**Research paper**

**Psoas muscle mass index as a predictor of long-term mortality and severity of complications after major intra-abdominal colorectal surgery – a retrospective analysis**

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**Abstract**

**Study objective** Determine ifpsoas muscle area measured in routine preoperative computed tomography scans (CT) can be used to identify patients at increased risk of adverse postoperative outcomes after major elective abdominal surgery.

**Design** Retrospective analysis of data from a single-centre cohort study conducted in York Hospital between the 1st August of 2015 and the 31st of august of 2020.

**Setting** Preoperative clinic.

**Patients** 639 patients who attended the preoperative assessment clinic prior to major elective colorectal surgery and had an abdominal CT scan done up to 120 days before surgery.

**Interventions** Psoas muscle area at the L3 level was measured in preoperative CT scans and normalised to patient height (psoas muscle index). The lowest sex-stratified tertile of psoas muscle index (PMI) was classed as sarcopenic.

**Measurements** The primary outcome was 2-year mortality. Secondary outcomes included postoperative complications assessed using Clavien-Dindo graded major and minor complications, comprehensive complication index (CCI), and length of stay

**Main results** Multivariable regression analysis showed that sarcopenia was associated with 2-year mortality (aOR 1.79, 95% CI 1.03-3.10; p=0.037) and survival at 2-years was significantly reduced in sarcopenic patients (log-rank test, p=0.012). Sarcopenia was the only statistically significant predictor of major complications in multivariable logistic regression analysis (aOR 1.69, 95% CI 1.04-2.74, p=0.034) and associated with an estimated increase of 16.6% in the comprehensive complication index (CCI) score of patients that had complications in multivariable linear regression analysis. Sarcopenia was not associated with length of stay.

**Conclusions** Sarcopenia defined by psoas muscle mass is an independent predictor of 2-year mortality, major complications and severity of complications after major colorectal surgery and may be used for preoperative risk assessment.

**Keywords:** frailty, major abdominal surgery, mortality, psoas, sarcopenia

**1. Introduction**

In 2019, approximately one in five people in the UK were aged 65 or older, and this proportion is projected to increase over time[1]. In addition the surgical population is ageing at a disproportionate rate, with the demand for surgery increasing with age[2]. Older patients have increased morbidity and mortality following surgery[3], and consideration of differences in physiologic status and reserve is required to discriminate those at higher risk of adverse outcomes, and who might benefit from targeted interventions and optimisation before surgery[4]. Several scoring systems have been proposed to estimate perioperative risk[5], but addition of a frailty measure can improve stratification[6–8]. Biomarkers such as brain natriuretic peptide(BNP), NT-proBNP and cardiac troponins have emerged as potentially useful risk tools in predicting adverse cardiac events and all-cause mortality after non-cardiac surgery[9] but further studies are needed to clarify their role and to compare these to a frailty measure.

Frailty can be defined as a decline in physiological reserve and function and is a risk factor for adverse postoperative outcomes [10]. There is however a lack of consensus on a definition or a standardised measurement tool that can be applied in the perioperative period[11]. Existing tools for evaluating frailty can be time-consuming or rely on subjective or self-reported assessments of activity and dependence, and are infrequently performed in perioperative care[11,12].

Cardiopulmonary exercise testing has been used as an objective measure of physiological reserve and has been shown to predict complications and both short and long term mortality after intra-abdominal surgery[13], but is not universally available, is resource intensive and may not be feasible to perform on all patients.

Sarcopenia encompasses primary age-related muscle changes and those secondary to systemic processes and it has a significant overlap with the physical phenotype of frailty[14,15]. Sarcopenia increases significantly with increasing age from between 5-13% in those aged 60-70 years to between 11-50% in those 80 or above[16]. Inactivity and malnutrition can exacerbate age-related changes in skeletal muscle[17]. Disease-related muscle changes resulting from an imbalance in muscle anabolic and catabolic processes have been described in several chronic conditions[18] including diabetes[19], cardiovascular disease[20], chronic kidney disease[21], liver cirrhosis[22], amongst others, and can further accelerate the decline in muscle mass and function.

Decreased muscle mass has emerged as a potential risk assessment tool and has been associated with a higher risk of mortality in patients undergoing abdominal aortic aneurysm repair[23], as well as morbidity, mortality and length of stay in colorectal cancer resection[24].

