Complex aortic aneurysm management: from technical outcomes to patient-centered insights

Warmerdam, W.C.M.

CHAPTER 4

The association be and adverse outco endovascular aorti

Britt W.C.M. Warmerdam, MD,[a] Carla S.P. van Rijswijk, MD, PhD,[b] Anneke Droop, BSc.,[c] Claudia J. Lucassen, MSc.,[c] Jaap F. Hamming, Prof., MD, PhD,[a] Jan van Schaik, MD,[a*] Joost R. van der Vorst, MD, PhD[a*]

[*] Both authors contributed equally and share final authorship.
[a] Department of Surgery, [b] Department of Radiology, [c] Department of Dietetics, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands.

tween sarcopenia
mes after complex
c aneurysm repair

Published: Warmerdam BW, van Rijswijk CS, Droop A, et al. The association between sarcopenia and adverse outcomes after complex endovascular aortic repair. *J Cardiovasc Surg (Torino)*. 2024;65(3):256-264. doi:10.23736/S0021-9509.23.12821-7.

ABSTRACT

Background

Sarcopenia is identified as a predictive factor for adverse outcomes after complex endovascular aortic repair (complex EVAR). Consensus on preferred parameters for sarcopenia has not yet been reached. The current study compares three CT-assessed parameters for their association with adverse outcomes after complex EVAR.

Methods

This was a single-center retrospective cohort study. Psoas muscle index (PMI), skeletal muscle index (SMI), and lean psoas muscle area (LPMA) were examined by CT-segmentation. PMI, SMI, and LPMA were analyzed as continuous variables. In addition, cut-off values from previous research were used to diagnose patients as sarcopenic or non-sarcopenic. Outcomes were: all-cause mortality, Major Adverse Events (MAE), length of hospital stay, and non-home discharge. A sub-analysis was made for severely sarcopenic patients; sarcopenia based on any of the parameters, combined with low physical performance (based on gait speed, Timed Up and Go test, and/or Metabolic Equivalent of Task-score).

Results

We included 101 patients. A higher PMI (HR:0.590, CI:0.374-0.930, p=0.023), SMI (HR:0.453, CI:0.267-0.768, p=0.003), and LPMA (HR:0.559, CI:0.333-0.944, p=0.029) were associated with a lower risk of mortality. Being identified as sarcopenic based on cut-off values for PMI and LPMA was not significantly associated with survival. Sarcopenia based on SMI did present a higher mortality risk (p=0.017). A sub-analysis showed that severely sarcopenic patients were at even higher risk of mortality (p=0.036). None of the parameters were significantly associated with the other outcomes.

Conclusion

SMI had a slightly stronger association with mortality compared to PMI and LPMA. High-risk patients were selected by adding physical performance scores. Future research could focus on complex EVAR-specific PMI and LPMA cut-off values.

BACKGROUND

Complex endovascular aortic repair (complex EVAR), including fenestrated EVAR (FEVAR) and branched EVAR (BEVAR), provides a less invasive treatment option compared to open repair for patients with juxtarenal and suprarenal aortic aneurysms.[1-2] Although complex EVAR provides better early postoperative outcomes compared to open repair, it is an extensive surgical procedure with considerable morbidity and mortality.[3-5] This necessitates evidence-based patient risk assessment and selection. A systematic review on risk factors for mortality after aortic aneurysm repair, including FEVAR, defined oxygen-dependent chronic obstructive pulmonary disease (COPD) and dialysis as the greatest risk factors. In addition, female gender, diabetes, age, and ASA-score were negatively associated with survival.[6]

In other surgical fields, especially oncologic surgery, sarcopenia has been established as a predictive factor for adverse outcomes.[7-8] According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is defined as a progressive skeletal muscle disease. It is of multifactorial cause; age, malnutrition, physical inactivity, and systemic disease can play a role, among other factors. Sarcopenia is suspected when a patient has low muscle strength and is confirmed by low muscle quantity or quality. It is considered severe if combined with low physical performance.[9-10] For muscle quantity, CT-assessed muscle area is an often-used parameter.[11-12] However, definitive consensus on the preferred method and cut-off points is not yet reached.[13]

Recently, studies have focused on sarcopenia in complex EVAR patients and have shown that sarcopenia based on CT-assessed low psoas muscle mass is a predictor for adverse outcomes.[14-17] Due to time-effectiveness, psoas muscle area is often used to identify muscle quantity. However, measuring whole skeletal muscle area (SMA) at the level of lumbar 3 has been proposed as a more accurate method.[18-20] The current study reports on sarcopenia in complex EVAR patients by using three parameters based on CT-assessed psoas muscle, as well as total skeletal muscle. Our aim is to compare the different parameters on their association with adverse outcomes, and to identify whether CT-assessed sarcopenia combined with physical performance scores can assess the highest-risk complex EVAR patients. Not only could it serve as a tool for patient selection, it could also provide a target for prehabilitation, as sarcopenia is partially modifiable.[21]

METHODS

Patient inclusion and data collection

All patients that underwent complex EVAR between July 2013 and June 2022 in the Leiden University Medical Center (LUMC) were consecutively included based on their date of surgery. Complex EVAR included FEVAR, BEVAR, and branched or fenestrated arch-

EVAR. A decision to treat is usually made when the aneurysm reaches a diameter of 6 cm. Data on patient characteristics and complications during follow-up were subtracted from patients' medical records and entered into a computerized secure database. A certificate of no objection was issued by the LUMC Medical Ethics Committee (METC), as is required in our institution (registration number: 2022-034, July 5, 2022). Due to the merely retrospective character of our study and the fact that there was no interference in the standard care pathway, explicit patient consent was not obtained.

Identifying sarcopenia

All patients routinely underwent a preoperative CT-scan. A cross-sectional slice of 5 mm thickness at the level of L3 was identified and examined in the arterial contrast-phase. A slice was selected on which the lateral tips of both transverse processes were visible. If multiple slices at L3 met this criterion, the most cranial one was used. Slices were analyzed using SliceOmatic (Tomovision, Montreal, QC, Canada); a software tool, clinically available and widely used for this purpose.[22-23] Muscle (including m. rectus abdominis, m. obliquus internus and externus, m. transversus, m. psoas major and minor, m. erector spinae, and m. quadratus lumborum) was identified by using a Hounsfield unit threshold of -29 to +150 (figure 1).[24-26] Based on visual evaluation of the segmented contours, adjustments were made if necessary. For each scan, segmentation time was registered (seconds).

