Does sarcopenia predict perioperative mortality in patients with advanced ovarian cancer?

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Abstract. – **OBJECTIVE:** The aim of this study was to assess prognostic value of frailty for the prediction of surgical complications and mortality in women with end-stage ovarian cancer subjected to curative oncological surgery and its value for long-term follow-up.

PATIENTS AND METHODS: A total of 75 advanced-stage consecutive ovarian cancer patients who underwent elective surgery were investigated. The demographic data and clinical information related to the oncologic treatment were collected in the electronic and physical case records and included the following: age, ethnic group, comorbidities, staging of cancer, surgical procedure details, lymphadenectomy, American Society of Anesthesiology (ASA) grade, anesthetic technique, operative blood loss, operative time, and residual disease. A radiologist, who was blinded to patient outcomes, performed quantitative assessment of psoas muscle areas using the available computed tomography scan images at the caudal end of the third lumbar vertebra.

RESULTS: The mean age was 61.2 ± 18.2 years, and the percentage of patients over 65 years was 78%. Comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, renal insufficiency) were seen in 37 patients (49%). Histological types were adenocarcinoma in all patients (0) mostly serous adenocarcinoma (62%) and stage 3 (58%). According to psoas muscle measurement, 55 patients (73%) were nonsarcopenic and 20 patients (26%) were sarcopenic. Debulking procedures were performed on all patients. Also, bowel resection was applied in 40% of patients. Preoperative anesthetic examinations had shown that they were mostly ASA score 2 (44 patients). Moreover, 26 patients were ASA score 3. Generally, total operative time was between 121-240 minutes, and total blod loss was generally under 500 ml. Postoperative complications were seen in 26% of the patients. Non-surgical complications were observed in 14% of the patients, while non-surgical complications were observed in 12%. Length of the hospital stay >10 days was seen in 10 patients. Mortality was seen in 1 patient during 30 days after operation. Nonsurgical complications (pneumonia, urinary tract infections, cardiac complications) were significantly higher in comparison to nonsarcopenic patients. However surgical complications were comparable between each group. Mortality after hospitalization and length of hospital stay were significantly higher in sarcopenic patients in comparison with the nonsarcopenic group.

CONCLUSIONS: The use of the value of the psoas muscle region is considered to be a method to predict the in-hospital mortality when there is an available abdominal CT scan that has already been performed for ovarian cancer patients with a significant comparable clinical and laboratory background. According to the findings, patients had worse surgical outcomes and higher postoperative nonsurgical complication rate when sarcopenic patients were compared to nonsarcopenic patients. Moreover, postoperative mortality and length of hospital stay were significantly higher in sarcopenic patients in comparison to non-sarcopenic group.

Key Words:
   Sarcopenia, Ovarian cancer, Mortality.

Introduction

Ovarian cancers have a high risk of morbidity and mortality. In addition, there are ongoing efforts to rapidly and accurately assess ovarian cancer patients, establish treatment plans and mobilise the necessary resources to provide the highest level of care to reduce mortality and morbidity in the long term[1,2]. The cornerstone of

appropriate ovarian cancer management is surgery, which aims to establish staging, assess the extent of the disease and attempt to remove all visible tumor. Studies[3-7] have demonstrated early mortality of 2% (up to 30 days after intervention) in gynecological oncologic surgery. Postoperative prognosis is multifactorial, being determined by tumor-related factors as well as patient characteristics such as age, obesity and the presence of comorbidities[8-10]. Among the modifiable factors, those related to physical status seem to have an important role in surgical outcomes.

Frailty is a complex health condition and an important indicator of physical condition associated with increased vulnerability. The negative consequences of frailty include disability, falls, hospitalization and death. Several studies[11-15] have confirmed a close relationship between frailty and poor prognosis in patients with various malignancies.

However, diagnosis is complex, especially in perioperative cases, due to the coexistence of other conditions related to advanced age and the lack of an accepted clinical definition. Sarcopenia, or age-related loss of skeletal muscle and muscle strength, is an important physical component of frailty. Both qualitative and quantitative methods have been used in research for the diagnosis of sarcopenia. Three basic measurements have been used to date: measurement of total abdominal muscle area at the level of the lumbar spine, psoas muscle area at the level of the lumbar spine and thigh muscles at mid-thigh level. Computed tomography (CT) scans performed during diagnosis, therapy and follow-up procedures allow the location of the psoas muscle to be identified. This study aimed to assess the prognostic value of frailty for the prediction of surgical complications and mortality in women with ovarian cancer subjected to curative oncological surgery, as well as its value for long-term follow-up.