Potential measures of muscle mass include lumbar skeletal muscle area or psoas muscle area at the third lumbar vertebra (L3) level on computed tomography (CT) scan[25,26]. CT scans are routinely performed prior to major abdominal surgery, and so psoas muscle measurements could be easily obtained without the need for additional investigations.

Sarcopenia might be amenable to intervention. Resistance exercise has been shown to improve strength[27] and increase lean body mass[28] in older adults. Recently, in the SPRINTT multicentre randomised controlled trial, a multicomponent intervention of physical activity and nutritional counselling was associated with a lower incidence of mobility disability in sarcopenic patients[29]. Therefore, identifying patients with low muscle mass would potentially allow targeted intervention and prehabilitation before surgery[30].

In this retrospective study we hypothesise that psoas muscle area as a measure of sarcopenia can discriminate patients at higher risk of mortality and complications after elective major colorectal surgery in comparison to other commonly collected risk factors including an assessment of frailty.

**2. Methods**

2.1 Study design

This was a retrospective analysis of prospectively acquired data from patients who attended the preoperative assessment clinic at York and Scarborough Teaching Hospitals NHS Foundation Trust. The study was sponsored by York and Scarborough Teaching Hospitals NHS Foundation Trust and approved by the UK Health Research Authority (HRA, IRAS 281127). The requirement for written informed consent was waived by the HRA. This manuscript adheres to the STROBE statement guidelines.

2.2 Study population

All adult patients referred for preoperative evaluation before major intra-abdominal colorectal surgery between the 1st of August of 2015 and the 31st of August of 2020 that had an abdominal computed tomography (CT) scan performed up to 120 days before surgery were included. Patients who did not undergo surgery or did not have valid imaging were excluded. Patients were also excluded where an accurate measurement of psoas muscle area was not possible.

2.3 Data collection

Data extracts were anonymised and prospectively recorded. Data included demographics, co-morbidities, medications and laboratory data (Appendix 1), as well as The Canadian Study of Health and Aging Clinical Frailty Scale (CFS)[31], American Society of Anaesthesiologists Physical Status (ASA), surgery type and approach and complications graded according to the Clavien-Dindo classification[32]. Complication data was gathered prospectively in hospital by perioperative specialist nurses on postoperative days 3,5,7 and 10. Frailty was defined as a CFS score>4.

Length of hospital stay, status at discharge (alive or deceased) and survival time were collected after hospital discharge from the Trust’s core patient database. CT scan data extracted retrospectively included date of study, type of scan (contrast, non-contrast, CT colonoscopy), scanner ID and slice thickness.

2.4 Psoas measurement

Abdominal CT scans were analysed retrospectively on Philips Vue PACS (Philips Electronics UK LTD, Farnborough, UK) software. The cross-sectional area of both psoas muscles was measured using a free-hand drawing technique in the axial slice where both L3 transverse processes were visible (supplementary figure 1). The psoas muscle index (PMI) was calculated by adding the right and left psoas area and standardising to the patient’s height (bilateral psoas area/height2). Patients were grouped into sex-stratified PMI tertiles and those in the lowest tertile were defined as sarcopenic[33].

Measurements were performed by a single investigator who received training in psoas measurements from an experienced consultant radiologist. A subset of 29 scans were independently measured by both investigators and inter-observer reliability was assessed. Investigators were blinded to the outcomes at the time of radiological measurements.

2.5 Outcome measures

The primary outcome was 2-year mortality. Secondary outcomes included postoperative complications assessed using Clavien-Dindo[32] graded major and minor complications and comprehensive complication index (CCI)[34], and length of stay. The CCI score is a composite of the number and severity of postoperative complications, measured on a continuous scale of zero, patients that did not experience any complication, to 100, patients that died as a result of postoperative complications[34]. Major complications are defined in appendix 2. Outcome measures were defined *a priori.*

2.6 Statistical analysis

Data were tested for normality by visual inspection of histograms and using Shapiro-Wilk’s W-test. Continuous data are presented as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if non-normally distributed and categorical data as number and percentage.

Intraclass correlation coefficients (ICC) for observer agreement of psoas area were calculated based on double rating, absolute agreement and 2-way mixed-effects model.

