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Research Article

Is Preoperative Sarcopenia a Good Predictor of Postoperative Complications and Outcomes after Pelvic Exenteration Surgery?

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ABSTRACT

Background: Sarcopenia is common in oncology patients and has been found to be associated with poorer outcomes after surgery. Pelvic exenteration is a major surgery associated with high rates of morbidity. The aim of this study was to determine if preoperative sarcopenia is associated with postoperative complications and outcomes after pelvic exenteration surgery.

Methods: A retrospective study was conducted including 64 oncology patients who had undergone pelvic exenteration surgery between August 2015 and January 2018 and had available preoperative lumbar CT images. Skeletal muscle index (SMI) was calculated by analysing CT images using body composition software. Sarcopenia was determined by using previously published SMI sex-specific cut-offs. Preoperative nutritional status, nutritional indicators and other clinical factors were also collected.

Results: There was no association between preoperative sarcopenia and outcomes after pelvic exenteration surgery, however, increased weight ($p=0.027$) and BMI ($p=0.025$) were associated with a greater number of total complications. Increasing age was also significant ($p=0.001$) in explaining the greater number of complications. Greater complexity of surgery itself was associated with greater postoperative complications ($p=0.014$) and increased length of hospital stay ($p=0.001$).

Conclusion: Preoperative sarcopenia, using dichotomous cut-off points, is not sensitive enough to predict postoperative complications and outcomes in oncology patients undergoing pelvic exenteration surgery; however, other preoperative factors such as weight, BMI and age, and the complexity of surgery, do affect outcomes. Assessment tools that incorporate several clinical and physical factors, such as frailty assessments, should be used in future studies to identify risk factors in such major surgeries.

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Introduction

Pelvic exenteration is a major surgical procedure for the treatment of advanced or recurrent cancer of the pelvis [1]. The surgery involves complete or partial resection of organs, soft tissue and/or bones of the pelvis and is associated with high morbidity rates [1-3]. Due to the radical nature of this surgery and its association with high complication rates, it is important to identify other contributing risk factors for postoperative complications, such as sarcopenia, to reduce risk and improve patient outcomes.

Sarcopenia is defined as a rapid reduction of muscle mass [4, 5]. It is common in oncology patients as muscle wastage is a consequence of the condition [6]. Sarcopenia has become an important measure in oncology patients, as it has been shown to be associated with reduced responses to therapies, poorer outcomes after surgery and decreased survival rates [7-9]. Although emerging evidence is conflicting, sarcopenia has been reported to be associated with increased postoperative complications and length of stay (LOS) in pelvic cancer surgery, noting these surgeries are much less complex than pelvic exenteration surgery [5, 10, 11].

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Computed tomography (CT) images at the third lumbar vertebrae (L3) can be used for estimating muscle mass and identifying sarcopenia [8, 9]. Whole-body muscle mass can be calculated using specific software and used to determine low muscle mass using predetermined reference ranges [9]. CT is routinely performed in pelvic exenteration patients as part of standard care and monitoring before and after surgery. To date, no studies have assessed the link between preoperative sarcopenia and postoperative complications and outcomes after pelvic exenteration surgery.

The aim of this study, therefore, is to investigate if preoperative sarcopenia, determined using CT scan assessment, is associated with postoperative complications and other outcomes in oncology patients undergoing pelvic exenteration surgery.

Materials and Methods

I Design

A retrospective study was conducted to determine preoperative sarcopenia by analysing CT scans of consecutive patients who had undergone pelvic exenteration surgery at a quaternary hospital in Australia, from August 2015 to January 2018.

II Study Population

Inclusion criteria for this study consisted of patients who (i) had pelvic exenteration surgery for cancer and for cure, (ii) provided consent for their data collection, and (iii) had non-contrast scans available to analyse, to ensure consistent assessments and comparisons of skeletal muscle index (SMI) [12]. Exclusion criteria included patients who (i) were <18 years of age, (ii) were unable to consent due to language barriers or cognitive function, (iii) had no available CT image at L3 within three months prior to surgery, which is consistent with other literature, (iv) had a CT of poor quality, and (v) had a CT that was not accessible via electronic health records [13].

