Effects of Sarcopenia and Malnutrition on Morbidity and Mortality in Gynecologic Cancer Surgery: Results of a Prospective Study

Jalid Sehouli[1] *, Kristina Mueller[1]*, Rolf Richter[1], Markus Anker[2], Hannah Woopen[1], Julia Rasch[1], Jacek P. Grabowski[1], Eva Prinz-Theissing[1], Melisa Guelhan Inci[1]

[1]Charité – University Medicine of Berlin, Campus Virchow Klinikum, Department of Gynecology, Center of Oncological Surgery, Berlin, Germany,

[2]Division of Cardiology and Metabolism, Department of Cardiology (CVK), Charité University Medicine Berlin, Berlin, Germany; Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany; DZHK (German Centre for Cardiovascular Research), partner site Berlin, Germany; Department of Cardiology (CBF), Charité University Medicine Berlin, Berlin, Germany;

Correspondence to: Guelhan Inci, Charité – University Medicine of Berlin, Campus Virchow Klinikum, Department of Gynecology, European Competence Center for Ovarian Cancer, Augustenburger Platz 1, 13353 Berlin, Germany. Email: guelhan.inci@charite.de, Telephone: +49 30 450664346, Fax: +49 30 450564902

*shared authorship

These results have been presented partially at the 12th International Conference on Cachexia, Sarcopenia and Muscle Wasting in Berlin, Germany.

Abstract

Background: Malnutrition and sarcopenia often occur simultaneously in cancer patients and are thought to have harmful effects on both surgical and oncological outcomes. Therefore, we want to evaluate the effects of sarcopenia and malnutrition on severe postoperative complications and overall survival in gynecologic cancer patients.

Methods: We assessed nutritional parameters and run a bioelectrical impedance analysis in 226 women. Extracellular mass to body cell mass index, phase angle alpha, muscle mass and fat mass were evaluated. To determine if patients suffer from sarcopenia, we ran the Timed "Up and Go" test, performed hand grip strength and calculated a skeletal muscle index. Postoperative complications were categorised using Clavien-Dindo Classification. Utilising ROC analysis and logistic regression, we determined predictive clinical factors for severe postoperative complications. Kaplan-Meier method and log-rank test were used for overall survival analysis.

Results: Of 226 female patients, 120 (53%) had a BMI ≥ 25 kg/m², 56 (26%) had a phase angle < 4.75° and 68 (32%) were sarcopenic according to skeletal muscle index < 27%. Within 30 days after surgery, 40 (18%) patients developed severe postoperative complications and 4% had died. According to multivariable regression analysis, ECOG status > 1 (OR 4.56, 95% CI: 1.46-14.28, p=0.009), BMI ≥ 25 kg/m² (OR 8.22, 95% CI: 3.01-22.48, p<0.001), phase angle < 4.75° (OR 3.95, 95% CI: 1.71-9.10, p=0.001), and tumor stage ≥ III A (OR 3.65, 95% CI: 1.36-9.76, p=0.01) were predictors of severe postoperative complications. During 59 months of follow-up, 108 (48 %) patients had died. According to multivariable Cox regression ECOG status > 1 (HR 2.51, 95% CI: 1.25-5.03, p=0.01), hypoalbuminemia (HR 2.15 95 % CI: 1.28-3.59, p=0.004), phase angle < 4.5° (HR 1.76, 95% CI 1.07-2.90, p=0.03), tumor stage ≥ III A (HR 2.61, 95% CI: 1.53-4.45, p<0.001), and severe postoperative complications (HR 2.82, 95% CI: 1.80-4.41, p<0.001) were predictors of overall mortality.

Conclusion: We observed that preoperatively assessed ECOG status > 1, BMI > 25 kg, as well as phase angle alpha < 4.75° and FIGO stage ≥ III A are significantly associated with severe postoperative complications within the first month. Whereas ECOG status > 1, hypoalbuminemia, phase angle < 4.5° as well as FIGO stage ≥ III A and severe postoperative complications within 30 days correlate significantly with poor overall survival.

Keywords: sarcopenia, malnutrition, postoperative complications, gynecologic oncology, overall survival

Introduction

Gynecologic cancer surgeries are often complex and include various multivisceral surgical procedures, which can be associated with life-threatening complications [1]. Several studies have shown harmful effects of malnutrition and sarcopenia on both oncological and surgical outcomes, including higher rates of infections, longer hospitalisation and lower rates in progression-free and overall survival [2-5].

Defined by the European working group on sarcopenia in older people (EWGSOP) sarcopenia is an acute or chronic muscle disease and its key characteristic is impaired muscle strength accompanied by low muscle quantity and quality [6]. Whereas malnutrition is classified as a deficiency in energy and nutrient supply with adverse and measurable consequences [7].

Malnutrition and sarcopenia have analogies regarding their physiological mechanisms and often occur simultaneously, characterised by mutual features like changes in body composition and decreased functions. Moreover, sarcopenia can be caused by malnutrition [8]. The term “malnutrition-sarcopenia syndrome” was already proposed in research in order to integrate both conditions in one screening [9]. Both syndromes are associated with negative outcomes, involving decreased quality of life and functionality, increased hospitalisation rates, morbidity and mortality [8,10,11]. In cancer patients undernourishment and weight loss occur due to many factors, including the tumor metabolism, the host response to the tumor and anticancer treatments [12]. Malnutrition is proven to be a major problem in gynecologic cancer patients, particularly among those with ovarian cancer [13].

Former studies have shown that malnutrition and muscle attenuation are correlated with poor oncologic outcomes in gynecologic cancer patients [14-19]. Nevertheless, these studies were mostly done retrospectively and have applied different definitions and measurements.

Therefore, we wanted to demonstrate the association of malnutrition and sarcopenia with severe postoperative complications as well as overall mortality in gynecologic cancer patients.

