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Research Article

Pre and Postoperative Muscle Wastage and Sarcopenia Using CT Scans in Patients Undergoing Pelvic Exenteration Surgery

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ABSTRACT

Background: Sarcopenia is associated with poor postoperative outcomes in oncology patients. Computed tomography (CT) scans can be used to identify muscle wasting and sarcopenia. This study aimed to investigate if pelvic exenteration surgery leads to muscle wastage and thus, induction or exacerbation of sarcopenia.

Methods: This is a retrospective review involving the analysis of CT scans before and after pelvic exenteration surgery to determine skeletal muscle index and diagnose sarcopenia. Other clinical and nutritional factors were collected.

Results: A total of 34 patients met the inclusion criteria. Postoperative skeletal muscle index was significantly lower compared to preoperative skeletal muscle index (p=0.008). The incidence of sarcopenia was 62% preoperatively and rose to 74% postoperatively (p=0.073). Postoperative sarcopenia was not significantly associated with complications or mortality.

Conclusion: The skeletal muscle index significantly decreased postoperatively, indicating that pelvic exenteration surgery leads to muscle wastage. The use of CT scans to recognise sarcopenia would allow focusing of resources for those at risk.

Introduction

Pelvic exenteration is a major surgical procedure for the treatment of advanced or recurrent cancer of the pelvis. It involves the en-bloc resection of the pelvic viscera, vessels, muscles, ligaments and part of the pelvic bone [1]. Removal of these anatomic structures may be complete or partial, depending on what is required for the tumor to be removed with a clear resection margin (R0) [1, 2]. Despite the radical nature of the surgery and its associated high morbidity of approximately 70%, this surgery is being increasingly performed as it is the only potentially curative option for locally advanced and recurrent rectal cancer [2, 3]. For those not receiving the surgery and being treated with radiotherapy alone, 5-year survival rates are as low as 3%, compared to a 5-year survival rate of 53% in those treated with pelvic exenteration surgery in an Australian quaternary hospital [3, 4].

A common complication in oncology patients is a reduction in body stores, including muscle wasting and subcutaneous fat loss [5]. Sarcopenia is defined by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death [6]. In the oncology setting, low muscle mass alone has been used to diagnose sarcopenia [7]. As other nutritional assessment tools and indicators are unable to predict changes in lean and adipose tissue, Computed Tomography (CT) scans can be used to identify sarcopenia through quantifying muscle area and density [8].

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Sarcopenia is associated with poor postoperative outcomes in oncology patients [9]. It has been identified that length of hospital stay, morbidity and mortality are all increased in oncology patients with sarcopenia, along with functional decline and a reduction of disease-free survival [10, 11]. CT scans can therefore be used to identify patients who have undergone pelvic exenteration with high postoperative risk secondary to sarcopenia. To our knowledge, there are currently no studies investigating if pelvic exenteration surgery leads to muscle wasting, and thus the induction or exacerbation of sarcopenia. An awareness of this would allow tailoring of pre and postoperative care to optimise patient outcomes. The aim of this study was to determine if muscle wastage and the proportion of sarcopenia varies before and after pelvic exenteration surgery via assessment of a protocolised and validated body composition analysis using CT.

Methods

I Study Design

This is a retrospective cohort study comparing muscle mass and sarcopenia status pre- and post-pelvic exenteration surgery. The patients were selected from a single-blinded randomized controlled trial (2015-2018) comparing the impact of preoperative immunonutrition to standard polymeric supplements on those undergoing pelvic exenteration [12]. As there was no significant difference found between groups, the results of this study should not be affected by the different supplements instituted preoperatively.

II Study Population

Individuals who underwent pelvic exenteration surgery between January 1st, 2015 and January 31st, 2018, at a quaternary hospital in Sydney, Australia, were assessed for eligibility. Inclusion criteria were that participants must: i) be 18 years or older; ii) have CT scans at L3 before and after surgery. Participants were excluded if: i) their CT scans were taken greater than 3 months pre- or post-surgery; ii) their CT image was of poor quality; iii) their CT image was not accessible via electronic health records. Ethics approval was granted by the Sydney Local Health District Human Ethics Review Committee.