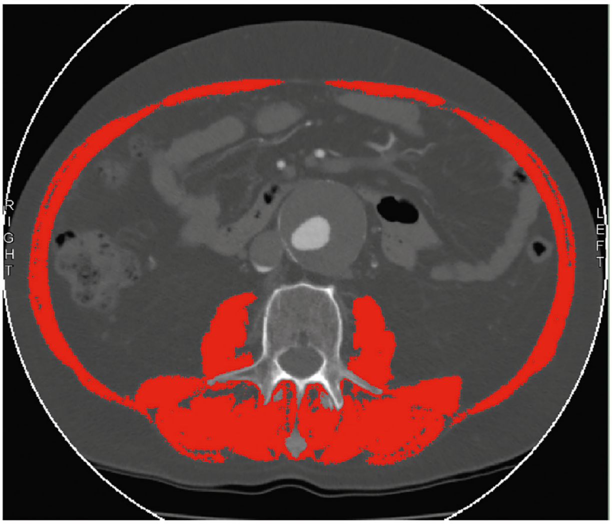


Figure 1: Example of a segmented scan at L3 for total skeletal muscle area.

Because muscle area is related to total body muscle mass, SMA and PMA were corrected for height into the Skeletal Muscle Index (SMI) and Psoas Muscle Index (PMI, cm^2/m^2). LPMA (cm^2xHU) was calculated as ((PMA right + PMA left) / 2) x mean psoas muscle density (HU). Definitive consensus on cut-off values for sarcopenia is not yet reached. In order to place our results in existing literature, the values used in this paper are based on previous research. SMI values were 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women.[24] For PMI, these values were 5.40 cm^2/m^2 and 3.56 cm^2/m^2 for men and women respectively.[27] For LPMA, sarcopenia was considered present if LPMA was <350 cm^2xHU.[15]

Outcomes of interest

Baseline patient characteristics were: demographics, comorbidities, American Society of Anesthesiologists (ASA)-score, body mass index (BMI, kg/m^2), procedure complexity, PMI, SMI, and LPMA. It was assessed whether the presence of sarcopenia based on PMI, SMI, and LPMA was associated with adverse outcomes. These parameters were also analyzed as continuous variables. The primary outcome was all-cause mortality. Secondary outcomes were: increased length of hospital stay, discharge to a rehabilitation center, and Major Adverse Events (MAE). MAE were defined as complications with a Clavien-Dindo score of ≥3. This included all complications needing a (minor or major) radiological, surgical, or laparoscopic intervention, as well as organ failure leading to ICU admission (including spinal ischemia), and death.[28]

As of 2017, complex EVAR patients were routinely referred for preoperative geriatric, physiotherapeutic, and dietetic screening. Timed Up and Go-test (TUG) and gait speed were performed. Metabolic Equivalent of Task-score was assessed during preoperative anesthetic screening.[29] A sub-analysis for the primary outcome and MAE was made for severely sarcopenic patients. This was considered to be the case if a sarcopenic patient (based on either PMI, SMI, or LPMA) had a low physical performance based on low MET-score (1-4), slow gait speed (≤0.8 m/s), and/or high TUG-score (≥20 sec).[30-31,10]

Statistics

To compare baseline characteristics, patients were divided into six groups: patients with and without sarcopenia based on PMI (group 1a and 1b), patients with and without sarcopenia based on SMI (group 2a and 2b), and patients with and without sarcopenia based on LPMA (group 3a and 3b). Categorical patient characteristics were expressed by number of patients and percentages. Continuous variables were tested for normal distribution using histograms, Q-Q plots, and the Shapiro-Wilk test. Normally distributed data were expressed as mean with the standard deviation (SD). Median with the interquartile range (Q1-Q3) was used in case of skewed distribution. Groups 1a vs. 1b, 2a vs. 2b, and 3a vs. 3b were compared on baseline characteristics using the independent t-test for continuous normally distributed data, chi-square test for categorical data, and the Mann-Whitney U-test for skewed data. When less than 5 events occurred, the Fisher's exact test was used instead of chi-square.

All-cause mortality in group 1a vs. group 1b, group 2a vs. 2b, and group 3a vs. 3b was tested by Kaplan-Meier with log-rank testing. Cox regression was used for a multivariate analysis of survival, corrected for variables that were associated with survival in univariate analysis. The association of PMI, SMI, and LPMA with adverse outcomes was also tested with these parameters as continuous variables. PMI, SMI, and LPMA were adjusted by dividing them by their standard deviations, in order to compare hazard ratios. To compare secondary outcomes in the different groups, the same tests were used as for the baseline characteristic analyses. With PMI, SMI, and LPMA as continuous outcomes, logistic regression analysis was used to assess the categorical secondary outcomes and linear regression analysis for continuous secondary outcomes. All analyses were made using IBM SPSS Statistics version 27.

RESULTS

Selection of CT-scans

Figure 2 shows a flow-chart of patient inclusion. Between 2013 and June 2022, 104 patients underwent complex EVAR in the Leiden University Medical Center (LUMC). In three patients, the preoperative CT-scan was not suitable for muscle segmentation, either because it did not extend to the level of L3 (n=2), or because the correct level could not be determined due to extreme scoliosis (n=1). This left 101 patients to be included in the analysis. In 7 patients, the scan was suitable for segmentation of the psoas muscles but not for whole skeletal muscle. This was either due to anatomic aberrations, or due to the scan being cut off on both sides, impeding segmentation of the abdominal wall muscles. In four patients the arterial phase was not suitable for segmentation, and the non-contrast scan was used. Median time between the scan and surgery was 140.0 days (IQR: 110.0-175.8).

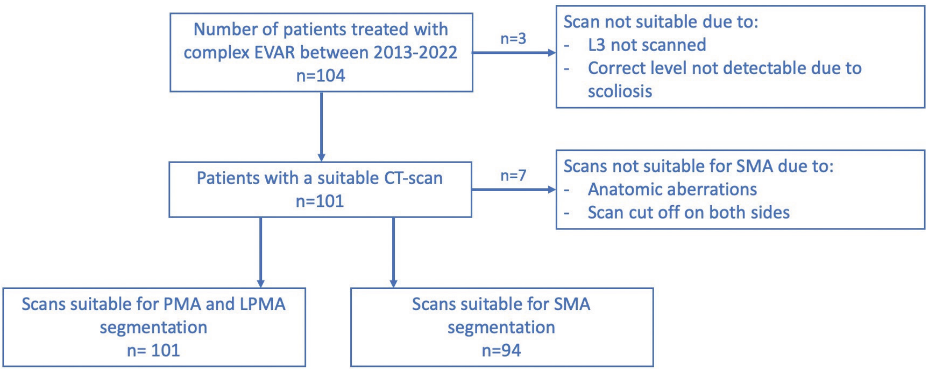


Figure 2: Flow-chart of patient inclusion.