Methods

Patients, study design, study measures

The data presented are part of the results of a prospective clinical cohort study (the RISC-GYN trial by Inci et al.) on women undergoing gynecologic cancer surgery at a licensed gynecologic oncology center of Charité - University Medicine of Berlin, Germany. From October 2015 to January 2017 we screened 237 women older than 18 years, who presented a gynecologic malignant tumor disease and were expected to undergo an elective surgery longer than 60 minutes. The Charité's Ethics Committee gave the ethical consent for this study with the approval ID EA2/122/15 and we obtained written consent from all women included.

The prospective screening included a detailed patient history, preoperative blood values, performance status (ECOG), quality of life parameters and geriatric assessments. Intraoperatively information on the tumor dissemination and the operative procedure were noted. During ovarian cancer surgery the Interoperative Mapping of Ovarian Cancer (IMO) was applied for precise tumor documentation [20]. Surgery was performed by qualified gynecologic oncology surgeons and surgical complications were categorised using Clavien-Dindo Classification [21]. The Clavien-Dindo grading system ranks complications according to their required therapy and it consists of seven grades. In addition, patients were subdivided into two groups, by severity of their postoperative complications [lower grade (Clavien-Dindo 0 – III a) vs. higher grade complications (Clavien-Dindo III b - V)] to look for differences in patient characteristics in these cohorts. We only considered severe complications with grade III b or higher in statistical analyses.

Our assessment was performed one to three days preoperatively by medically trained staff and took about 90 minutes per patient. Each woman was visited daily after surgery and postoperative complications were noted within the first 14 days. After discharge from the hospital a follow up call was made after 3 months in order to record later occurring postoperative complications. Follow-up for overall mortality was done until September 2020. In order to display the course of the study we included a consort diagram (Figure 1).

Assessment of nutritional status

Preoperatively assessed nutritional parameters included albumin, BMI, and whether the patient had a weight loss ≥ 10% during the last 3 months. The Nutritional Risk Screening 2002 was used to identify women with a high risk of malnutrition. Additionally, we utilised parameters of bioelectrical impedance analysis such as phase angle alpha, extracellular mass to body cell mass index, fat mass and muscle mass. Phase angle alpha displays the metabolic activity of the examined body, which is correlated with

the training and nutritional state. A value of ≥ 5.0 ° is understood to be adequate for women [22]. The extracellular mass to body cell mass index is a parameter for assessing the nutritional state. In healthy, well-nourished humans, the body cell mass is greater than extracellular mass and the index is less than one [22]. Bioelectrical impedance analysis was applied in a standardised procedure using BIACORPUS RX 4004M (Medical HealthCare GmbH, Karlsruhe Germany).

Assessment of sarcopenia

Sarcopenia was measured according to the European consensus definition of the EWGSOP as an analysis of strength, performance and muscle mass [6]. To identify these parameters we examined grip strength in both hands (SAEHAN Handdynamometer SH5001), ran the Timed "Up and Go" test and calculated the skeletal muscle index. Since hand grip strength values are age-related, we established age-dependent cut-offs and used values of the stronger hand. In order to obtain the skeletal muscle index, we calculated the amount of skeletal muscle mass (SMM) using the formula of Janssen et al., that includes a parameter from bioelectrical impedance analysis (BIA) [23].

$$SMM\ (kg) = ([height^{\,2}/BIA\ resistance\ \times 0.401] + [gender \times 3.825] + [age\ \times -0.071]) + 5.102$$

Height in centimetres; resistance in ohms; gender: women = 0; age in years

Ultimately we calculated the skeletal muscle index: SMM/body mass × 100, where the patients' muscle mass was transformed to percentage muscle mass and adjusted for nonskeletal muscle tissues, as originally introduced by Janssen et al. [24].

Statistical analysis

This study was primary powered for postoperative complications. To achieve a high predictive value (ppW) with a high sensitivity, the proportion in the risk group had to correspond to the complication rate. For this study a risk score that reaches a ppW of 80% was developed. The 95% confidence interval (95% CI) is between 70% and 88% in the target group with complications. The assumption was that the complication rate would be 40%, as in previous studies. The total number of cases, including 5% failure, should therefore be 237 patients.

To analyse comparisons between groups we used the chi test for normal variables, Fisher´s exact test for dichotomous variables, Kendall´s tau b for ordinal variables and Kruskal-Wallis test or Mann-Whitney test for continuous variables. We evaluated the predictive accuracy of continuous variables by performing receiver-operator characteristics (ROC) curve analyses to differentiate women with severe complications from those without and in order to define cut-offs. Using logistic regression

analysis, we obtained crude and adjusted odds ratios (ORs) with corresponding 95% CI. We performed a multivariable logistic regression analyses stepwise forward with p in = 0.05 and p out = 0.10. Kaplan-Meier method and log-rank test were used for overall survival analysis. Applying multivariable Cox proportional hazards model, we obtained independent factors for overall survival, shown as hazard ratios (HRs) with corresponding 95% CI.

We excluded cases with missing data (<5%) from the multivariable analyses. IBM® SPSS® Statistics 25 (SPSS Inc. an IBM Company, Chicago, Illinois, USA) was utilised for statistical analysis, and statistical significance was obtained when p was < 0.05.

Results

Initially we enrolled 237 patients into our study. Subsequently 11 patients were excluded, either due to a postoperatively histologically confirmed benign tumor entity or a surgery duration under one hour, resulting in a final cohort of 226 gynecologic cancer patients. The study consort diagram is shown in Figure 1.

Patient demographics and clinical features

59 years was the median age of patients with a range of 18 to 87 years. Ovarian cancer was the most common entity, with 160 cases (71%). 146 (67%) patients had FIGO (International Federation of Gynecology and Obstetrics) stage III A - IV A. Only 10 (4%) women received neoadjuvant chemotherapy. A severe risk of malnutrition was noted in 97 (43%) patients according to a Nutritional Risk Screening 2002 score ≥ 3. 24 (11%) women reported weight loss > 10% within the last three months. 23 (10%) had a BMI < 20 kg/m². Hypoalbuminemia with less than 35.6 g/L was found in 26 (12%) patients and 56 (26%) had a phase angle < 4.75°. 68 (32%) gynecologic cancer patients were sarcopenic according to a skeletal muscle index < 27%. In 47 (21%) cases impaired hand grip strength was noted. 55 (25%) women presented a lower physical performance according to a Timed “Up and Go” test > 9.5 seconds. Baseline characteristics, including nutritional- and muscle status, are presented in Table 1.