III Clinical Data

All data were collected and managed using REDCap electronic data capture tools hosted by the study site [14]. Baseline data, collected as part of standard practice, were recorded within three months prior to surgery and included sex, age, cancer diagnosis, type of surgery, weight (kg), height (m), body mass index (BMI) determined using the standard equation (kg/m^2), handgrip strength using kg and % expected strength, and nutritional status determined using the Patient Generated Subjective Global Assessment (PG-SGA). A JAMAR hand dynamometer was used to take handgrip measurements in line with the Southampton grip strength measurement protocol [15].

The percentage of expected handgrip strength was determined using the National Isometric Muscle Strength (NIMS) Database Consortium equations [16]. The PG-SGA is a validated tool used in oncology patients [17] that accounts for variables including weight history, nutritional intake, clinical symptoms, medical conditions and a physical assessment to determine nutritional status (well nourished (A), suspected malnutrition or moderately malnourished (B), and severely

malnourished (C)). This is partnered with a numerical score that indicates whether more aggressive nutritional intervention is required (the higher the score, the greater the need for intervention).

Postoperative complications, LOS and 30-day mortality data were collected. Postoperative complications were captured as per previously published literature [18]. These complications were grouped into the following categories: wound complications, gastrointestinal complications, urological complications, cardiovascular complications, respiratory complications and sepsis. Complications were not reported using Clavien-Dindo classifications as this grading system focuses on the severity of complications which have already been investigated and published in this patient cohort [19-21]. This study aimed to investigate how preoperative sarcopenia may affect specific types of complications; hence the above complication categories were selected.

IV Image Analysis

The cross-sectional area (cm^2) of skeletal muscle was determined by analysing CT images at the L3 vertebral level using Slice-o-matic™ version 4.3 (TomoVision, Canada). Body composition components in the CT images were manually tagged based on the following Hounsfield Unit (HU) thresholds: -29 to 150 for skeletal muscle, -150 to -50 for visceral adipose tissue and -190 to -30 for intramuscular and subcutaneous adipose tissue [22].

The total cross-sectional area of skeletal muscle was normalised by height squared to obtain an SMI (cm^2/m^2). CT images were divided among three trained investigators (VC, FR and SC) to analyse. A fourth trained investigator (SH) analysed 30% of the same scans to assess inter-observer variation. SMIs were compared to assess for inter-observer variability by testing the coefficient of variation; results were within the expected range of 1.3% [23]. A Consultant Radiologist (SL) provided assistance if investigators had queries regarding anatomy when analysing the scans. Participants were defined as having sarcopenia using previously established sex-specific cut-offs: SMI <38.5 cm^2/m^2 for women and <52.4 cm^2/m^2 for men [9].

V Statistical Analysis

Data were analysed using IBM SPSS Statistics (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to determine the normality of data. Mean and standard deviation were used to describe parametric data. Median and inter-quartile range were used to describe non-parametric data. Baseline differences were assessed using χ^2 , independent samples *t*-tests and Mann-Whitney U tests.

Differences between sarcopenic and non-sarcopenic groups, the complexity of surgery and postoperative complications were assessed using χ^2 , independent samples *t*-tests and Mann-Whitney U tests. Pearson product-moment correlation coefficient tests were used to assess correlations between age, LOS and postoperative complications. A stepwise backward linear regression was used to assess which measures could explain the incidence of the total number of complications. For all tests, the significance level was set at $P < 0.05$.