Patients and Methods

This retrospective study recruited 75 consecutive patients with ovarian cancer who had undergone elective primary debulking surgery at the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, between January 2013 and June 2017. The study obtained clearance from the human research ethics committee of the institution. Age, ethnicity, comorbidities, cancer staging, surgical procedure specifics, lymphadenectomy, American Society of Anesthesiology (ASA) grade, anaesthetic technique, operative blood loss, operative time and residual disease were among the relevant demographic data and clinical information gathered in the electronic and physical case records.

Inclusion criteria were the presence of malignancy and the availability of CT scans taken up to 45 days before treatment. Women previously diagnosed with another type of cancer, those with synchronous tumors and those receiving neoadjuvant chemotherapy for ovarian cancer were excluded from the study.

We used the psoas area measurement technique for the determination of sarcopenia levels. Psoas area measurement was performed by a radiologist who was blinded to patient outcomes. Quantitative assessment of psoas muscle areas was carried out using the available CT scan images of the caudal end of the third lumbar vertebra (L3). Left and right psoas were measured three times, with mean values being used for analysis. Psoas muscle area values were normalized by dividing body surface area by the sum of the right and left psoas muscle areas (Figure 1). Sarcopenia was defined as SMI < 39.0 cm^2/m^2. Patients were divided into two groups, sarcopenic and non-sarcopenic, and clinicopathologic characteristics and survival outcomes were compared according to sarcopenia presence. Morbidities were also divided into two
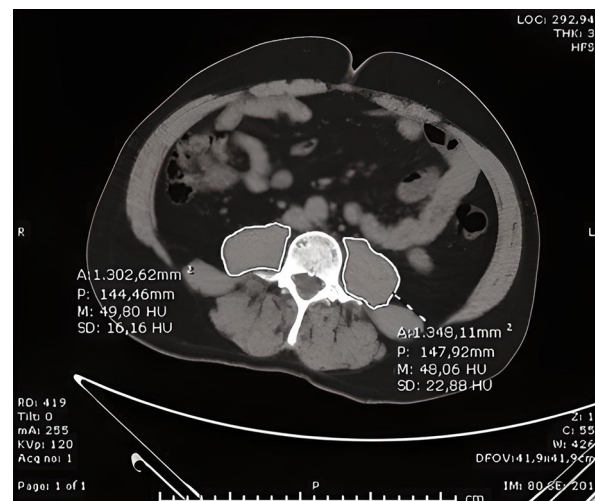
Figure 1. Psoas area measurement was done by a radiologist who, blinded to patient outcomes, performed quantitative assessment of psoas muscle areas using the available CT scan images at the caudal end of the third lumbar vertebra (L3).

groups, surgical and non-surgical. Peritonitis, intraperitoneal bleeding and intestinal obstruction were classified as postoperative surgical complications. Pneumonia, infections at blood vessel catheterisation, urinary tract infection and cardiac complications were classified as non-surgical complications. Morbidity, mortality and postoperative courses were compared between sarcopenic and non-sarcopenic groups.

Statiscal Analysis

All analyses were carried out using SPSS, version 22 (IBM Corp., Armonk, NY, USA). The data were normalised using the Shapiro-Wilk's test. Continuous data were analysed by *t*-test and are presented as means with standard deviation. Categorical data were tested for significance using the chi-square test, where appropriate, and are reported as proportions. Pearson correlation analysis was performed to examine the associations of in-hospital mortality with clinical parameters. All statistical tests were two-tailed, and *p*-value < 0.05 was established as the statistical significance level.

Results

The baseline demographic and clinical characteristics of the study group are summarised in Table I. The mean age was 61.2 ± 18.2 years, and 78% of patients were aged > 65 years. Comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease and renal insufficiency) were seen in 37 patients (49%). Histological types were adenocarcinoma in all patients (100%), mainly serous adenocarcinoma (62%) and stage 3 (58%). According to psoas muscle measurements, 55 patients (73%) were non-sarcopenic, and 20 patients (26%) were sarcopenic. Surgical characteristics and postoperative complications are summarised in Table II. Debulking procedures were performed on all patients, while bowel resection was also applied in 40% of the patients. Preoperative anesthetic examinations had shown that the majority of patients were ASA score 2 (44 patients), with 26 patients classed as ASA score 3. In general, the total operative time was between 121 and 240 minutes, with total blood loss < 500 ml. Postoperative complications were seen in 26% of patients, while non-surgical complications were observed in 14% of patients, and 12% experienced non-surgical complications. Length of hospital stay >10 days were seen in 10 patients,

and mortality was seen in one patient within 30 days of surgery.

Non-surgical complications (pneumonia, urinary tract infections and cardiac complications) were significantly higher in sarcopenic patients than in non-sarcopenic patients are summarized in Table III. However, surgical complications were comparable in the two groups. In addition, mortality after hospitalisation and length of hospital stay were significantly higher in sarcopenic patients, compared with the non-sarcopenic group.