40 (18%) women developed severe postoperative complications and 9 (4%) of these patients died within 30 days after surgery. Patients with severe postoperative complications had significantly lower preoperative albumin levels and a significantly higher median weight as well as a higher BMI than the cohort with low grade postoperative complications. Moreover, patients with severe postoperative complications had significantly lower phase angle values, a lower skeletal muscle index, higher fat mass and a higher extracellular mass to body cell mass index. Their ECOG score and American Society of

Anaesthesiologists physical status (ASA PS) classification system score were considerably higher as well (Table 1).

Univariable analysis of nutritional and muscle status for postoperative complications

Hypoalbuminemia (≤ 35.6 g/L) was a predictive indicator for severe postoperative complications (OR 5.28, 95% CI: 1.85-15.08, p=0.002). A phase angle < 4.75° was highly associated with severe postoperative complications (OR 3.52, 95% CI: 1.68-7.35, p=0.001) and the extracellular mass to body cell mass index > 1.35 was significant as well (OR 4.46, 95% CI: 1.86-10.69, p=0.001). Overweight (BMI > 25 kg/m^2) was a predictive factor for severe complications (OR 6.59, 95% CI: 2.64-16.44, p<0.001). Also, fat mass > 27. 5 kg (OR 7.63, 95% CI: 2.72-21.44), p<0.001) and muscle mass < 21.8 kg (OR 3.16, 95% CI: 1.51-6.63), p=0.002) were both significant parameters in predicting severe postoperative complications. At a cut-off of < 27 % the skeletal muscle index was notably associated (OR 2.80, 95% CI: 1.36-5.77, p=0.005) with severe postoperative complications. Low age-dependent hand grip strength had an impact on postoperative complications (OR 2.85 95% CI: 1.35-6.00, p=0.006) and the Timed "Up and Go" test > 9.5 seconds was closely associated with severe complications (OR 8.18, 95% CI: 2.58-25.93, p<0.001) as well. The univariable analysis of nutritional and muscle status associated with severe postoperative complications is presented in Table 2.

Multivariable analysis of nutritional and muscle status for postoperative complications

In stepwise logistic regression including FIGO stage, BMI, ECOG status, ASA PS, Charlson Comorbidity Index, Nutritional Risk Screening 2002, weight loss, albumin, phase angle alpha, fat mass, muscle mass, skeletal muscle index, Timed „Up and Go" test and hand grip strength we found BMI > 25 kg/m² (OR 8.22, 95% CI: 3.01-22.48, p<0.001) as well as ECOG > 1 (OR 4.56, 95% CI: 1.46-14.28, p=0.009) as significant predictors of severe postoperative complications. Moreover, severe complications were predicted by phase angle < 4.75° (OR 3.95, 95% CI: 1.71-9.10, p=0.001) and FIGO ≥ III A (OR 3.65 95% CI: 1.36-9.76, p=0.01). The significant results of multivariable analysis are presented in Table 2. The conducted ROC analysis for significant nutritional parameters, including AUC (Area Under the Curve), specific cut-off, sensitivity, specificity and p-value are shown in Figure 2.

Association between nutritional and muscle status and overall survival

Within 59 months 108 (48%) patients died. The median observation period was 37.6 months (range: 0 to 59 months) and the median overall survival was 49.1 months.

In patients with albumin less than 35.5 g/L the median overall survival was 9.7 months whereas in women with higher albumin levels the median survival was 53.5 months (p<0.001). Patients with a phase angle smaller than 4.5° had a median overall survival of 9.7 month and those with a higher angle

of 53.5 months (p<0.001). Women with an extracellular mass to body cell mass index higher than 1.3 showed a significant decreased median survival of 18.6 months compared to 52.9 months in women with a smaller index (p<0.001). Moreover, women with a Timed “Up and Go” test slower than 11 seconds presented a reduced median survival of 20.5 months compared to 52.9 months, of those with faster gait speed (p=0.02). Overweight and underweight measured by BMI were not statistically significant for poor survival (p=0.98). The results of the overall survival analysis are shown in Table 3. Unadjusted HRs with corresponding 95% CI are presented in Table 4.

According to multivariable Cox regression ECOG status > 1 (HR 2.51, 95% CI: 1.25-5.03, p=0.01), hypoalbuminemia (HR 2.15 95 % CI: 1.28-3.59, p=0.004), phase angle < 4.5° (HR 1.76, 95% CI 1.07-2.90, p= 0.03) as well as FIGO stage ≥ III A (HR 2.61, 95% CI: 1.53-4.45, p<0.001) and severe postoperative complications (HR 2.82, 95% CI: 1.80-4.41, p<0.001) resulted as significant parameters for poor overall survival. Results of multivariable Cox regression are presented in Table 4. The conducted Kaplan-Meier curves of significant factors for poor survival are shown in Figure 3.

Discussion

Our work is one of few prospective studies evaluating the impact of malnutrition and sarcopenia on severe postoperative complications and overall survival in gynecologic malignancies systematically and multidimensionally. We observed that preoperatively assessed ECOG status > 1, BMI > 25 kg, as well as phase angle alpha < 4.75° and FIGO stage ≥ III A are significantly associated with severe postoperative complications within the first month. Whereas ECOG status > 1, hypoalbuminemia, phase angle < 4.5° as well as FIGO stage ≥ III A and severe postoperative complications within 30 days correlate significantly with poor overall survival.