Patient characteristics

Eighty-four of 101 patients (83%) were male, and mean age was 73.8 (SD: 6.1) years. Based on PMI cut-off values, 24 patients (24%) were sarcopenic. Using LPMA, 53% was considered sarcopenic. Of the 94 patients included in skeletal muscle segmentation, 64 (68%) were considered sarcopenic. Median segmentation time was 41.1 seconds (IQR: 34.6-51.6) for the psoas muscles and 163.1 seconds (IQR: 133.9-193.7) for total skeletal muscle.

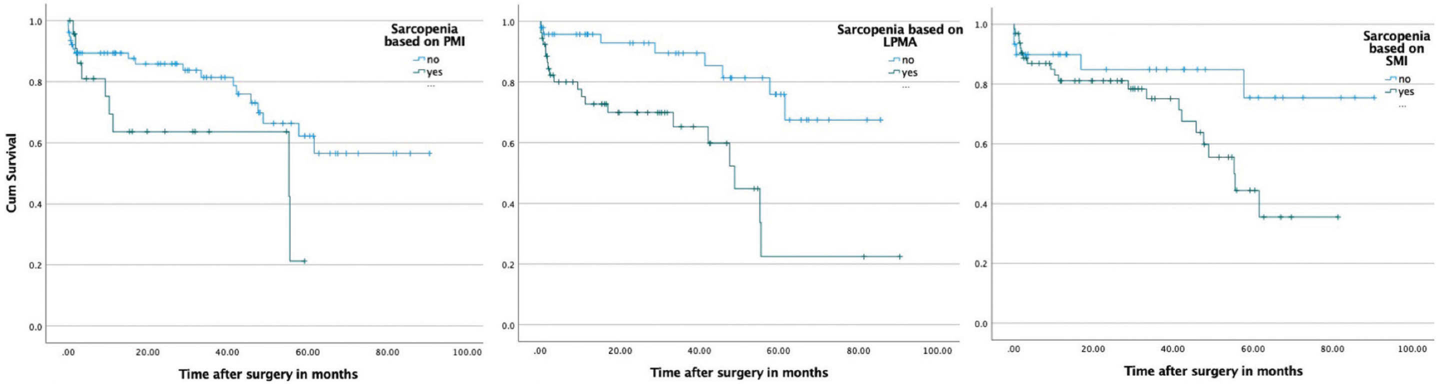
A comparison of sarcopenic versus non-sarcopenic patients (Table 1) based on PMI showed that a higher number of patients in the sarcopenic group had undergone previous AAA repair (38% vs. 13%, p=0.014). A comparison of the groups based on LPMA showed that there were significantly more women in the sarcopenic group (17 (40%) vs. 0, p <0.001) and more patients with cardiovascular comorbidities other than AF or MI/ACS (22 (42%) vs. 10 (21%), p=0.033). The same analysis based on SMI showed that sarcopenic patients in this subgroup had a significantly lower mean BMI (25.5, SD: 3.5 vs. 28.3, SD: 3.6, p<0.001).

Association between sarcopenia and mortality

Median follow-up time was 26.0 months (IQR: 4.0-47.9). All-cause mortality during follow-up was 28% (n=28). Based on PMI, estimated mean survival in months was 38.3 (95% CI: 27.2-49.4) and 65.9 (95% CI: 57.0-74.9) for sarcopenic and non-sarcopenic patients respectively (p=0.049). Using LPMA cut-off values, mean survival was 45.3 (95% CI: 33.0-57.6) in the sarcopenic group, and 71.1 (95% CI: 62.3-79.9) in the non-sarcopenic group (p<0.001). Based on SMI, estimated mean survival was 52.1 (95% CI: 43.2-61.0) and 74.6 (95% CI: 62.0-87.1) for sarcopenic and non-sarcopenic patients respectively (p=0.064). Figure 3 depicts the survival curves.

Table 2 shows that female gender, AF, other cardiovascular disease, ASA≥3, higher procedure complexity, and previous AAA repair were associated with a higher chance of mortality. A multivariate analysis for sarcopenia based on PMI cut-off values (HR: 1.574, 95% CI: 0.591-4.190, p=0.364) no longer showed a statistically significant association with mortality. The same accounted for LPMA (HR: 2.534, 95% CI: 0.940-6.829, p=0.066), whereas the association between sarcopenia based on SMI became statistically significant after adjustment (HR: 3.624, 95% CI: 1.263-10.398, p=0.017).

PMI, SMI, and LPMA were also analyzed as continuous variables. They were adjusted by dividing them by their SD (1.5, 7.7, and 146.5 respectively), in order to be able to compare hazard ratios (HR). Univariate analysis showed that a higher PMI (HR: 0.434 per 1 standard deviation, 95% CI: 0.287-0.656, p<0.001), SMI (HR: 0.496, 95% CI: 0.334-0.736, p<0.001), and LPMA (HR: 0.361, 95% CI: 0.222-0.589, p<0.001) were associated with a lower mortality risk. In a multivariate cox regression analysis, the statistically significant negative association remained present for PMI (HR: 0.590, 95% CI: 0.374-0.930, p=0.023), SMI (HR: 0.453, 95% CI: 0.267-0.768, p=0.003), and LPMA (HR: 0.559, 95% CI: 0.333-0.944, p=0.029). Table 3 shows an overview of these results. No multicollinearity was shown between SMI, PMI, and LPMA and the factors in de multivariate analyses, as well as possible other factors causing collinearity in our dataset (COPD, BMI, Diabetes Mellitus); all variance inflation factors were below 2, and tolerance was above 0.1.



No. at risk

Sarcopenia: no	**77**	**47**	**30**	**13**	**4**
Sarcopenia: yes	24	8	4	0	0

No. at risk

Sarcopenia: no	**48**	**32**	**22**	**11**	**2**
Sarcopenia: yes	53	23	12	2	2

No. at risk

Sarcopenia: no	**30**	**17**	**13**	**7**	**3**
Sarcopenia: yes	64	36	20	6	1

Figure 3: Kaplan-Meier curves for PMI (38.3, 95% CI: 27.2-49.4 vs. 65.9, 95% CI: 57.0-74.9, p=0.049), for LPMA (45.3, 95% CI: 33.0-57.6 vs. 71.1, 95% CI: 62.3-79.9, p<0.001), and SMI (52.1, 95% CI: 43.2-61.0 vs. 74.6, 95% CI: 62.0-87.1, p=0.064), for sarcopenic and non-sarcopenic patients respectively.