Discussion

Methods to determine preoperative risk in ovarian cancer patients would greatly assist in the prediction of endpoints before surgery and in the identification of high-risk patients.

In the current retrospective analysis of ovarian cancer patients with significantly comparable clinical and laboratory backgrounds, psoas muscle area measurement (using previously acquired abdominal CT scans) was evaluated as a simple procedure to predict in-hospital mortality. The

Table I. Patient sociodemographic, clinical and skeletal muscle parameters (n = 75).

Characteristic	Ovarian n = 75 (%)
Mean age	
Age category, y, n (%)	61
> 65 y	59 (78)
< 65 y	16 (22)
Comorbidity, n (%)	
No	38 (51)
Yes	37 (49)
Comorbidity type, n (%)	
Hypertension	19 (51)
Diabetes	4 (11)
COPD	7 (18)
Renal Insufficiency	7 (18)
Histologic type, n (%)	
Adenocarcinoma	75 (100)
Sarcoma	(0)
Histologic subtype, n (%)	
Endometrioid	7 (9)
Serous	47 (62)
Others	21 (29)
Stage, n (%)	
III	44 (58)
IV	31 (42)
Sarcopenia, n (%)	
No	55 (73.3)
Yes	20 (26.7)

Table II. Surgical characteristics and postoperative complications.

Characteristic	Ovarian n = 75 (%)
Surgical procedure, n (%)	
Total hysterectomy with bilateral salpingo-oophorectomy+omentectomy	40 (53)
Salpingo-oophorectomy+omentectomy	5 (7)
Total hysterectomy with bilateral salpingo-oophorectomy+omentectomy+bowel resection	30 (40)
Lymphadenectomy, n (%)	
No	0 (0)
Yes	75 (100)
ASA score n (%)	
1	5 (6.6)
2	44 (58.6)
3	26 (34.6)
Operative time (min), n (%)	
≤ 120	9 (12)
121-240	40 (53.3)
> 241	26 (34.6)
Operative blood loss (mL), n (%)	
≤ 500	59 (78.7)
500-1000	13 (17.3)
> 1000	3 (4)
Anesthetic technique, n (%)	
General	75 (100)
Postoperative complications, n (%)	
No	55 (73.4)
Yes	20 (26.6)
Length of stay in hospital (d), n (%)	
< 4	21 (28.0)
4-6	32 (42.6)
7-9	12 (16)
> 10	10 (13.3)
Death 30 day after operation, n (%)	
No	74 (99)
Yes	1 (1)

Values showed are medians (range) or n (%).

Table III. Comparison of morbidity, mortality, and postoperative courses between sarcopenic and nonsarcopenic patients.

	Sarcopenic group n = 20 (%)	Nonsarcopenic group n = 55 (%)	*p*-value
Age	64 ± 3	61 ± 2	0.58
Postoperative complications	3 (15)	6 (12)	
Peritonitis	2 (10)	2 (4)	0.45
Intraperitoneal bleeding	1 (5)	3 (6)	0.71
Intestinal obstruction	0 (0)	1 (2)	0.22
Nonsurgical complications	8 (40)	3 (6)	0.01
Pneumonia	5 (25)	1 (2)	0.01
Infections at blood vessel catheterization	1 (5)	0 (0)	0.05
Urinary tract infection	1 (5)	1 (2)	0.01
Cardiac complications	1 (5)	1 (2)	0.01
Mortality	1 (5)	0 (0)	0.03
Lenght of hospital stay (median)	9	6	0.56
< 4	4 (20)	17 (31)	0.06
4-9	9 (45)	35 (63)	0.02
> 10	7 (35)	3 (6)	0.01
Death < 30 day after operation			
No	19 (95)	55 (100)	0.06
Yes	1 (5)	0 (0)	0.03

Values showed are medians (standard deviation) or n (%).

findings indicated that sarcopenic patients experienced worse surgical outcomes and higher post-operative complication rates than non-sarcopenic patients. Decreased rates of in-hospital mortality were correlated with increased psoas muscle area. Moreover, in long-term follow-up of the patients, lower psoas muscle area correlated with worse outcomes. Although there have been previous studies[16] on frailty and survival in patients with ovarian cancer, our study differed from others in that the age range was homogeneous, all patients were at an advanced stage of disease, and only the ovarian cancer group of gynaecological cancers was included.

Interestingly, a study by Reiser et al[17] showed that the vast majority of frail patients had significantly shorter progression-free and overall survival. This study[17] included not only patients with ovarian cancer, but also all subgroups of gynecological cancers. Moreover, the ovarian cancer group was the smallest gynecological patient subgroup of the study.