Referring a the study on 154 women with gynecologic tumors the chance of malnutrition in ovarian cancer patients is 19-times higher than in benign gynecologic tumor patients [13]. 43% of our patients were at considerable risk of malnutrition, according to a Nutritional Risk Screening 2002 score of three and more. Diagnosing malnutrition with conventional criteria, such as a low BMI or weight loss, is insufficient and can be deceptive, as an accumulation of ascites increases the body weight, while body cell mass is truly decreasing. Consequently, a reasonable explanation why measures like weight loss > 10%, Nutritional Risk Screening 2002 ≥ 3 and BMI < 20 kg/m² did not correlate with severe postoperative complications or poor overall survival in our study is that cachectic patients were only partially detected. Malnutrition is a complex and multifactorial syndrome, which can be assessed using several anthropometric measures and serum protein markers, including albumin [25]. Many published studies demonstrate the predictive value of hypoalbuminemia on surgical outcomes [26-30]. Moreover, surgical complications, such as septicaemia and disturbed wound healing, are associated

with a preoperative serum albumin concentration ≤ 30 g/L in ovarian cancer patients [28]. According to our outcomes, hypoalbuminemia was not predictive for severe postoperative complications within 30 days, but emerged as a significant factor for poor overall survival. This was also shown in large a meta-analysis on 3884 ovarian cancer patients, where the authors determined hypoalbuminemia as an important predictor for reduced overall survival [29].

Furthermore, our results indicate that overweight and obesity are associated with severe postoperative complications. The median body weight as well as the median BMI of women with serious complications in our study are notably high (81 kg, 29 kg/m²). Obese ovarian cancer patients have a higher incidence of postoperative wound complications and longer hospitalisation after surgery [31]. Corresponding to a retrospective analysis of more than 500 patients with ovarian cancer, patients with a BMI ≥ 40 kg/m² have increased rates of postoperative complications, develop higher 90-day postsurgical mortality and have an ASA score ≥ 3 more frequently [32]. In uterine cancer, obesity is correlated with higher rates of surgical complications such as thrombophlebitis, infections, wound complications and longer clinic stay [33, 34].

Moreover, a phase angle smaller than 4.75° is prognostic for severe postoperative complications and an angle smaller than 4.5° is predictive for poor overall survival in our investigation. Phase angle alpha displays the metabolic activity of the examined body, which is correlated with the training and nutritional state [22]. Research on the prognostic capability of phase angle on oncological outcomes has been increasing lately. A broad review, that includes 27 research articles about the value of bioelectrical impedance analysis in cancer patients, indicates that the usage of BIA measures and phase angle alpha can be beneficial for tumor patients in prevention, prognosis and outcomes [35]. The first prospective investigation, that included ovarian cancer patients, was done in 2016 by our working group, here an angle smaller than 4.5° was associated with poor overall survival as well [36]. Additionally, a prospective study in patients with advanced ovarian malignancy determined phase angle alpha as a prognostic forecaster for perioperative complications and residual tumor disease after cytoreductive surgery [37]. More studies are consistent with our results and introduce phase angle alpha as a predictor for adverse outcomes in various patient cohorts [38-41].

Previous studies determined sarcopenia as an indicator of poor outcomes, particularly of decreased overall survival, in surgical oncology [5] and gynecologic oncology [18, 19, 42].
According to our results other factors, including ECOG performance status, were more important in predicting severe postoperative complications and poor overall survival than the measured sarcopenia parameters. The ECOG performance status refers to fitness and functioning in daily life of oncological patients and can be utilised as a complementary tool in assessing the patients' functional health status [43]. In a prospective study on gynecologic cancer patients our study group could reveal

that ECOG status can predict severe postoperative complications more precisely than Fried Frailty Score [44].

Our investigation has some limitations. The enrolled patients had different types of gynecologic cancers in varying stages of disease (FIGO I to FIGO IV A). More studies in the mentioned subgroups should be performed to confirm our results. Nevertheless, the inclusion of different tumor entities and stages make our outcomes suitable to a wider patient range. Furthermore, bioelectrical impedance analysis calculates the body composition indirectly with an equation, which is a possible source of error. However, phase angle alpha is a raw value and independent from calculations, making it a reliable and promising parameter. Strengths of our analysis include its prospective design and the exploration of multiple variables, in a preoperative assessment lasting around 90 minutes. Additionally, each woman was visited daily after surgery with systematical application of Clavien-Dindo criteria. Our study was the first to combine a multidimensional analysis of malnutrition with the analysis of sarcopenia, including bioelectrical impedance analysis, in a large cohort of gynecologic cancer patients.

Conclusion

The prevalence of malnutrition and sarcopenia in gynecologic cancer patients is significantly high. Besides FIGO stage and ECOG status, the preoperative nutritional status, including BMI and phase angle, is an important indicator for severe postoperative complications. Additionally to these factors, hypoalbuminemia and sever postoperative complication are essential predictors of poor overall survival. These findings express the need to integrate a nutritional assessment, involving bioelectrical impedance analysis, into preoperative counselling to effectively determine high-risk patients as a mandatory procedure. Physicians can intervene on that basis and improve patient outcomes by optimising the nutritional as well as functional status prior to surgery.

Acknowledgments

This study was funded by the ALLIMOGI- Foundation.
The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. [45]

Conflict of interest

Dr. Anker reports personal fees from Servier, outside the submitted work. All other authors declare no conflict of interest.

References

1. Romeo A, Gonzalez MI, Jaunarena J, Zubieta ME, Favre G, Tejerizo JC. Pelvic exenteration for gynecologic malignancies: Postoperative complications and oncologic outcomes. *Actas Urol Esp*. 2018;42(2):121-125.

2. Su H, Ruan J, Chen T, Lin E, Shi L. CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. *Cancer Imaging*. 2019;19. doi:10.1186/s40644-019-0270-0

3. Otten L, Stobäus N, Franz K, et al. Impact of sarcopenia on 1-year mortality in older patients with cancer. *Age Ageing*. 2019;48(3):413-418.

4. Reisinger KW, van Vugt JLA, Tegels JJW, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg*. 2015;261(2):345-352.

5. JOGLEKAR S, NAU PN, MEZHIR JJ. The Impact of Sarcopenia on Survival and Complications in Surgical Oncology: A Review of the Current Literature. *J Surg Oncol*. 2015;112(5):503-509.