Association between sarcopenia and secondary adverse outcomes

The secondary outcomes were MAE (a composite endpoint of complications with a Clavien-Dindo score of ≥3, including death by surgical complications), non-home discharge, and length of hospital stay. These outcomes were compared between patients with and without sarcopenia based on SMI, PMI, and LPMA. In addition, these parameters were analyzed as continuous variables (Table 4a-b). None of the outcomes were statistically significant, which is presented in further detail below.

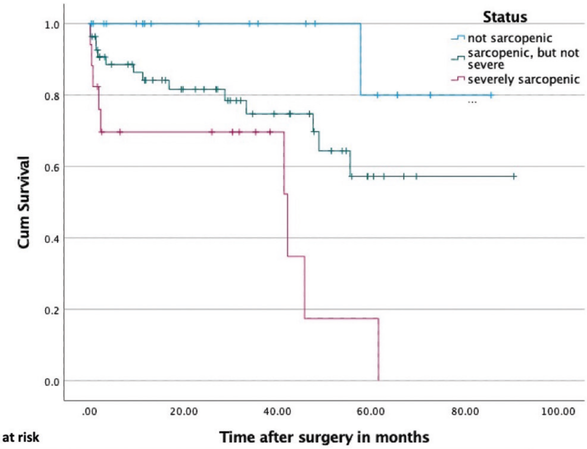
In the total patient group, 32 patients (32%) suffered a MAE, of whom 7 died (7%). There was no statistical difference in the number of patients with a MAE when comparing patients with and without sarcopenia based on PMI (8 (33%) vs. 24 (31%), p=1.000), based on SMI (19 (30%) vs. 12 (40%), p=0.353), and based on LPMA (20 (38%) vs. 12 (25%), p=0.202). Logistic regression also showed no statistically significant association between the different parameters and MAE (Table 4a-b).

For PMI, 5 patients (23%) in the sarcopenic group and 14 patient (19%) in the non-sarcopenic group were discharged to a rehabilitation center or nursing home (p=0.765). For SMI, this was 14 (23%) vs. 4 (15%) for sarcopenic and non-sarcopenic patients respectively (p=0.568), and for LPMA 12 (26%) sarcopenic vs. 7 (15%) non-sarcopenic patients (p=0.304). Logistic regression also showed no significant association for PMI and LPMA (Table 4a-b). However, logistic regression did show a negative association between SMI and non-home discharge. Corrected for male gender (OR: 0.233, 95% CI: 0.068-0.800, p=0.021) and COPD (OR: 3.000, 95% CI: 1.033-8.708, p=0.043), which were identified as being associated with non-home discharge, this was no longer significant (Table 4a).

A comparison of the length of hospital stay showed no statistically significant differences between sarcopenic and non-sarcopenic patients, based on PMI (median: 5.0, IQR: 3.0-10.0 vs. median: 6.5, IQR: 5.0-12.0, p=0.300), LPMA (median 6.0, IQR: 5.0-13.0 vs. median: 6.0, IQR: 3.0-9.0, p=0.172), and SMI (median: 6.0, IQR: 5.0-12.8 vs. median: 7.0, IQR: 4.0-12.0, p=0.828). A linear regression analysis also showed no statistically significant association for these parameters as continuous variables (Table 4a).

Association of severe sarcopenia with mortality and MAE

Physical performance based on gait speed, TUG-score, and/or MET-score was assessed in 90 of 101 patients (89%). In this subgroup, 17 patients were considered severely sarcopenic (17%), 55 patients (55%) were sarcopenic but not severe, and 18 patients (18%) did not have sarcopenia based on either PMI, SMI, or LPMA. There were two patients with a low physical performance score, without having sarcopenia. Kaplan Meier survival analysis (Figure 4) showed a statistically significant difference in mortality risk between severely sarcopenic (33.6 months, 95% CI: 21.1-46.1) and sarcopenic patients (63.9 months, 95% CI: 52.6-75.3, p=0.012), and between severely sarcopenic and non-sarcopenic patients (80.0 months, 95% CI: 70.3-89.8, p<0.001). A multivariate cox-regression analysis, adjusted for the previously identified confounders also showed a statistically significant association between severe sarcopenia and mortality (HR: 10.525 95% CI: 1.163-95.239, coefficient 2.354, p=0.036), compared to non-sarcopenic patients in this subgroup. There was no significant difference in the number of MAE's in severely sarcopenic (n=8, 47%), sarcopenic (n=17, 31%), and non-sarcopenic patients (n=4, 22%, p= 0.286).



No. at risk

Not sarcopenic	**18**	**10**	**7**	**4**	**1**
Sarcopenic, not severe	55	30	18	5	1
Severely sarcopenic	17	9	4	1	0

Figure 4: Kaplan-Meier curves for severely sarcopenic patients (33.6 months, 95% CI: 21.1-46.1), compared to non-sarcopenic (80.0 months, 95% CI: 70.3-89.8, p<0.001), and sarcopenic patients (63.9 months 95% CI: 52.6-75.3, p=0.012), in the sub-group analysis.

DISCUSSION

Association of PMI, SMI, and LPMA with adverse outcomes

After adjustment for confounding factors, a lower PMI, SMI, and LPMA were all associated with a higher risk of mortality, with a slightly stronger association for SMI. Sarcopenia based on cut-off values for PMI and LPMA was not significantly associated with survival, whereas sarcopenia based on SMI did lead to a significantly higher mortality risk. A sub-analysis based on physical performance parameters showed that severely sarcopenic patients were at even higher risk of mortality. None of the parameters were significantly associated with secondary adverse outcomes. The fact that psoas muscle measurements take less time, in addition to more scans being appropriate for psoas segmentation, would favor PMI and LPMA over SMI in clinical application.

The discrepancy between the significant association of PMI and LPMA with mortality as continuous variables and the non-association of these variables based on cut-off values could indicate that the cut-off values did not fit our population. Cut-off points depend on various characteristics, such as age and height, and therefore vary between different countries and patient cohorts. The number of patients in our cohort impedes the identification of robust cut-off points. A recent study by *Bradley et al.* defined cut-off points for SMI and PMI in a cohort of patients undergoing EVAR (n=674), including fenestrated- and branched-EVAR (n=133).[32] When comparing their cut-off points with the values used in our study, *Bradley et al.* defines slightly lower cut-off values for SMI and slightly higher for PMI. This could indicate an underestimation of the number of sarcopenic patient in our cohort based on PMI and an overestimation based on SMI, although these cut-off points were identified for conventional and complex EVAR patients combined. Future studies on complex EVAR patients could focus on validating these cut-off points by *Bradley et al.,* in order for these parameters to be applied in clinical practice.