Associations between preoperative data and mortality were tested using logistic regression analysis. Variables found to be significant on univariate analysis as well as factors agreed *a priori* (surgery for cancer resection, BMI, CFS) were initially included in multivariable analysis. Results are presented as unadjusted odds ratio (OR) and adjusted odds ratio (aOR), for univariate and multivariable analyses respectively with 95% confidence intervals (CI). The principle of 10 events per variable in multivariable analysis was not violated. Factors were tested for collinearity and excluded if their variance inflation factor was >10. Goodness-of-fit was assessed using the Hosmer-Lemeshow test. Influential covariate patterns and outliers were identified, their effect on the models was assessed and removed if appropriate. Given the low incidence of high CFS scores, this was not a significant predictor in most outcomes analysed. Models with and without CFS were compared using likelihood-ratio test, Akaike’s information criterion and Bayesian Information criterion and CFS was excluded when it did not significantly improved models.

Kaplan-Meier curves were constructed to compare cumulative survival between sarcopenic and non-sarcopenic patients and tested using the log-rank test.

Associations between baseline variables and CCI score were initially tested using linear regression analysis. At diagnostics the model violated the assumptions of homocedasticity and normality of residuals (supplementary table 1 and supplementary figure 2) and logarithmic transformation was unsuccessful in resolving this due to the high zero count in the outcome measure. Addition of a small random positive number to the zero values prior to transformation is a validated method of addressing this issue[35], however this was also unsuccessful in meeting the assumptions. Therefore, validated alternative methods of analysis were explored[36] and a two-part model was created. Patients were firstly classified as having had complications (CCI score >0) or no complications (CCI score =0), and logistic regression analysis was used to explore associations between explanatory variables and the presence of a complication. Linear regression was then used to model the CCI score in those patients that had complications, employing a logarithmic transformation of the outcome scores. Results are presented as coefficients with 95% CI and percentage of change in CCI score.

Missing data was excluded from analysis. Statistical analyses were performed using Stata (Stata/IC 16.1, StataCorp, Texas, USA). A p-value of less than 0.05 was considered statistically significant.

**3. Results**

Data were available on 780 patients who attended the preoperative assessment clinic prior to major colorectal surgery. Overall, 141 patients were excluded; 9 who did not undergo their planned surgery, 47 who did not have a CT scan prior to surgery, and 83 who had a CT scan greater than 120 days prior to surgery. Two subjects were excluded from analysis due to an inability to obtain an accurate psoas area. A total of 639 patients were included in the analysis and the study flowchart is shown in supplementary figure 3.

3.1 Population characteristics

Patient demographics and characteristics are shown in table 1. Patients were classified as being sarcopenic if they were on the lowest tertile based on PMI measurements. The median age was 71 years (IQR 64-78 years) and 58.4% of the population were male. The majority of the surgery was for colorectal malignancy (93.6%). Of the cohort 594 patients (93.0%) had a CFS score documented, of which 530 (89.2%) were classed as very fit, fit or well (scores 1-3), 47 (7.9%) as vulnerable (score of 4) and 17 (2.9%) as frail (score$\geq $5).

3.2 Psoas measurements

The ICC for psoas area measurement between two observers was 0.994 (95% CI of 0.965-0.998) for the validation sample. Bland-Altman analysis is shown in supplementary figure 4. The bias for PMI was -67.02 mm2 (95% CI of -96.45--37.59) and upper and lower limits of agreement were 91.46 mm2 and -225.50 mm2, respectively. The median time between imaging and surgery was 33 days (IQR 22–49).

Mean PMI was 474.2 mm2.m-2 (118.2) for females and 634.5 mm2.m-2 (153.5) for males. Sarcopenia was defined as the lowest sex-specific tertile for PMI, and subjects were classified as sarcopenic if PMI <421.5 mm2.m-2 for females and <564.0 mm2.m-2 for males.

3.3 Mortality

Sixty-seven (10.5%) patients died within 2 years of surgery. Age, haemoglobin, ASA class and sarcopenia were significantly associated with 2-year mortality in univariate logistic regression (table 2). In multivariable analysis age (adjusted odds ratio (aOR) for a 10-year increase 1.71, 95% CI 1.22-2-40; p=0.002) and sarcopenia (aOR 1.79, 95% CI 1.03-3.10; p=0.037) were associated with mortality.