6. Sarcopenia: revised European consensus on definition and diagnosis. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6322506/. Accessed December 12, 2019.

7. Bauer JM, Volkert D, Wirth R, et al. Diagnostik der Mangelernährung des älteren Menschen. *DMW - Dtsch Med Wochenschr*. 2006;131(5):223-227.

8. Lardiés-Sánchez B, Sanz-París A. Sarcopenia and Malnutrition in the Elderly. *Frailty Sarcopenia - Onset Dev Clin Chall*. August 2017. doi:10.5772/intechopen.68426

9. Vandewoude MFJ, Alish CJ, Sauer AC, et al. Malnutrition-Sarcopenia Syndrome : Is This the Future of Nutrition Screening and Assessment for Older Adults? Clinical Nutrition and Aging. doi:10.1201/9781315364971-3

10. Saka B, Ozkaya H, Karisik E, et al. Malnutrition and sarcopenia are associated with increased mortality rate in nursing home residents: A prospective study. *Eur Geriatr Med*. 2016;7(3):232-238.

11. Beaudart C, Zaaria M, Pasleau F, Reginster J-Y, Bruyère O. Health Outcomes of Sarcopenia: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2017; doi:10.1371/journal.pone.0169548

12. von Meyenfeldt M. Cancer-associated malnutrition: an introduction. *Eur J Oncol Nurs Off J Eur Oncol Nurs Soc*. 2005;9 Suppl 2:S35-38.

13. Laky B, Janda M, Bauer J, Vavra C, Cleghorn G, Obermair A. Malnutrition among gynaecological cancer patients. *Eur J Clin Nutr*. 2007;61(5):642-646.

14. Kathiresan ASQ, Brookfield KF, Schuman SI, Lucci JA. Malnutrition as a predictor of poor postoperative outcomes in gynecologic cancer patients. *Arch Gynecol Obstet*. 2011;284(2):445-451.

15. Ubachs J, Ziemons J, Minis-Rutten IJG, et al. Sarcopenia and ovarian cancer survival: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2019;10(6):1165-1174.

16. Uppal S, Al-Niaimi A, Rice LW, et al. Preoperative hypoalbuminemia is an independent predictor of poor perioperative outcomes in women undergoing open surgery for gynecologic malignancies. *Gynecol Oncol*. 2013;131(2):416-422.

17. Kumar A, Torres ML, Cliby WA, et al. Inflammatory and Nutritional Serum Markers as Predictors of Peri-operative Morbidity and Survival in Ovarian Cancer. *Anticancer Res*. 2017;37(7):3673-3677.

18. Aust S, Knogler T, Pils D, et al. Skeletal Muscle Depletion and Markers for Cancer Cachexia Are Strong Prognostic Factors in Epithelial Ovarian Cancer. *PLoS ONE*. 2015;10(10). doi:10.1371/journal.pone.0140403

19. Kumar A, Moynagh MR, Multinu F, et al. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. *Gynecol Oncol*. 2016;142(2):311-316.

20. Sehouli J, Könsgen D, Mustea A, et al. ["IMO"--intraoperative mapping of ovarian cancer]. *Zentralbl Gynakol*. 2003;125(3-4):129-135.

21. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg*. 2004;240(2):205-213.

22. Stobäus N, Norman K, Pirlich M. Phasenwinkel und Bioelektrische Impedanzvektoranalyse – Klinische Anwendbarkeit der Impedanzparameter. *Aktuelle Ernährungsmedizin*. 2010;35(03):124-130.

23. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol*. 2000;89(2):465-471.

24. Janssen I, Heymsfield SB, Ross R. Low Relative Skeletal Muscle Mass (Sarcopenia) in Older Persons Is Associated with Functional Impairment and Physical Disability. *J Am Geriatr Soc*. 2002;50(5):889-896.

25. Bharadwaj S, Ginoya S, Tandon P, et al. Malnutrition: laboratory markers vs nutritional assessment. *Gastroenterol Rep*. 2016;4(4):272-280.

26. Kim J, Shim S-H, Oh I-K, et al. Preoperative hypoalbuminemia is a risk factor for 30-day morbidity after gynecological malignancy surgery. *Obstet Gynecol Sci*. 2015;58(5):359-367.

27. Ataseven B, Bois A du, Reinthaller A, et al. Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery. *Gynecol Oncol*. 2015;138(3):560-565.

28. Obermair A, Hagenauer S, Tamandl D, et al. Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer. *Gynecol Oncol*. 2001;83(1):115-120.

29. Ge L-N, Wang F. Prognostic significance of preoperative serum albumin in epithelial ovarian cancer patients: a systematic review and dose–response meta-analysis of observational studies. *Cancer Manag Res*. 2018;10:815-825.

30. Aletti GD, Eisenhauer EL, Santillan A, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. *Gynecol Oncol*. 2011;120(1):23-28.

31. Smits A, Lopes A, Das N, et al. Surgical morbidity and clinical outcomes in ovarian cancer - the role of obesity. *BJOG Int J Obstet Gynaecol*. 2016;123(2):300-308.

32. Kumar A, Bakkum-Gamez JN, Weaver AL, McGree ME, Cliby WA. Impact of obesity on surgical and oncologic outcomes in ovarian cancer. *Gynecol Oncol*. 2014;135(1):19-24.

33. Gunderson CC, Java J, Moore KN, Walker JL. The impact of obesity on surgical staging, complications, and survival with uterine cancer: a Gynecologic Oncology Group LAP2 ancillary data study. *Gynecol Oncol*. 2014;133(1):23-27.

34. Mahdi H, Jernigan AM, Aljebori Q, Lockhart D, Moslemi-Kebria M. The impact of obesity on the 30-day morbidity and mortality after surgery for endometrial cancer. *J Minim Invasive Gynecol*. 2015;22(1):94-102.