Results in context

Previous research based on PMA by *Alenezi et al.* reported an increased all-cause mortality risk for lower PMA. Although a different parameter was used, this is in accordance with our findings that a higher psoas muscle quantity, whether it be adjusted for height into PMI or for density into LPMA, is associated with a lower mortality risk.[16] *Kärkkäinen 2020 et al.* reported a comparable hazard ratio for LPMA and all-cause mortality (0.59, 95% CI: 0.40-0.87, p=0.008), compared to our hazard ratio (0.56, 95% CI: 0.33-0.94, p=0.029).[15] Using their LPMA cut-off values, we were able to detect a difference in all-cause mortality between sarcopenic and non-sarcopenic patients. However, after adjustment for confounders this was no longer significant (p=0.066).

Alenezi et al. (PMA) and *Kärkkäinen 2021 et al*. (LPMA) found that their parameters were predictive for MAE, while this was not supported by our results, even when analyzing severely sarcopenic patients. Although these discrepancies might be due to the fact that both studies included substantially larger patient cohorts of 257 and 504 patients respectively, it is an interesting finding which might indicate that in our cohort sarcopenic patients were fit enough to undergo surgery, but were more likely to die of other causes on a longer-term compared to non-sarcopenic patients.[14,16]

The EWGSOP-criteria propose that physical performance status can be used to identify severely sarcopenic patients at an even higher risk for adverse outcomes.[10] This was supported by our results, by using TUG, gait speed, and MET-score as indicators of physical performance. In *Kärkkäinen 2021 et al.*, ASA-score was used for risk stratification of extremely high-risk patients. Future research could focus on identifying preferred physical performance parameters.

Clinical application

The decision if and when an aneurysm should be treated, is mainly based on weighing the risk of rupture against the short-term and long-term risks of surgery.[33-34] Being at higher risk of mortality due to individual characteristics could be taken into this equation. Sarcopenia combined with physical performance parameters is proposed as such a characteristic, although regarding short term mortality due to surgery-related complications this is not supported by our results.

As opposed to other risk factors for adverse outcomes, such as COPD and age, sarcopenia is partially modifiable. Malnutrition and physical inactivity, two contributors to sarcopenia, have been targeted for optimization in prehabilitation programs.[21] Given the fact that complex EVAR is generally elective surgery, time during surveillance or time between the decision to treat and the actual procedure could be used to optimize patients. A meta-analysis on prehabilitation programs for patients undergoing major abdominal surgery concluded that pulmonary morbidity can be reduced by prehabilitation.[35] Another review on prehabilitation prior to intra-abdominal surgery stated that pulmonary and all-cause complications can be reduced by prehabilitation, but was inconclusive on the ability to decrease mortality.[36] A review on prehabilitation in open and endovascular aortic repair concluded that exercise therapy might reduce cardiac and renal complications.[37]

However, all reviews stated that more research is necessary to validate these findings. Furthermore, these studies investigated whether prehabilitation improved physical function, and did not comment on post-prehabilitation changes in sarcopenia. A randomized controlled trial showed a significant increase in SMI in community-dwelling healthy elderly, who underwent a resistance-exercise intervention program.[38] A study among elderly nursing-home residents reported a decrease in the prevalence of sarcopenia after three months of resistance-exercise training, but found no significant decrease in SMI.[39] To our knowledge, the safety of such programs and their effect on muscle mass has not yet been studied among *complex* aneurysm patients.

Limitations

This study presented a real-world complex EVAR patient group in a non-high-volume university hospital. Consequently, the sample size was relatively small. This limits the analyses that can be performed, and could confine the external validity. However, a comparison with larger sized studies showed comparable results for the main outcome.

Several baseline characteristics were analyzed as possible confounders or factors of multicollinearity. For example, physical inactivity can cause sarcopenia, which is likely to be present in patients suffering from COPD. COPD could therefore correlate with sarcopenia in a predictive model for mortality. In our data however, no significant collinearity was shown and we adjusted for confounding factors in our multivariate analyses. However, it is possible that we did not examine all relevant variables. Due to the restricted sample size, the number of variables in multivariate analysis is limited. As mentioned in the introduction, sarcopenia is a disease of multifactorial cause. It could also be argued whether, in a way, sarcopenia is already partially adjusted for these confounding factors, and whether including these confounding factors in multivariate analyses will have the desired effect.

CONCLUSION

As continuous variables, PMI, SMI, and LPMA were all associated with mortality, with SMI as a slightly stronger predictor. When using cut-off values for PMI, SMI, and LPMA, only sarcopenia based on SMI was associated with mortality after adjustment for confounders. In our cohort, none of the factors were associated with MAE, including surgery-related death. Psoas segmentation took less time, was possible in a higher number of scans, and therefore has practical advantages compared to total skeletal muscle segmentation. Future research, preferably with a higher number of patients, could be conducted to determine optimal PMI and LPMA cut-off values for complex EVAR patients. Furthermore, the highest-risk patients were identified by adding physical parameters. Selecting high risk patients can aid in clinical decision-making and identifies a group that might benefit from prehabilitation strategies.

INTERIM SUMMARY

In this chapter, sarcopenia was examined as a predictor of adverse outcomes after complex EVAR. All parameters on a continuous scale showed to be associated with mortality. However, based on cut-off values from previous research, only sarcopenia based on SMI was associated with a lower estimated mortality in Kaplan Meier analysis. This might indicate that PMI and LPMA cut-off values are not yet optimized for the complex EVAR patient cohort. As it appears to be partially modifiable, sarcopenia could be a target for preoperative prehabilitation strategies during the watchful waiting period before the treatment threshold has been reached or while waiting for the custom-made stent. Additionally, identifying sarcopenic patients who are at risk for adverse outcomes, can improve clinical decision-making and patient counseling. Understanding what patients perceive as important and what they expect from treatment, is essential in this matter. The next part of this thesis attributes to patient involvement and counseling by analyzing patient preferences and by reviewing Dutch disciplinary law in order to identify factors underlying patient dissatisfaction.