Kaplan-Meier curves for 2-year mortality for sarcopenic and non-sarcopenic patients are shown in figure 1 and significantly reduced in sarcopenic patients (log-rank test, p=0.012).

Sarcopenic patients have reduced 1-year survival, but survival at 90 days is equivalent between sarcopenic and non-sarcopenic patients (supplementary figure 5).

3.4 Complications

Overall, 292 (48.75%) patients had a major or minor postoperative complication. Factors associated with having a postoperative complication are shown in table 3. In multivariable analysis, open surgery (aOR 2.62, 95% CI 1.60-4.28, p<0.001), converted surgery (aOR 6.79, 95% CI 1.28-36.02, p=0.024), a CFS score $\geq $5 (aOR 10.81, 95% CI 1.15-101.8, p=0.038) and eGFR (aOR for an increase of 15 ml.min-1.1.73 m2 0.70, 95% CI 0.54-0.93, p=0.038) were significantly associated with postoperative complications, whilst sarcopenia was not. In patients that had complications, increasing age, open surgery and sarcopenia were associated with more severe complications defined as a higher CCI score (table 4). Sarcopenic patients had an estimated increase of 16.6% in the CCI score compared to non-sarcopenic patients. An increase of 10 years in age was associated with an average increase of 9.1% in the CCI score, while open surgery was associated with a 20.8% increase in the CCI score compared with laparoscopic surgery.

A total of 85 (13.7%) patients experienced major complications. Sarcopenia was the only significant factor associated with having major complications in multivariable analysis (supplementary table 2) (aOR 1.69, 95% CI 1.04-2.74, p=0.034).

3.5 Length of stay

Median length of stay for the cohort was 6 days (IQR 4-9). There was no statistically significant difference in median length of stay between sarcopenic (6 days, IQR 4-9) and non-sarcopenic patients (6 days, IQR 4-8.5).

**4. Discussion**

This study demonstrated that sarcopenia, defined as the lowest sex-stratified tertile of PMI, was independently associated with 2-year mortality after elective major colorectal surgery. It was also associated with the occurrence of major complications and severity of complications overall.

Previous studies used CT measurements to identify sarcopenic patients among heterogenous cohorts[26,37], but there are significant variations in the methodology and thresholds used to define sarcopenia. One commonly used method is lumbar skeletal muscle area (SMA), which is the sum of the area of all muscles present on an axial slice[38], but is more time-consuming than using psoas muscle area, and often requires specialized image processing software, both of which are barriers against routine clinical implementation. Decreased psoas muscle area has been shown to be associated with increased risk of morbidity, mortality, and length of stay in patients undergoing colorectal cancer surgery[39,40], emergency laparotomy[41], and both endovascular[42] and open[43] abdominal aortic aneurysm repair.

The PMI cut-off values used in this analysis were <564mm2.m-2 in males and <421.5mm2.m-2 in females. These correspond to the lowest sex-stratified tertile and are similar in value to previously reported studies. PMI thresholds based on receiver operating curves for survival after resection of pancreatic cancer for PMI were <589.6mm2.m-2 and <406.7mm2.m-2  for males and females, respectively[44], whilst in colorectal cancer resection patients several studies used the cut-offs defined for SMA in the international consensus of definition and classification of cancer cachexia[45] of <545mm2.m-2  for males and <385mm2.m-2  for females. These thresholds predicted the occurrence of major complications[46], length of stay and 1-year mortality[39].

In the multivariable model for 2-year mortality only age and sarcopenia were significantly associated with mortality. Associations between sarcopenia and mortality have been consistently shown in observational studies. A systematic review of colorectal cancer resection patients found associations between sarcopenia and postoperative mortality, overall survival and disease-free survival[24]. Low muscle mass has also been shown to be associated with mortality after elective abdominal aortic aneurysm repair[23] and both elective and emergent major abdominal surgery[47]. Other pre-operative factors that have been associated with reduced survival include age, which was confirmed in this analysis, but also a reduced BMI, ASA class and haemoglobin. Sarcopenia increases significantly with age[16], but activity level, nutrition and presence of chronic disease can significantly influence muscle protein metabolism[18]. Sarcopenia is not a measure of ageing and remains significantly associated with 2-year mortality in our multivariate model after adjusting for age. The American College of Surgeons National Surgical Quality Improvement Database showed that underweight patients (BMI <18.5kg.m-2) had an increased risk of mortality after noncardiac surgery[48], however we did not see this association, most likely due to the low number of patients meeting this criteria. Low BMI is distinct from sarcopenia and even though there is an increased prevalence of sarcopenia among individuals with low BMI, sarcopenia is also present in normal, overweight and obese individuals[49]. Preoperative haemoglobin and ASA class have been associated with postoperative mortality in several studies[50,51], and were significant predictors in univariate analysis, but did not remain so when adjusting for confounders.