III Clinical Data

Data were obtained retrospectively from a RedCap database set up for the randomized controlled trial [13]. Baseline data were collected for each eligible participant, which included age, gender, cancer diagnosis, type of pelvic exenteration surgery, weight (kg), height (m), BMI (kg/m^2), handgrip strength (HGS) (kg and % expected strength) and nutritional status using the patient-generated subjective global assessment (PG-SGA). On postoperative day 7, weight, percentage weight change, BMI, HGS and nutritional status were collected. On postoperative day 14, weight, percentage weight change, BMI and HGS were collected. On postoperative day 21- and three-months post-operation, weight, percentage weight change and BMI were collected. HGS was measured using the JAMAR hand-dynamometer according to the Southampton grip strength measurement protocol [14]. These results were calculated as a percentage of the patient's expected HGS, according to the National Isometric Muscle Strength (NIMS) Database consortium equation [15].

Nutritional status was determined using the PG-SGA which is a validated nutritional assessment tool designed for oncology patients [16]. It categorises patients as well-nourished (A), suspected or moderately malnourished (B), and severely malnourished (C) and provides a numerical number outlining the severity of symptoms. Mortality was assessed at 30 days. Postoperative complications and length of stay were also collected. Complications were reported as sepsis, wound, gastrointestinal, urological, cardiovascular, and respiratory complications in order to determine any correlation between sarcopenia and these complications.

IV Image Analysis

CT scans were collected within 3 months before and after pelvic exenteration surgery. Muscle cross-sectional areas (cm^2) were calculated for each lumbar 3 (L3) vertebra CT image, using the software Slice-o-matic™, version 5.0 (Tomovision, Montreal, Quebec, Canada). The L3 vertebra was used as it has been shown to be the most accurate single image cross-sectional region for correlation to whole-body skeletal muscle mass [8]. Image analysis was performed by three trained observers (CW, SH and SC), with body tissues being identified and tagged based on the use of Hounsfield Unit thresholds: -29 to 150 for skeletal muscle, -150 to -50 for visceral adipose tissue and -190 to -30 for intramuscular and subcutaneous adipose tissue [17]. Tissue cross-sectional area was calculated by multiplying the tagged area by the pixel density. The skeletal muscle cross-sectional area was normalised for stature in metres squared (m^2) and reported as skeletal muscle index (SMI) (cm^2/m^2). Observer accuracy was confirmed by testing the coefficient of variation for the SMI between observers which did not exceed 1.3% [18]. Participants were defined as sarcopenic if analysis of their CT scan indicated their SMI as less than $38.5 cm^2/m^2$ for women and $52.4\ cm^2/m^2$ for men as determined by Prado *et al.* (2008).

V Statistical Analysis

Differences between sarcopenia and muscle wastage before and after surgery were statistically analysed. Postoperative sarcopenia was assessed to determine its impact on outcomes of mortality, length of stay and complications. Nutritional markers were assessed with their relation to postoperative sarcopenia, including postoperative weight, BMI, and handgrip strength at follow-up. Additionally, preoperative characteristics were analysed to identify any predictors of postoperative sarcopenia. The analysis was performed using SPSS version 24 (IBM, Armonk, New York, USA). As the data was assumed to be non-parametric, baseline demographic data was described using median and interquartile range (IQR). Statistical analysis was performed using a Chi-square test for sarcopenia status, a Wilcoxon signed rank test for SMI and Mann Whitney U tests for outcome variables. P values <0.05 were considered significant for all tests.

Results

A total of 79 patients who underwent pelvic exenteration were assessed for eligibility. Thirty-four patients were identified as suitable for

enrolment to the study, with the primary exclusion being no postoperative scan available for assessment. Of the 34 patients, 21 patients (62%) had preoperative sarcopenia on the assessment of their preoperative CT scans. Preoperative patient demographics are outlined in (Table 1). Table 2 outlines the overall postoperative results of patients undergoing pelvic exenteration. Of the 34 patients, 25 of them were considered sarcopenic after surgery. Eighteen were classified as malnourished (53%); and weight change progressively declined over 3 months after surgery to 9% of total body weight. Thirty-day mortality was zero.

Table 1: Preoperative patient demographics.