There is a lack of consensus regarding the optimal method of assessing sarcopenia and frailty[18-20]. Multiple techniques of sarcopenia assessment exist, including a wide range of clinical scales and several radiological and biochemical evaluation methods, including ultrasound, dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and CT[5-7]. In particular, CT is considered a clinically accurate method of assessing skeletal muscle mass. It enables the estimation of muscle mass from abdominal cross-sections and offers crucial quantitative information regarding muscle composition and distribution through high-quality images, spatial accuracy, and location features. Abdominal CT scans or enhanced examinations are usually performed before ovarian cancer surgery to evaluate the tumor stage. Measurement of L3 skeletal muscle mass at the same time would mean that costs would not be increased, reducing the burden on patients. The complexity of DEXA, nuclear MRI and bioelectrical impedance test methods means that these testing processes incur additional patient inspection costs. The prospects for clinical application of these methods are less promising, compared with CT examinations.

Moreover, the widespread use of preoperative CT imaging of the abdomen provides the opportunity for a CT-based marker of frailty to be integrated into clinical practice. This may offer an easy, quick, reproducible and objective marker of sarcopenia utilising currently available imaging

at no additional expense. Such a method could provide details to direct patient management as well as aid the creation of perioperative pathways to enhance recovery in older people with sarcopenia. Compared with other recent studies[20-24], the major differences found in our study mainly resulted from (1) differences in test methodology, including measurement of muscle mass, muscle strength and physical status agonists, (2) choice of patients, such as chronic *vs.* acute disease status, (3) the sensitivity and specificity of tests and (4) the non-uniform cut-off values recorded. Unfortunately, no gold standard is available for the measurement of sarcopenia, which accounts for the wide range of sarcopenia prevalence showed in previous studies[25-28]. The use of different methods for assessing the psoas major muscle means that evaluation of frailty is somewhat complex, yielding variable results as the chosen imaging methods (ranging from ultrasound-based systems to X-ray methods) are based on different principles; in addition, the selected cut-off values chosen to define sarcopenia can vary. Moreover, consensus definitions for the diagnosis of sarcopenia have used cut-off values for low muscle mass based on DEXA or BIA measurements. Regarding CT-based methods, as low levels of muscle mass are part of the ageing process, especially in terms of primary sarcopenia, ranges or mean values of skeletal muscle mass obtained by CT will vary in different populations due to factors such as ethnic and cultural differences, nutritional habits and physical activity levels. In our study, age-specific mean or cut-off values of muscle mass were used. Moreover, the use of age-specific estimation values led to a greater number of age-specific frail patients in this study, compared with literature.

Limitations

There were several limitations in our study. First, this was a retrospective study of patients with advanced-stage ovarian cancer (Stage IIIC-IVB), and some residual confounding factors could not be ruled out, possibly leading to a certain degree of deviation. Second, as a single institution provided the study population, the findings might not be generalisable to the entire population. Finally, there were fewer samples in the ovarian cancer group. Multi-centre and longitudinal studies with larger sample sizes are needed to verify the association between mortality and sarcopenia in patients with ovarian cancer. Moreover, the findings of this study reveal the

importance of perioperative risk assessment of these ovarian cancer patients. To create detailed and careful care plans based on patients' physical status, physicians need to take into account the appropriate medical treatments, management of sarcopenia, treatable causes of weight loss, and other causes of frailty.

Conclusions

The use of psoas muscle area is considered to be a method to predict in-hospital mortality in ovarian cancer patients with comparable clinical and laboratory backgrounds, based on the availability of previously performed abdominal CT scans. The findings showed that sarcopenic patients had worse surgical outcomes and higher postoperative non-surgical complication rates, compared with non-sarcopenic patients. Moreover, postoperative mortality and length of hospital stay were significantly higher in sarcopenic patients in comparision to non-sarcopenic group.

Conflict of Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Approval
Ethical committee approval was received by the Ethics Committee of University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital (Approval No.: February 2, 2021.01.31).

Informed Consent
Written informed consent was obtained from all participants who participated in this study.

Authors' Contribution
Concept – Esra Can; Design – Esra Can; Supervision – Özgür Akbayır; Materials – Esra Can, Süleyman Sönmez, Merve Konal, Hicran Acar Şirinoglu, Niyazi Alper Seyhan; Data Collection and/or Processing – Esra Can, Süleyman Sönmez, Merve Konal, Hicran Acar Şirinoglu, Niyazi Alper Seyhan; Analysis and/or Interpretation – Esra Can, Merve Konal; Literature Review – Esra Can, Süleyman Sönmez, Merve Konal, Hicran Acar Şirinoglu; Niyazi Alper Seyhan; Writing – Esra Can, Merve Konal; Critical Review – Esra Can, Süleyman Sönmez, Merve Konal, Hicran Acar Şirinoglu, Niyazi Alper Seyhan.

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