skeletal muscle mass was associated with our secondary outcome infectious complications (OR 2.32; 95%CI 1.09–4.92), but not with any other of the secondary outcome measurements. In the sensitivity analysis with a cut-off at the lowest quartile or with SMI as continuous variable, infectious complications were no longer associated with low skeletal muscle mass (OR 1.77; 95%CI 0.85–3.70 and OR 0.95; 95% CI 0.89–1.02, respectively) and the other outcomes were still not associated.

3.3.3. Multivariable analysis

Table 3 shows outcomes of univariable and multivariable analyses for the predictors that were used to build the multivariable prediction model. Five of the fifteen pre-selected potential predictors for any postoperative complication ≤ 30 days after surgery had a p-value < 0.20 in univariable logistic regression analysis and were selected for multivariable analysis. The most statistically significant predictor in our univariable analysis, besides low skeletal muscle density, was KATZ-ADL ≥ 2 (OR 3.11; 95%CI 1.05–9.20). The prediction model with KATZ-ADL ≥ 2 as strongest predictor (C-statistic 0.55) did not significantly improve by adding any of the other selected predictors. Adding low skeletal muscle density to this model did significantly improve the model (step Chi-Square statistic $p = 0.01$; C-statistic 0.60). Low skeletal muscle density was therefore of added value to existing predictors in a multivariable prediction model (OR 2.57; 95%CI 1.21–5.45). There was no collinearity between KATZ-ADL ≥ 2 and low skeletal muscle density in this analysis (tolerance value 0.98).

4. Discussion

In this study we explored whether postoperative outcomes in older patients receiving surgery for ovarian cancer can be predicted by preoperative skeletal muscle mass and density. Preoperative low skeletal muscle density was associated with developing any postoperative complication, severe complications, infectious complications and discharge to a care facility. Discharge to a care facility can indicate postoperative functional decline, which older patients often find highly relevant. [27] In a multivariable prediction model including functional impairment, skeletal muscle density showed an added value in predicting any postoperative complication. For preoperative low skeletal muscle mass we did only find an association with infectious complications, but not with other postoperative outcomes. These hallmarks of sarcopenia can be helpful with clinical decision making in the future.

To our best knowledge, this is one of the first studies to assess skeletal muscle mass and density specifically in older patients (≥ 70 years old) with ovarian cancer. [28] Previous studies performed on the predictive value of low skeletal muscle mass and density in younger patients with ovarian cancer (mean age < 70 years old) were inconclusive. [19,29] A recent meta-analysis of eight studies performed in patients with a mean age between 55 and 68 years old with ovarian carcinoma found that muscle mass was associated with overall survival. The association between the muscle mass and surgical complications had borderline statistical significance. [19] However, in another recent

Table 2
Descriptive Statistics of Primary and Secondary Outcomes for Skeletal Muscle Density.

Outcome	Patient group*		
	Low Muscle Density† (n = 41)	Normal Muscle Density (n = 172)	p-value
Any postoperative complication within 30 days	22 (53.7)	50 (29.1)	**0.005**
Severe complications‡	7 (17.1)	11 (6.4)	0.05
Infectious complications	14 (34.1)	27 (15.7)	**0.01**
Postoperative delirium ($n = 212$)	4 (9.8)	7 (4.1)	0.23
Extended length of hospital stay (> 14 days)	5 (12.2)	9 (5.2)	0.15
Discharge to care facility without living there preoperatively (n = 211)	8 (20.0)	13 (7.6)	**0.04**
Readmission within 30 days	5 (12.2)	7 (4.1)	0.06
30-day mortality ($n = 210$)	1 (2.4)	1 (0.6)	0.35
6-month mortality ($n = 207$)	2 (5.0)	9 (5.4)	1.00
12-month mortality ($n = 197$)	6 (15.4)	28 (17.7)	0.82
Unintentional discontinuation of adjuvant chemotherapy ($n = 206$)	7 (17.5)	20 (12.0)	0.43

Boldface data are statistically significant. If a variable has missing values, the number presented behind a variable represents the number of patients included in this analysis.
* Number (valid %) of patients, unless indicated otherwise.
† Low skeletal muscle density is defined as a mean Muscle Attenuation (MA) < 22.55 HU.
‡ Complications ≥ Clavien-Dindo grade 3.

Table 3
Results from Univariable and Multivariable Analysis of Predictors used to build the Multivariable Prediction Model for Postoperative Complications within 30 Days after Surgery.