Sarcopenia was also associated with postoperative morbidity. Among the patients that had complications, sarcopenia predicted an estimated increase of 16.6% in the CCI score. This is similar to the result of a study in which sarcopenia, assessed by skeletal muscle area, predicted an increase in CCI score of 14.45% after colorectal resection[52]. Sarcopenia was the only significant factor associated with major complications in multivariable logistic regression analysis, consistent with previous studies showing a higher risk of severe and cardiopulmonary complications after colorectal cancer resection[24] and major postoperative morbidity after major abdominal surgery[53] in those that are sarcopenic. No association was seen between sarcopenia and overall complications, likely because of the large incidence (overall 48.75% of patients had any complication, whereas only 13.7% of patients had a major complication). Major complications and increased severity of complications (increased CCI score) are clinically more relevant outcomes than overall complications when considering preoperative risk stratification.

No association was seen between sarcopenia and length of stay. Even though sarcopenic patients had increased risk of major complications, the incidence of major complications in this cohort was quite low, 11.6% in non-sarcopenic patients and 17.9% in sarcopenic patients, and this small absolute difference may not be enough to drive a significant difference in length of stay.

There is significant overlap between sarcopenia and the physical phenotype of frailty, but frailty is a complex syndrome and represents a broader concept[14]. The CFS is one of the best studied frailty tools, based on a simple visual scale[31]. It is easy to perform and not as time-consuming as other tools[11], but relies on subjective assessment and patient reported outcomes. The CFS was not associated with mortality in this analysis, however only 2.9% of patients were classified as frail. A CFS score of 5 or more was associated with the occurrence of overall complications, but with a large confidence interval, likely denoting imprecision due to the small number of patients in this category. It was not associated with any other analysed outcome measures. In contrast, PMI is an objective measure and performed better in discriminating patients at risk of 2-year mortality and severe complications in this cohort.

Finally, if sarcopenia is a marker of risk it could be optimised before surgery. Data so far suggest prehabilitation can reduce morbidity[4,54] and it would be interesting to test whether an intervention targeting sarcopenic individuals could increase muscle mass and improve risk.

One of the main strengths of this study is that it used a simple measure that can be obtained from routinely performed preoperative scans with no need for additional image analysis software or training. This methodology can therefore be easily implemented. Furthermore, this study had a reasonable sample size, included a homogeneous cohort with a high percentage of lower gastrointestinal cancer resection patients and an appropriate number of events per variable in all outcomes analysed. All preoperative data and complications were prospectively collected, and results are controlled for many common baseline variables.

The main limitation of this study is its retrospective nature and single-centre analysis, hence the results obtained might not be generalisable. The analysis also included data from different CT scanners and modalities, and scans up to 120 days before surgery, which could lead to measurement imprecision. Another limitation is the absence of a standardised cut-off for PMI.

In conclusion, this study showed that a low PMI is associated with mortality and morbidity after major colorectal surgery. PMI performed better than frailty assessed using CFS. Moreover, only a remarkably small number of patients were identified as frail, questioning the clinical utility of this frailty tool for surgical risk stratification in this patient group. This study employed a practical and feasible measuring method that can easily be implemented in clinical practice. Identification of high-risk patients in the preoperative setting improves the consent process and promotes the discussion of goals of care and alternative interventions. Further studies are needed to clarify optimal cut-off values and future research should focus on whether prehabilitation can increase psoas muscle area before surgery and whether this improves outcomes.

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**Conflicts of interest**

The authors declare no competing interests.

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**Captions for figures**

Figure 1: Kaplan-Meier survival curves for mortality at 2 years, comparing sarcopenic and non-sarcopenic patients (log-rank test, p=0.012).