Results

One hundred and thirty-seven patients were assessed for eligibility. Sixty-four patients met the inclusion criteria with a mean age of 61.5 years. Of the 64 patients, 36% were female. Most patients had either advanced primary or recurrent rectal cancer (73%), followed by other primary or recurrent cancer (27%). The mean SMI for the cohort was $46 \pm 9.3 \text{ cm}^2/\text{m}^2$. Thirty-eight participants (59%) were classified as being sarcopenic prior to pelvic exenteration surgery. Baseline characteristics are presented in (Table 1), including differences between sarcopenic and

non-sarcopenic patients. Baseline statistics show sarcopenic participants had a higher incidence of having rectal cancer than other cancers ($p=0.038$). Participants identified as being malnourished preoperatively were also more likely to be diagnosed with sarcopenia ($p=0.019$); sarcopenic participants had significantly higher PG-SGA numerical scores than non-sarcopenic patients ($p=0.032$). Preoperative weight and BMI were lower in sarcopenic patients than non-sarcopenic patients ($p=0.001$ and $p<0.0001$, respectively). There was no significant difference in gender, age, primary and recurrent cancer diagnoses, type of pelvic exenteration surgery or handgrip strength.

Table 1: Baseline characteristics between sarcopenic and non-sarcopenic participants.

	Total (n = 64)	Sarcopenic (n = 38)	Non-sarcopenic (n=26)	p-value
Participants (n)				
Male	41	24	17	1.000
Female	23	14	9	
Age (years)	62 (53-68)	59 (47-68)	63 (57-68)	0.292
Time between CT scan and surgery date (days)	39 (27-64)	33 (25-63)	46 (30-67)	0.286
Cancer diagnosis				
Primary rectal cancer	21	15	6	0.065
Recurrent rectal cancer	26	17	9	
Primary other	3	2	1	
Recurrent other	14	4	10	
Total rectal cancer	47	32	15	0.038*
Total other cancer	17	6	11	
Type of surgery				
Partial Pelvic Exenteration	21	13	8	0.986
Complete Pelvic Exenteration	43	25	18	
Preoperative Nutritional Status				
PG-SGA - A	45	22	23	0.019*
PG-SGA - B or C	19	16	3	
Total PG-SGA numerical score	4.0 (1.8-8.3)	6.0 (2.0-10.0)	3.0 (1.3-4.8)	0.032*
Preoperative weight (kg)	77.6 \pm 17.1	72.1 \pm 17.5	85.6 \pm 12.9	0.001*
Preoperative BMI (kg/m²)	27.1 \pm 5.2	24.8 \pm 4.5	30.5 \pm 4.1	<0.0001*
Handgrip strength (kg)	32.0 (25.5-37.5)	32.0 (22.5-36.8)	33.5 (31.0-38.5)	0.173
Handgrip strength (% of expected handgrip strength)	87.9 \pm 20.7	85.6 \pm 21.2	91.3 \pm 19.8	0.279

Abbreviations: n: number; PG-SGA: patient generated subjective global assessment; BMI: body mass index; *significant at $P<0.05$.

Mann-Whitney U Tests showed no statistical differences between sarcopenia and postoperative complications (Table 2). There were no differences between sarcopenia and LOS ($p=0.507$). There were no mortalities reported in either group. These results indicate sarcopenic patients do not have an increased number of postoperative complications, greater LOS or higher mortality rates compared to non-sarcopenic patients after pelvic exenteration surgery. The effect of other baseline characteristics, including SMI and preoperative nutritional indicators on postoperative complications after pelvic exenteration surgery, is outlined in (Table 3). The results show that increased

preoperative weight and BMI is associated with the number of total complications experienced after pelvic exenteration surgery. The association between preoperative SMI, nutritional indicators and postoperative outcomes with increasing surgical complexity is described in (Table 4). There were no differences between SMI and nutritional indicators with surgical complexity. However, the results do indicate that the more complex the surgery, the greater the occurrence of postoperative complications and the increased length of hospital stay.

Table 2: Number of sarcopenic and non-sarcopenic patients with complications after pelvic exenteration surgery.