Potential Predictors	Odds ratio	95% confidence interval	*p*-value	Odds ratio	95% confidence interval	*p*-value
	Univariable analysis			Multivariable analysis (n = 178)		
Low skeletal muscle density*	2.83	1.41–5.67	**0.003**	2.57	1.21–5.45	**0.01**
KATZ-ADL ≥ 2 (n = 178)	3.11	1.05–9.20	**0.04**	2.67	0.88–8.12	0.08
Candidate predictors associated with postoperative complications ($p < 0.20$), but not improving the model						
Bowel surgery (n = 210)	1.92	0.90–4.12	0.09			
FIGO stage IV	1.61	0.87–2.99	0.13			
Charlson Comorbidity Index ≥ 2	0.61	0.32–1.18	0.14			
Polypharmacy†	1.55	0.85–2.82	0.15			
Candidate predictors not associated with postoperative complications ($p \geq 0.20$)						
Living at home with help (n = 210)	1.62	0.72–3.65	0.24			
Undifferentiated tumor (n = 195)	4.67	0.30–73.38	0.27			
Use of walking aid (n = 178)	1.52	0.66–3.49	0.32			
Risk for malnutrition (n = 117)	1.42	0.65–3.08	0.38			
ASA score 3‡ (n = 211)	1.50	0.58–3.87	0.40			
Body Mass Index	1.03	0.96–1.09	0.46			
History of confusion during illness (n = 181)	1.43	0.31–6.58	0.65			
Fall risk (n = 173)	1.21	0.51–2.87	0.66			
Age	0.99	0.92–1.06	0.72			
Pre-existing memory problems (n = 181)	0.79	0.20–3.18	0.74			

KATZ-ADL = Six-item Katz Index of Independence in Activities of Daily Living; FIGO = International Federation of Gynecology and Obstetrics; ASA = American Society of Anesthesiologists.
Boldface data are statistically significant. If a variable has missing values, the number presented behind a variable represents the number of patients included in this analysis.
* Low skeletal muscle density is defined as a mean Muscle Attenuation (MA) < 22.55 HU.
† Polypharmacy was defined as the daily use of ≥ 5 different medicines.
‡ The ASA classification (measured before surgery) ranges for 1 to 6, with higher scores indicating a worse physiological status and a higher operative risk. [11].

systematic review and meta-analysis among younger patients (mean age 55–67 years) no significant association between low skeletal muscle index and overall survival was found. A low skeletal muscle density seemed a better predictor in this population. [29] In pooled data of four studies performed in patients with a mean age between 60 and 65 years old with ovarian carcinoma, skeletal muscle density was associated with poor overall survival. [19] Two previous studies assessed preoperative low skeletal muscle density in relation to postoperative complications in gynecological cancer. Among patients with ovarian cancer, Rutten et al. found it to be associated with severe complications (Clavien–Dindo ≥ 3) in univariable but not in multivariable regression. [30] Silva de Paula et al. found an association with complications, severe postoperative complications and duration of hospital stay in a mixed cohort of ovarian and endometrial cancer patients. [31] However, since there is no standardized cut-off point, all studies used different definitions of low skeletal muscle mass and density. This hinders sound interpretation of the results. Also the quality of the evidence of the included studies, as assessed with the GRADE checklist, was very low. [19,29] Therefore no strong conclusions could be drawn yet in this population.

Current evidence suggests that in patients with a gynecological malignancy as well as in other oncological surgical populations, skeletal muscle density also seems a stronger predictor for postoperative complications and survival than skeletal muscle mass. [29,32,33] The stronger association of low skeletal muscle density with negative postoperative outcomes could be explained by skeletal muscle density being a better proxy for physical performance and frailty. In a recent study in 316 healthy older volunteers, skeletal muscle density was more strongly associated with muscle strength and, in women, with physical performance (measured by the Timed Up and Go test) than muscle size. [34] Low physical performance has earlier been shown to predict long-term outcome in older patients with cancer (gynecological, gastro-intestinal and urological cancer). [35] Besides the association with physical performance, skeletal muscle density is also more associated with frailty than muscle quantity. In a cohort of 162 patients with cancer with a mean age of 73 years old, decreased skeletal muscle density also showed stronger associations with frailty than skeletal muscle mass, even after controlling for age and gender. [36] In our study, patients with low skeletal muscle density showed significantly more frailty markers compared to patients with normal skeletal muscle density, while this difference was not seen between low and normal skeletal muscle mass.