TABLES

Table 1: Comparison of patient characteristics

Variable	Sarcopenic PMI n= 24	Not sarcopenic PMI n= 77	p-value	Sarcopenic SMI n=64
Male gender	22 (92)	62 (81)	0.348	55 (86)
Age	75.3 (6.0)	73.4 (6.1)	0.199	74.83 (6.5)
BMI	25.4 (4.4)	26.7 (3.3)	0.115	25.5 (3.5)
ASA-score				
2	7 (29)	31 (40)	0.219	26 (41)
3	15 (63)	44 (57)		36 (56)
4	2 (8)	2 (3)		2 (3)
Aneurysm size	62.0 (59.0-74.3)	65.0 (58.5-70.0)	0.867	64.5 (60.0-69.0)
Procedure complexity*				
Grade 1	5 (21)	9 (12)	0.709	9 (14)
Grade 2	10 (42)	34 (44)		32 (50)
Grade 3	7 (29)	27 (35)		18 (28)
Grade 4	2 (8)	7 (9)		5 (8)
MI/ACS	9 (38)	26 (34)	0.808	21 (33)
AF	4 (17)	11 (14)	0.750	7 (11)
Other cardiovascular disease	11 (46)	21 (27)	0.130	21 (33)
COPD	6 (25)	17 (22)	0.784	19 (30)
Diabetes type 2	3 (13)	11(14)	1.000	6 (9)
Previous AAA repair**	9 (38)	10 (13)	0.014	11 (17)
PVD	4 (17)	13 (17)	1.000	10 (16)
Stroke	3 (13)	20 (26)	0.265	14 (22)
Malignancy				
Active	1 (4)	4 (5)	0.501	2 (3)
Past	8 (33)	17 (22)		16 (25)
Smoking				(n=63)
Active	7 (29)	22 (29)	0.706	15 (24)
Past	11 (46)	41(53)		33 (52)
Hypertension	15 (63)	61 (79)	0.111	48 (75)
Hypercholesterolemia	6 (25)	29 (38)	0.329	23 (36)
MET-score	(n=20)	(n=69)		(n=56)
Low (1-4)	5 (25)	11 (16)		11 (20)
Average (4-7)	14 (70)	56 (81)	0.349	42 (75)
High (7-10)	1 (5)	2 (3)		3 (5)
PMI	4.8 (4.2-5.2)	6.3 (5.8-7.3)	<0.001	5.6 (1.2)
SMI	40.6 (5.411)	48.0 (7.5)	<0.001	44.3 (38.6-48.1)
LPMA	226.5 (160.9-331.2)	379.5 (305.4-478.2)	<0.001	328.0 (110.3)

Abbreviations: SD: standard deviation, IQR: interquartile range (Q1-Q3), BMI: Body Mass Index (kg/m^2), ASA: American Association of Anesthesiologists, MI/ACS: myocardial infarction/acute coronary syndrome, AF: atrial fibrillation, COPD: chronic obstructive pulmonary disease, AAA: aortic aneurysm repair, PVD: peripheral vascular disease, MET: Metabolic Equivalent of Task, PMI: Psoas Muscle Index, SMI: Skeletal Muscle Index

Not sarcopenic SMI n=30	p-value	Sarcopenic LPMA n=53	Not Sarcopenic LPMA n=48	p-value
22 (73)	0.158	36 (68)	48 (100)	<0.001
72.6 (5.1)	0.076	74.3 (6.2)	73.3 (6.1)	0.394
28.3 (3.6)	<0.001	26.2 (4.2)	26.7 (3.0)	0.518
9 (30)	0.507	18 (34)	20 (42)	0.822
19 (63)		33 (62)	26 (54)	
2 (7)		2 (4)	2 (4)	
66.0 (58.0-76.0)	0.403	64.0 (60.0-69.5)	65.5 (58.0-74.8)	
4 (13)	0.597	4 (8)	10 (21)	0.169
11 (37)		22 (42)	22 (46)	
12 (40)		21 (39)	13 (27)	
3 (10)		6 (11)	3 (6)	
12 (40)	0.643	15 (28)	20 (42)	0.209
6 (20)	0.336	8 (15)	7 (15)	1.000
8 (27)	0.636	22 (42)	10 (21)	0.033
4 (13)	0.122	14 (26)	9 (19)	0.477
7 (23)	0.106	6 (11)	8 (17)	0.567
4 (13)	0.768	11 (21)	9 (19)	0.622
7 (23)	0.397	9 (17)	8 (17)	1.000
8 (27)	0.794	8 (15)	15 (31)	0.061
3 (10)	0.419	3 (6)	2 (4)	0.593
6 (20)		11 (21)	14 (29)	
		(n=52)		
10 (33)	0.264	12 (23)	17 (35)	0.382
17 (57)		30 (58)	22 (46)	
23 (77)	1.000	42 (79)	34 (71)	0.363
10 (33)	0.822	17 (32)	18 (38)	0.676
(n=26)		(n=44)	(n=45)	
4 (15)		10	6 (13)	
22 (8)	0.638	32	38 (84)	0.408
0		2	1 (2)	
7.2 (1.5)	<0.001	5.2 (4.7-6.1)	6.9 (6.1-7.8)	<0.001
55.5 (52.5-57.9)	<0.001	42.4 (6.6)	51.0 (6.3)	<0.001
451.0 (177.1)	0.001	289.3 (229.8-318.0)	457.3 (385.5-531.4)	<0.001

* Grade 1: 1 or 2 fenestrations. Grade 2: 3 or 4 fenestrated EVAR. Grade 3: branched-EVAR. Grade 4: branched-fenestrated EVAR combinations, arch EVAR, and emergency cases.
**either open or endovascular

Table 2: Univariable analyses for all-cause mortality

Variable	HR	95% CI	Coefficient	p-value
Gender (male)	0.318	0.144-0.705	-1.145	0.005*
Age	0.974	0.917-1.035	-0.026	0.392
BMI	0.936	0.831-1.055	00.066	0.280
ASA of ≥3	2.524	1.063-5.995	0.926	0.036*
Hypertension	1.367	0.553-3.377	0.313	0.498
Smoking				
Past	0.983	0.388-2.494	-0.017	0.972
Active	0.859	0.311-2.374	-0.152	0.770
Diabetes	1.021	0.627-1.662	0.021	0.933
Hypercholesterolemia	0.625	0.275-1.423	-0.470	0.263
MI/ACS	0.506	0.215-1.191	-0.682	0.119
AF	2.469	1.039-5.864	0.904	0.041*
Other cardiovascular disease	4.625	2.135-10.020	1.532	<0.001*
Stroke	0.687	0.276-1.708	-0.376	0.419
COPD	1.572	0.690-3.582	0.453	0.281
PVD	1.237	0.500-3.061	0.212	0.646
Previous AAA repair	2.757	1.237-6.142	1.014	0.013*
Malignancy				
Past	1.067	0.430-2.651	0.065	0.889
Active	0.738	0.099-5.510	-0.304	0.738
Procedure complexity**				
Grade 2	1.241	0.332-4.780	0.216	0.754
Grade 3	2.039	0.527-7.270	0.712	0.272
Grade 4	4.389	1.032-18.670	1.479	0.044*
PMI	0.573	0.435-0.755	-0.556	<0.001*
SMI	0.913	0.868-0.961	-0.091	<0.001*
LPMA	0.993	0.990-0.996	-0.007	<0.001*