Complications	Total (n=64)	Sarcopenic (n=38)	Non-Sarcopenic (n=26)	P-value
Wound complications	31 (48.4%)	22 (57.9%)	9 (34.6%)	0.115
Gastrointestinal complications	29 (45.3%)	20 (52.6%)	9 (34.6%)	0.243
Urological complications	3 (4.7%)	2 (5.3%)	1 (3.8%)	1.000
Cardiovascular complications	11 (17.2%)	5 (13.2%)	6 (23.1%)	0.487
Respiratory complications	18 (28.1%)	8 (21.1%)	10 (38.5%)	0.216
Sepsis	25 (39.1%)	14 (36.8%)	11 (42.3%)	0.858

Abbreviations: n: number; Data presented as n (%).

Table 3: The effect of SMI and preoperative nutritional indicators on total postoperative complications after pelvic exenteration surgery.

Preoperative Nutritional Indicator	0-1 total number of complications (n=32)	2 or more total number of complications (n=32)	P value
SMI (cm ² /m ²)	44 ± 9	48 ± 9	0.156
BMI (kg/m ²)	26 ± 5	29 ± 5	0.025*
Weight (kg)	73 ± 18	82 ± 15	0.027*
HGS (%)	85 ± 19	91 ± 22	0.206
HGS (kg)	31 (21-37)	33 (31-39)	0.064
Total PG-SGA numerical score	4 (1-10)	4 (2-7)	0.951

Abbreviations: SMI: Skeletal Muscle Index; BMI: Body Mass Index; HGS: Handgrip strength; PG-SGA: Patient Generated - Subjective Global Assessment; *significant at P<0.05.

Table 4: The association between preoperative SMI, nutritional indicators and postoperative outcomes with surgical complexity for pelvic exenteration patients.

	1-2 pelvic compartments removed (n=11)	≥ 3 pelvic compartments removed (n=53)	p-value
<i>Preoperative SMI and Nutritional Indicators</i>			
SMI (cm ² /m ²)	43 ± 9	47 ± 9	0.178
BMI (kg/m ²)	26 ± 5	27 ± 5	0.442
Weight (kg)	70 ± 16	79 ± 17	0.135
HGS (%)	84 ± 13	89 ± 22	0.338
HGS (kg)	26 (22-35)	32 (28-39)	0.121
Total PG-SGA numerical score	4 (3-10)	4 (1-7)	0.512
<i>Postoperative Outcomes</i>			
Total complications (n)	0 (0-2)	2 (1-4)	0.014*
Length of stay (days)	15 (9-18)	25 (20-40)	0.001*

Abbreviations: SMI: Skeletal Muscle Index; BMI: Body Mass Index; HGS: Handgrip strength; PG-SGA: Patient Generated – Subjective Global Assessment; n: number; pelvic compartments include: anterior, posterior, central, right lateral and left lateral; *significant at P<0.05.

The relationships between age, LOS and total postoperative complications were investigated using Pearson product-moment correlation coefficients. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. There was a very strong, positive correlation between LOS and number of total complications, $r = 0.625$, $n = 64$, $p < 0.0005$ and a strong positive correlation between age and number of total complications, $r = 0.390$, $n = 64$, $p = 0.001$. These results indicate that an increased number of the total complications are correlated with greater LOS and increased age. A stepwise backward linear regression model was used to assess which measures might explain total number of complications for this patient population. This model included age, cancer diagnosis, type of surgery, weight, BMI, PG-SGA nutritional status, PG-SGA numerical score, HGS (kg), skeletal muscle index and sarcopenia status. In the final model, only age was significant in explaining 15.2% of variation in the number of total complications ($F_{11,134}$; $p < 0.001$), with a beta value of 0.390 ($p = 0.001$).

Discussion

The aim of this study was to investigate whether preoperative sarcopenia, determined using CT scan assessment, is associated with postoperative complications and other outcomes in oncology patients undergoing pelvic exenteration surgery. This retrospective study found no association between preoperative sarcopenia and postoperative complications, LOS or mortality after pelvic exenteration surgery, however other baseline characteristics and the complexity of the surgery itself did impact postoperative complications. This suggests more comprehensive tools and assessments, including a range of variables, should be used in order to predict outcomes after such a major surgery.