35. Grundmann O, Yoon SL, Williams JJ. The value of bioelectrical impedance analysis and phase angle in the evaluation of malnutrition and quality of life in cancer patients—a comprehensive review. *Eur J Clin Nutr*. 2015;69(12):1290-1297.

36. Sehouli J, Ali P, Braicu EI, Chekerov R, Grabowski JP. The impact of preoperative malnutrition on surgery outcome and overall survival in ovarian or peritoneal cancer patients: A prospective study. *J Clin Oncol*. 2016;34(15_suppl):5574-5574

37. Uccella S, Mele MC, Quagliozzi L, et al. Assessment of preoperative nutritional status using BIA-derived phase angle (PhA) in patients with advanced ovarian cancer: Correlation with the extent of cytoreduction and complications. *Gynecol Oncol*. 2018;149(2):263-269.

38. Barbosa-Silva MCG, Barros AJD. Bioelectric impedance and individual characteristics as prognostic factors for post-operative complications. *Clin Nutr Edinb Scotl*. 2005;24(5):830-838.

39. Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for prognostication of survival in patients with advanced cancer: preliminary findings. *Cancer*. 2014;120(14):2207-2214.

40. Toso S, Piccoli A, Gusella M, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. *Nutrition*. 2000;16(2):120-124.

41. Gupta D, Lammersfeld CA, Burrows JL, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. *Am J Clin Nutr*. 2004;80(6):1634-1638.

42. Ataseven B, Luengo TG, du Bois A, et al. Skeletal Muscle Attenuation (Sarcopenia) Predicts Reduced Overall Survival in Patients with Advanced Epithelial Ovarian Cancer Undergoing Primary Debulking Surgery. *Ann Surg Oncol*. 2018;25(11):3372-3379.

43. ECOG Performance Status. ECOG-ACRIN. https://ecog-acrin.org/resources/ecog-performance-status. Accessed March 12, 2020.

44. Inci, M. G. *et al.* Can Fried Frailty Score predict postoperative morbidity and mortality in gynecologic cancer surgery? Results of a prospective study. *J. Geriatr. Oncol.* (2020) doi:10.1016/j.jgo.2020.09.029.

45. Von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. J Cachexia Sarcopenia Muscle 2017;8: 1081-1083.

Table 1: Baseline Characteristics related to 30 day Postoperative Complications according to Clavien-Dindo

Characteristics	**Total n= 226 (range or %)**	**CDC 0-III a n= 186 (range or %)**	**CDC III b-V n = 40 (range or %)**	**p-value**
Age (years)	59* (18-87)	59* (18-86)	63* (31-87)	0.26
Age > 70 years	58 (26)	45 (24)	13 (33)	0.32
Weight (kg)	70* (44-160)	68*	81*	<0.001
ECOG PS > 1	19 (8)	9 (5)	10 (25)	<0.001
Ascites	72 (32)	55 (31)	17 (43)	0.02
Pleural effusion	25 (11)	18 (10)	7 (18)	0.08
FIGO stage				0.03
FIGO stage I-II B	72 (33)	65 (37)	7 (18)	
FIGO III A-IV A	146 (67)	113 (64)	33 (83)	
Entities				0.31
Ovarian-, fallopian tube-, peritoneal cancer	160 (71)	126 (68)	29 (73)	
Endometrial cancer	35 (15)	30 (16)	5 (13)	
Cervical cancer	22 (10)	16 (9)	6 (10)	
Vulval-, vaginal cancer	9 (4)	9 (5)	0 (0)	
Nutritional and Functional Parameters				
BMI (kg/m²)	25* (18-55)	25* (18 – 55)	29* (21 – 46)	<0.001
Underweight (< 20 kg/m²)	23 (10)	23 (12)	0 (0)	
Normal (20 – 24.9 kg/m²)	83 (37)	77 (41)	6 (15)	
Overweight (25 ≤ 30 kg/m²)	60 (27)	44 (24)	16 (40)	
Obese (> 30 kg/m²)	60 (27)	42 (23)	18 (45)	
Phase angle alpha < 4.75 °	56 (26)	38 (2)	18 (49)	0.002
Extracellular mass to body cell mass index > 1.35	27 (13)	16 (9)	11 (31)	0.001
Nutritional Risk Screening 2002 ≥ 3	97 (43)	76 (41)	21 (53)	0.22
Weight loss > 10% last 3 months	24 (11)	20 (11)	4 (10)	1.00
Albumin < 35.6 g/L	26 (12)	16 (9)	10 (25)	0.01
Fat mass > 27.5 kg	70 (33)	47 (26)	23 (62)	<0.001
Muscle mass < 21.8 kg	126 (58)	113 (63)	13 (35)	0.003
Skeletal muscle index < 27%	68 (32)	49 (27)	19 (51)	0.006
Age-dependent low hand grip strength	47 (21)	32 (17)	15 (38)	0.009
Timed “Up and Go” test > 9.5 s	55 (25)	36 (20)	19 (50)	<0.001

CDC, Clavien-Dindo Classification; BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics.
* Numbers represent median values.

Table 2: Analysis of Preoperative Factors Related to Severe Postoperative Complications according to Clavien-Dindo ≥ 3b

Variable	**Univariable analysis**	**p-value**	**Multivariable analysis***	**p-value**
	Unadjusted OR (95% CI)		**Adjusted OR (95% CI)**	
Age ≥ 70 years	1.54 (0.73-3.31)	0.27		
ECOG PS > 1	10.81 (3.62-32.26)	<0.001	4.56 (1.46-14.28)	0.009
FIGO ≥ III A	2.71 (1.14-6.48)	0.03	3.65 (1.36-9.76)	0.01
BMI ≥ 25 kg/m^2	6.59 (2.64-16.44)	<0.001	8.22 (3.01-22.48)	<0.001
Phase angle alpha < 4.75°	3.52 (1.68- 7.35)	0.001	3.95 (1.71-9.10)	0.001
Nutritional Risk Screening 2002 ≥ 3	1.60 (0.81-3.18)	0.89		
Weight loss > 10% last three months	0.92 (0.30-2.86)	0.90		
Albumin < 35.6 g/L	5.28 (1.85-15.08)	0.002		
Extracellular mass to body cell mass index > 1.35	4.46 (1.86-10.69)	0.001		
Fat mass > 27.5 kg	7.63 (2.72- 21.44)	<0.001		
Age-dependent low hand grip strength	2.85 (1.35-6.00)	0.006		
Timed “Up and Go” test > 9.5 s	8.18 (2.58-25.93)	<0.001		
Muscle mass > 21.8 kg	3.16 (1.51-6.63)	0.002		
Skleletal muscle index < 27%	2.80 (1.36-5.77)	0.005		

OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index.
* Multivariable logistic regression analyses stepwise forward.