Abbreviations: BMI: Body Mass Index (kg/m^2), ASA: American Association of Anesthesiologists, MI/ACS: myocardial infarction/acute coronary syndrome, AF: atrial fibrillation, COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, AAA: abdominal aortic aneurysm, PMI: psoas muscle index, SMI: skeletal muscle index, LPMA: lean psoas muscle area
* Statistically significant association, based on a p-value cut-off of <0.05.
** Procedure complexity: Grade 2: 3 or 4 fenestrated EVAR. Grade 3: branched-EVAR. Grade 4: branched-fenestrated EVAR combinations, arch EVAR, and emergency cases.

Table 3: Multivariate analysis of all-cause mortality adjusted for gender, ASA-score, AF, other cardiovascular disease, previous AAA repair, and procedure complexity

Variable	HR	95% CI	Coefficient	p-value
Unadjusted PMI	0.704	0.520-0.953	-0.351	0.023**
Unadjusted SMI	0.902	0.843-0.966	-0.103	0.003**
Unadjusted LPMA	0.996	0.992-1.000	-0.004	0.029**
Adjusted* PMI	0.590	0.374-0.930	-0.528	0.023**
Adjusted* SMI	0.453	0.267-0.768	-0.528	0.003**

Table 3: Multivariate analysis of all-cause mortality adjusted for gender, ASA-score, AF, other cardiovascular disease, previous AAA repair, and procedure complexity *(continued)*

Variable	HR	95% CI	Coefficient	p-value
Adjusted* LPMA	0.559	0.333-0.944	-0.581	0.029**
Sarcopenia based on PMI cut-off	1.574	0.591-4.190	0.453	0.364
Sarcopenia based on SMI cut-off	3.624	1.263-10.398	1.288	0.017**
Sarcopenia based on LPMA cut-off	2.534	0.940-6.829	0.930	0.066

Abbreviations: ASA: American Association of Anesthesiologists, AF: atrial fibrillation, AAA: abdominal aortic aneurysm, PMI: Psoas Muscle Index, SMI: Skeletal Muscle Index, LPMA: Lean Psoas Muscle Area
*PMI, SMI, and LPMA were divided by their standard deviation in order to enable interpretation of hazard ratios.
**Statistically significant association based on a p-value cut-off of <0.05.

Table 4a: Comparison of secondary outcomes between patients with and without sarcopenia based on SMI, PMI, and LPMA.

Outcome	Variable	OR	95% CI	P-value
MAE	SMI	0.970	0.917-1.027	0.296
	PMI	0.960	0.724-1.272	0.774
	LPMA	0.998	0.995-1.002	0.329
Non-home discharge	SMI	0.931	0.867-0.999	0.048*
	SMI corrected	0.964	0.890-1.044	0.370
	PMI	0.763	0.535-1.087	0.134
	LPMA	0.996	0.992-1.000	0.072
Length of stay	SMI	-0.135	-0.372-0.102	0.261
	PMI	-0.004	-1.159-1.151	0.994
	LPMA	-0.001	-0.130-0.110	0.873

Abbreviations: MAE: Major Adverse Events, SMI: Skeletal Muscle Index, PMI: Psoas Muscle Index, LPMA: Lean Psoas Muscle Area
*Statistically significant association based on a p-value cut-off of <0.05.

Table 4b: Odds ratios of SMI, PMI, and LPMA as continuous variables for the secondary outcomes.

Outcome	Variable	Sarcopenia		P-value
		Yes	No	
MAE (n, %)	SMI	19 (30)	12 (40)	0.353
	PMI	8 (33)	24 (31)	1.000
	LPMA	20 (38)	12 (25)	0.202
Non-home discharge (n, %)	SMI	14 (23)	4 (15)	0.568
	PMI	5 (23)	14 (19)	0.765
	LPMA	12 (26)	7 (15)	0.304
Length of stay (median, IQR)	SMI	6.0 (5.0-12.8)	7.0 (4.0-12.0)	0.828
	PMI	5.0 (3.0-10.0)	6.5 (5.0-12.0)	0.300
	LPMA	6.0 (5.0-13.0)	6.0 (3.0-09.0)	0.172

Abbreviations: MAE: Major Adverse Events, SMI: Skeletal Muscle Index, PMI: Psoas Muscle Index, LPMA: Lean Psoas Muscle Area, IQR: Interquartile Range

REFERENCES

1 Kansagra K, Kang J, Taon MC, et al. Advanced endografting techniques: snorkels, chimneys, periscopes, fenestrations, and branched endografts. *Cardiovasc Diagn Ther*. 2018;8(Suppl 1):S175-S183.

2 Malina M, Resch T, Sonesson B. EVAR and complex anatomy: an update on fenestrated and branched stent grafts. *Scand J Surg*. 2008;97(2):195-204.

3 Varkevisser RRB, O'Donnell TFX, Swerdlow NJ, et al. Fenestrated endovascular aneurysm repair is associated with lower perioperative morbidity and mortality compared with open repair for complex abdominal aortic aneurysms. *J Vasc Surg*. 2019;69(6):1670-1678.

4. Manunga J, Sullivan T, Garberich R, et al. Single-center experience with complex abdominal aortic aneurysms treated by open or endovascular repair using fenestrated/branched endografts. *J Vasc Surg*. 2018;68(2):337-347.

5 Ultee KHJ, Zettervall SL, Soden PA, et al. Perioperative outcome of endovascular repair for complex abdominal aortic aneurysms. *J Vasc Surg*. 2017;65(6):1567-1575.