Pelvic exenteration surgery is more complex than other surgeries for pelvic cancers. This is due to the large number of organs resected, requiring up to four surgical specialists involved in each case [18]. Previous literature has reported average surgical times of 8.5 hours, including averages of three days spent in ICU and 21-day hospital stays

[18, 20, 24]. As expected, this patient group has high rates of morbidity, with reported rates of 70% of patients experiencing complications, 8% returning to theatre and 5% requiring radiological intervention [18, 20]. With the extent of disease and associated complex surgery, it is not surprising that many factors, including the complexity of the surgery itself, influence postoperative complications and other outcomes [20]. This is consistent with the findings of this study that indicate the more compartments removed during surgery, the higher the number of postoperative complications experienced by participants and the greater their LOS. It could also explain why pelvic exenteration surgery may be too complex for preoperative sarcopenia, defined using dichotomous cut-offs, to influence postoperative complications and other factors need to be considered as well.

It has been well recognised in the literature that a high BMI is associated with increased complications after colorectal surgery [25]. The results of this study show that BMI was significantly higher in the group of patients who experienced two or more postoperative complications. He et al. [25] conducted a meta-analysis investigating the association between BMI and postoperative complications in colorectal surgery. They found that higher BMI scores increased overall operative time, total complications, wound complications, anastomotic leaks and postoperative ileus, all of which are common in pelvic exenteration patients [18, 25]. This is similar to the findings from this study and other studies investigating complex surgery, where higher BMI scores were associated with increased rates of total complications [26]. Future studies in this patient cohort need to report on weight and BMI to consolidate these findings in order to inform preoperative clinical practice, such as prehabilitation activities that reduce BMI but improve functional and physical capacity [27]. This also demonstrates there are other factors that impact postoperative outcomes and should encourage clinicians to investigate numerous preoperative indicators to provide a meaningful preoperative assessment and intervention.

Increasing age was strongly correlated to increased LOS and postoperative complications and significantly contributed to the rate of complications in the regression model. Although this is somewhat expected, it does suggest that frailty assessment may be a more thorough, comprehensive and accurate assessment that could predict outcomes in pelvic exenteration surgery. Frailty is commonly determined by evaluating five domains using specific criteria for each domain, including weight loss, exhaustion, leisure time activity, gait speed and grip strength [28, 29]. It is used to identify older persons at risk of morbidity and mortality [29, 30]. As age was strongly associated with postoperative outcomes after pelvic exenteration surgery, frailty may be a better predictor of outcomes and further studies should be conducted to investigate this.

There were limitations to this study. The retrospective nature of the study introduced restrictions to patient selection; however, it would be unethical to enforce patients to undertake a CT scan for prospective research purposes, so this limitation is universal with this methodology [31]. Due to the strict exclusion criteria around CT scans, several participant records were not included, which resulted in small numbers. The study was also conducted in a very specific cohort, and therefore, generalisability and reproducibility in other clinical areas is limited. Despite this, the results emphasise the complexity of pelvic exenteration

surgery and highlight other clinical factors and methods that could be used to identify increased risks. Greater sample size investigating more preoperative factors are required to support these findings.

Conclusion

Preoperative sarcopenia, using dichotomous cut-off points, is not sensitive enough to predict postoperative complications and outcomes in oncology patients undergoing pelvic exenteration surgery, however other preoperative factors such as weight, BMI, age and the complexity of surgery do affect outcomes. Pelvic exenteration surgery is complex, with many factors contributing to morbidity and mortality rates. Therefore, other assessment tools that incorporate several clinical and physical factors, such as frailty assessments, should be used to identify risk factors. Further investigations are required to consolidate these findings.

Author Contributions

Each author has made significant contribution to the research presented in line with the Journal of Surgical Oncology's authorship criteria.

Ethics Committee Approval

Ethics approval to conduct this research was obtained from the Sydney Local Health District Human Ethics Review Committee.

Conflicts of Interest

None.

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