Multivariable analysis of multiple potential preoperative predictors resulted in a model demonstrating that low skeletal muscle density and functional impairment are important predictors for postoperative complications. Our findings are in line with the findings of Souwer et al. in older patients with non-metastasized colorectal cancer, who found a strong association between physical performance (defined as the use of a walking aid) and poor surgical outcome and also stressed the importance of assessing clinical features. In this study physical performance was a stronger predictor than low skeletal muscle density. [33] Functional impairment is easy to assess in clinical practice (by using a questionnaire), it is a patient reported measurement, and reflects more clinical characteristics than sarcopenia only (e.g. cognitive function). Preserving independence is often considered very important by older patients. [27] Hence, to achieve a more comprehensive approach in predicting postoperative outcomes, it is valuable to assess functional impairment as well. Using KATZ-ADL only, a quite coarse measurement, might however overlook more subtle impairments that could possibly be detected by skeletal muscle density assessments. Thus, combining body composition measurements with clinical features, as also recommended by the EWGSOP [7], can result in improved prediction of postoperative complications in older patients with ovarian cancer.

5. Strengths and limitations

This study has several strengths: Firstly, we included all patients aged 70 years or older. Since there are no previous studies on preoperative skeletal muscle mass and density in the older gynecological oncological population, this study is a first step in assessing this predictive tool in a population with a high surgical risk and increased background risk of sarcopenia. Secondly, we were able to build a prediction model using other known predictors, enabling us to assess the added value of measuring skeletal muscle density on routinely performed CT scans. Although the C-statistic of the final model was not optimal, muscle density still can be valuable as first screening tool and should be further investigated in larger studies. Thirdly, as all analyses were performed using CT scans that were part of the routine diagnostic process, patients did not have to be burdened with additional scans. Lastly, CT measurements were performed by a board certified radiologist with experience in these measurements, making them highly reliable. [18]

Some limitations of this study have to be addressed. First, because of the retrospective, multicenter design, CT protocols were not completely standardized for this study. Therefore, per hospital slight differences in contrast enhancement could be present. However, all scans were acquired in the portal venous phase, so only minimal influence is to be expected. [37] Second, due to the retrospective data collection, not all potentially relevant predictors, such as surgical complexity or albumin, [38] and outcomes could be measured. More subtle functional decline than discharge to a care facility could have been missed. Also because of the retrospective nature, we encountered missing data in some of the baseline variables and secondary outcomes. Furthermore, due to a limited number of events, it was not possible to perform multivariable analysis on all outcome measures. Severe complications and functional decline can have major impact for patients. Since low skeletal muscle density was associated with these secondary outcomes, it would be of interest to assess this association in relation to other predictors as well. Finally, we were not able to include patients who did not undergo cytoreductive surgery, which limits extrapolation of the results to all patients starting neoadjuvant chemotherapy for ovarian cancer. Among patients with advanced stage ovarian cancer, extensive disease, functional status and patient preference are the most frequently mentioned reasons to refrain from surgery after NACT. [39] Since risk stratification should ideally help in the decision whether to undergo cytoreductive surgery, patients not receiving surgery are a highly relevant subgroup.

6. Future research

Further research in older patients with ovarian cancer should focus on which markers of sarcopenia are most predictive for negative postoperative outcomes (including patient reported outcomes and functional outcomes), which cut-off points are optimal in the older population, and which are most easy to use in clinical practice. Other CT-measured body composition assessments, such as visceral obesity, could be of value as well, [40] but should first be further investigated in the older population. This research should also include patients in whom cytoreductive surgery is omitted.

7. Conclusion

Preoperative low skeletal muscle density, measured on a routine CT scan in older patients with ovarian cancer, and functional impairment are both associated with postoperative complications. Combining both factors can better predict complications than the individual factors alone. Preoperative low muscle density has added predictive value over functional impairment. A low preoperative skeletal muscle density is also associated with discharge to a care facility, which can indicate postoperative functional decline. Hallmarks of sarcopenia might be helpful with clinical decision making in the future. In addition to the association between preoperative skeletal muscle density and postoperative outcomes, presence of functional impairments seems to play an important role in the prediction of negative postoperative outcomes and should be assessed as well.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.05.039.

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