6 Khashram M, Williman JA, Hider PN, et al. Systematic Review and Meta-analysis of Factors Influencing Survival Following Abdominal Aortic Aneurysm Repair. *Eur J Vasc Endovasc Surg*. 2016;51(2):203-215. doi:10.1016/j.ejvs.2015.09.007

7 Jones K, Gordon-Weeks A, Coleman C, Silva M. Radiologically Determined Sarcopenia Predicts Morbidity and Mortality Following Abdominal Surgery: A Systematic Review and Meta-Analysis. *World J Surg*. 2017;41(9):2266-2279.

8 Malietzis G, Aziz O, Bagnall NM, et al. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. *Eur J Surg Oncol*. 2015;41(2):186-196.

9 Cruz-Jentoft AJ, Sayer AA. Sarcopenia [published correction appears in Lancet. 2019 Jun 29;393(10191):2590]. *Lancet*. 2019;393(10191):2636-2646.

10 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis [published correction appears in Age Ageing. 2019 Jul 1;48(4):601]. *Age Ageing*. 2019;48(1):16-31.

11 Tolonen A, Pakarinen T, Sassi A, et al. Methodology, clinical applications, and future directions of body composition analysis using computed tomography (CT) images: A review. *Eur J Radiol*. 2021;145:109943. doi:10.1016/j.ejrad.2021.109943.

12 Amini B, Boyle SP, Boutin RD, Lenchik L. Approaches to Assessment of Muscle Mass and Myosteatosis on Computed Tomography: A Systematic Review. *J Gerontol A Biol Sci Med Sci*. 2019;74(10):1671-1678. doi:10.1093/gerona/glz034.

13 Albano D, Messina C, Vitale J, Sconfienza LM. Imaging of sarcopenia: old evidence and new insights. *Eur Radiol*. 2020;30(4):2199-2208.

14 Kärkkäinen JM, Oderich GS, Tenorio ER, et al. Psoas muscle area and attenuation are highly predictive of complications and mortality after complex endovascular aortic repair. *J Vasc Surg*. 2021;73(4):1178-1188.e1.

15 Kärkkäinen JM, Tenorio ER, Oksala N, et al. Pre-operative Psoas Muscle Size Combined With Radiodensity Predicts Mid-Term Survival and Quality of Life After Fenestrated-Branched Endovascular Aortic Repair. *Eur J Vasc Endovasc Surg*. 2020;59(1):31-39.

16 Alenezi AO, Tai E, Jaberi A, et al. Adverse Outcomes after Advanced EVAR in Patients with Sarcopaenia. *Cardiovasc Intervent Radiol*. 2021;44(3):376-383.

17 Mezzetto L, D'Oria M, Mani K, et al. Scoping review of radiologic assessment and prognostic impact of skeletal muscle sarcopenia in patients undergoing endovascular repair for aortic disease. J Vasc Surg. 2022;76(5):1407-1416. doi:10.1016/j.jvs.2022.05.005.

18 Rollins KE, Gopinath A, Awwad A, et al. Computed tomography-based psoas skeletal muscle area and radiodensity are poor sentinels for whole L3 skeletal muscle values. *Clin Nutr*. 2020;39(7):2227-2232.

19 Baracos VE. Psoas as a sentinel muscle for sarcopenia: a flawed premise. *J Cachexia Sarcopenia Muscle*. 2017;8(4):527-528.

20 Rutten IJG, Ubachs J, Kruitwagen RFPM, et al. Psoas muscle area is not representative of total skeletal muscle area in the assessment of sarcopenia in ovarian cancer. *J Cachexia Sarcopenia Muscle*. 2017;8(4):630-638. doi:10.1002/jcsm.12180

21 Whittle J, Wischmeyer PE, Grocott MPW, Miller TE. Surgical Prehabilitation: Nutrition and Exercise. *Anesthesiol Clin*. 2018;36(4):567-580.

22 van Vugt JL, Levolger S, Gharbharan A, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. *J Cachexia Sarcopenia Muscle*. 2017;8(2):285-297. doi:10.1002/jcsm.12158.

23 TomoVision. 2023 [Internet]. Available from: http://www.tomovision.com [cited 2023, Oct 26].

24 Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629-635.

25 Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985)*. 1998;85(1):115-122.

26 Lieffers JR, Bathe OF, Fassbender K, et al. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer*. 2012;107(6):931-936.

27 Bahat G, Turkmen BO, Aliyev S, et al. Cut-off values of skeletal muscle index and psoas muscle index at L3 vertebra level by computerized tomography to assess low muscle mass. *Clin Nutr*. 2021;40(6):4360-4365.

28 Dindo D, Demartines N, Clavien P. Classification of Surgical Complications. A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2004 Aug; 240(2): 205–213. 10.1097/01.sla.0000133083.54934.ae.

29 Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128(8):873-934.

30 Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.

31 Bradley NA, Walter A, Dolan R, et al. Evaluation of the prognostic value of computed tomography-derived body composition in patients undergoing endovascular aneurysm repair. J Cachexia Sarcopenia Muscle. 2023;14(4):1836-1847. doi:10.1002/jcsm.13262.

32 Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovasc Surg*. 2011;41 Suppl 1:S1-S58. doi:10.1016/j.ejvs.2010.09.011.

4

33 Chaikof EL, Dalman RL, Eskandari MK, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. *J Vasc Surg*. 2018;67(1):2-77.e2. doi:10.1016/j.jvs.2017.10.044.

34 Hughes MJ, Hackney RJ, Lamb PJ, et al. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World J Surg*. 2019;43(7):1661-1668. doi:10.1007/s00268-019-04950-y.

35 Moran J, Guinan E, McCormick P, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. *Surgery*. 2016;160(5):1189-1201. doi:10.1016/j.surg.2016.05.014.

36 Fenton C, Tan AR, Abaraogu UO, McCaslin JE. Prehabilitation exercise therapy before elective abdominal aortic aneurysm repair. *Cochrane Database Syst Rev*. 2021;7(7):CD013662. Published 2021 Jul 8. doi:10.1002/14651858.CD013662.pub2.

37 Lichtenberg T, von Stengel S, Sieber C, Kemmler W. The Favorable Effects of a High-Intensity Resistance Training on Sarcopenia in Older Community-Dwelling Men with Osteosarcopenia: The Randomized Controlled FrOST Study. *Clin Interv Aging*. 2019;14:2173-2186. Published 2019 Dec 16. doi:10.2147/CIA.S225618.

38 Martín Del Campo Cervantes J, Habacuc Macías Cervantes M, Monroy Torres R. Effect of a Resistance Training Program on Sarcopenia and Functionality of the Older Adults Living in a Nursing Home. *J Nutr Health Aging*. 2019;23(9):829-836. doi:10.1007/s12603-019-1261-3.

4