Table 3: Preoperative Factors with Cut-offs, obtained from Log-Rank Test, related to Overall Survival in Months

Variable	Median OS	p-value
Age ≥ 65 years	38.8 vs. 53.5	0.08
Nutritional Risk Screening 2002 ≥ 3	36.4 vs. 53.5	0.07
BMI ≥ 25-30 kg/m^2	44.6 vs. 50.0	0.76
Weight loss ≥ 10% last three months	27.9 vs. 50.0	0.39
Albumin < 35.5 g/L	9.7 vs. 53.5	<0.001
Phase angle alpha < 4.5°	9.7 vs. 53.5	<0.001
Extracellular mass to body cell mass index > 1.3	18.6 vs. 52.9	<0.001
Fat mass > 39 kg	19.2 vs. 50.0	0.20
Age-dependent low hand grip strength	37.9 vs. 52.3	0.20
Timped “Up and Go” test > 11 s	20.5 vs. 52.9	0.02
Muscle mass < 17 kg	37.9 vs. 50.0	0.35
Skeletal muscle index ≤ 24.5 %	23.6 vs. 52.3	0.12

OS, overall survival; BMI, body mass index.

Table 4: Univariable and Multivariable Analysis of Predictive Factors Related to Overall Survival

Variable	Univariable Unadjusted HR (95% CI)	p-value	Multivariable* Adjusted HR (95% CI)	p-value
Age ≥ 65 years	1.40 (0.95-2.04)	0.86		
Severe 30 day postoperative complications Clavien-Dindo ≥ III b	3.78 (2.48-5.75)	<0.001	2.82 (1.80-4.41)	<0.001
ECOG > 1	3.38 (1.78-6.41)	<0.001	2.51 (1.25-5.03)	0.01
FIGO stage ≥ III A	3.39 (2.04-5.63)	<0.001	2.61 (1.53-4.45)	<0.001
Albumin < 35.5 g/L	2.80 (1.71-4.58)	<0.001	2.15 (1.28-3.59)	0.004
Phase angle alpha < 4.5°	3.10 (1.96-4.90)	<0.001	1.76 (1.07-2.90)	0.03
Nutritional Risk Screening 2002 ≥ 3	1.42 (0.97-2.07)	0.07		
BMI ≥ 25-30 kg/m^2	1.11 (0.57-2.17)	0.76		
BMI > 30 kg/m^2	1.01 (0.51-2.01)	0.97		
Weight loss ≥ 10% last three months	1.30 (0.72-2.31)	0.39		
Extracellular mass to body cell mass index > 1.3	2.71 (1.74-4.24)	<0.001		
Fat mass > 39 kg	1.45 (0.82-2.54)	0.20		
Low hand grip strength	1.30 (0.87-1.93)	0.20		
Timed “Up and Go” test > 11 s	1.92 (1.09-3.37)	0.02		
Muscle mass < 17 kg	1.36 (0.71-2.62)	0.35		
Skeletal muscle index ≤ 24.5 %	1.45 (0.90-2.32)	0.13		

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performace status; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index.
* Multivariable logistic regression analyses stepwise forward.

Figure 1: Study consort diagram.

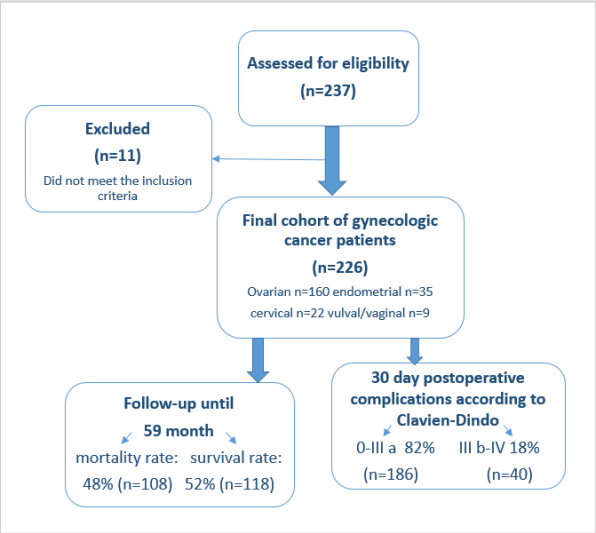
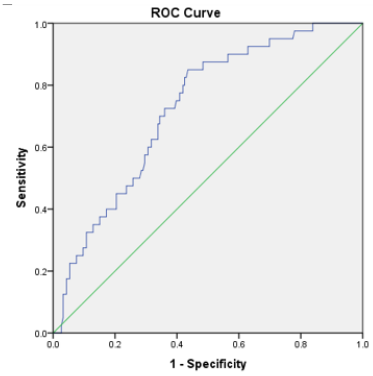


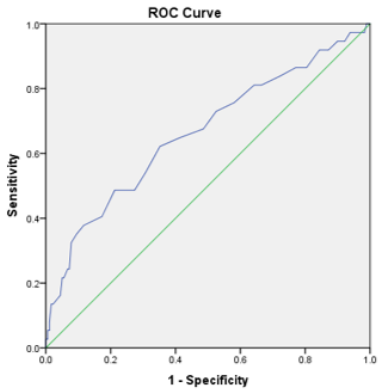
Figure 2: ROC-analysis for (A) body mass index and (B) phase angle for predicting severe postoperative complications including AUC, specific cut-offs, sensitivity, specificity and p-value.

A



Area	cut-off	p-value	sensitifity	specifity
0.724	BMI > 25	<0.001	85.0%	53.8%
	BMI > 30		45.0%	88.0%

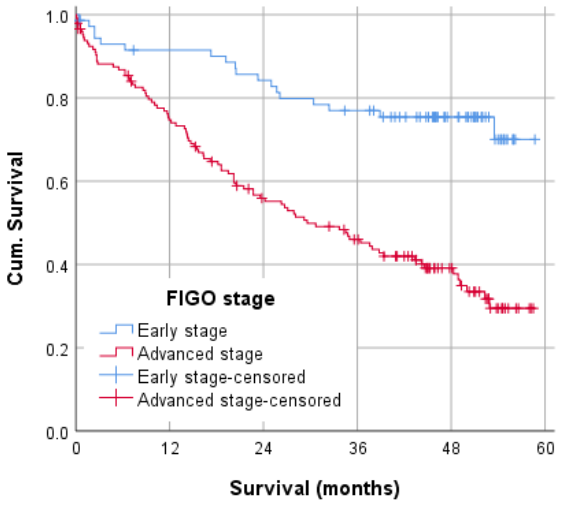
B



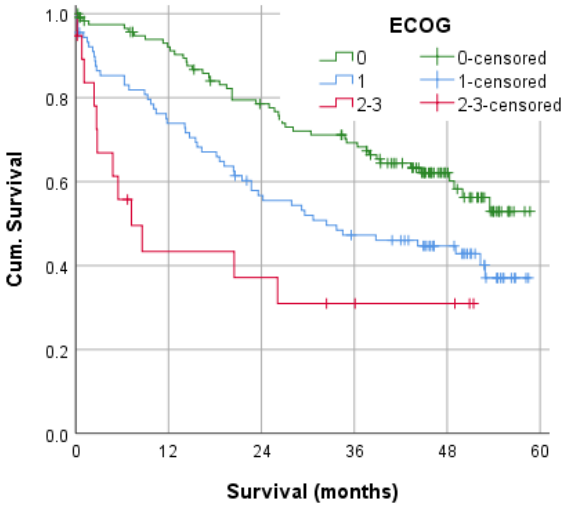
Area	cut-off	p-value	sensitifity	specifity
0.663	<4.75°	0.002	48,6%	78,8%

Figure 3: Kaplan-Meier curves for (A) FIGO stage ≥ III A versus I – II B, (B) for ECOG status, (C) for phase angle < 4.5° versus ≥ 4.5°, (D) for albumin < 35.5 g/L versus ≥ 35.5 g/L and (E) for severe postoperative complications Clavien-Dindo ≥ III b versus Clavien-Dindo 0 - III a.

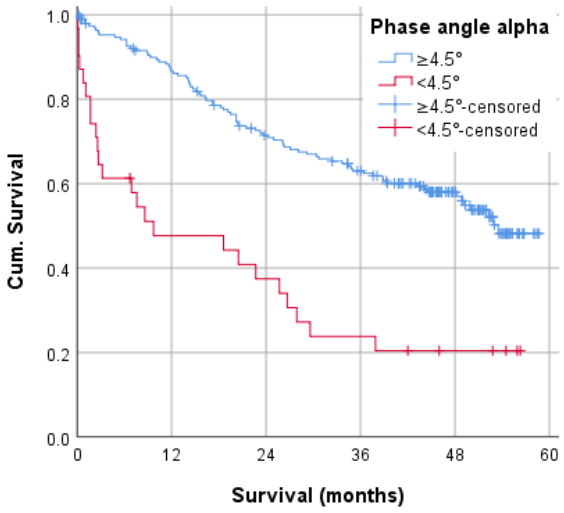
A



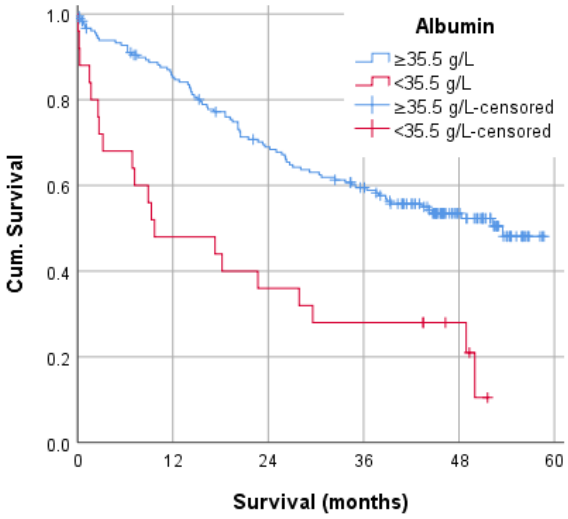
B



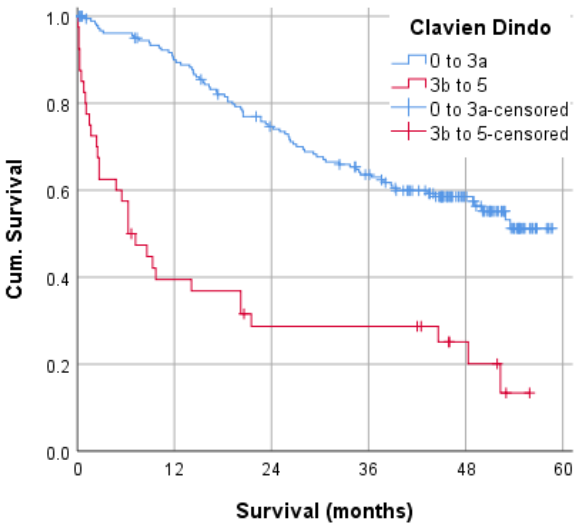
C



D



E


Clavien Dindo
0 to 3a
3b to 5
0 to 3a-censored
3b to 5-censored
Cum. Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
Survival (months)