Variable	**Results, n = 34**	
Age (years)	62	(28-79)
Gender:		
- Male	n = 23	(67%)
- Female	n = 11	(32%)
Type of cancer:		
- Primary rectal	n = 8	(24%)
- Rectal recurrence	n = 17	(50%)
- Primary other	n = 3	(9%)
- Other recurrence	n = 6	(18%)
Surgical resection:		
- Complete	n = 26	(77%)
- Partial	n = 8	(24%)
Preoperative sarcopenia	n = 21	(62%)
Preoperative weight (kg)	77.0	IQR (67.1-89.8)
Height (cm)	171.8	IQR (158.4-177.3)
Preoperative BMI (kg/m^2)	25.6	IQR (23.3-31.0)
Preoperative PG-SGA score	3.5	IQR (2.0-8.3)
Preoperative PG-SGA		
- A (well nourished)	n = 23	(67.6%)
- B/C (malnourished)	n = 11	(32.4%)
Preoperative HGS (kg)	31.5	(25.3-41.0)
Preoperative HGS (% predicted)	82.9	(76.0-106.0)
Preoperative SMI (cm^2m^2)	47.9	(36.1-54.9)

BMI: Body Mass Index; PG-SGA: Patient-Generated Subjective Global Assessment; HGS: Hand Grip Strength; SMI: Skeletal Muscle Index.

Table 2: Overall postoperative outcomes.

Variable	**Results, n = 34**	
30 day mortality	0	(0%)
Postoperative sarcopenia	25	(74%)
Postoperative SMI (cm^2m^2)	43.4	(35.7-51.1)
Postoperative length of stay (days)	28.5	(22.0-48.8)
7 day postoperative PG-SGA		
• A (well-nourished)	16	(47%)
• B/C (malnourished)	18	(53%)
7 days postoperative HGS (% predicted)	80	(63-89)
14 days postoperative HGS (% predicted)	82	(73-95)
7 days postoperative weight change (%)	-1.4	(-4.9 - +3.0)
14 days postoperative weight change (%)	-3.7	(-8.0 - +2.7)
21 days postoperative weight change (%)	-5.6	(-11.9 - -2.0)
3 months postoperative weight change (%)	-9.1	(-16.0 - -4.3)

SMI: Skeletal Muscle Index; PG-SGA: Patient-Generated Subjective Global Assessment; HGS: Hand Grip Strength.

I Muscle Wastage and Sarcopenia

Table 3 outlines sarcopenia status and SMI before and after pelvic exenteration surgery. The incidence of sarcopenia increased, but not significantly, from the pre to postoperative period (p=0.073). Nonetheless, the median SMI was significantly lower postoperatively compared to preoperatively (p=0.008). More specifically, the SMI was significantly lower after surgery compared to before surgery, irrespective of postoperative sarcopenia status.

Table 3: Sarcopenia status and SMI in the pre and postoperative periods of pelvic exenteration surgery.

	Preoperative n (%)		**Postoperative n (%)**		**p-value**
Sarcopenic patients	21	(62)	25	(74)	0.073
SMI (cm^2m^2)	47.9	(36.1-54.9)	43.4	(35.7-51.1)	0.008
SMI (cm^2m^2) of patients classified as non-sarcopenic after surgery SMI	57.4	(46.8-61.7)	54.2	(46.2-61.2)	0.002
SMI (cm^2m^2) of patients classified as sarcopenic after surgery	43.6	(35.2-50.9)	39.2	(34.1-47.9)	< 0.001

SMI: Skeletal Muscle Index

II Predictors of Postoperative Sarcopenia

Table 4 outlines preoperative and intraoperative differences between postoperative sarcopenic and non-sarcopenic patients. Neither gender nor age was predictive of postoperative sarcopenia. Unsurprisingly, preoperative sarcopenia was significantly associated with postoperative sarcopenia ($p < 0.001$). Lower BMI, weight and SMI were also predictive of postoperative sarcopenia. There was no correlation between the type of cancer or extent of surgical resection (partial vs complete) and postoperative sarcopenia.

Table 4: Preoperative and intraoperative characteristics.

	Postoperative sarcopenic patients (n = 25)		**Postoperative non-sarcopenic patients (n = 9)**		**p-value**
Gender					0.969
• Male	17	(68%)	6	(67%)	
• Female	8	(32%)	3	(33%)	
Age (years)	61	(52-67)	67	(61-75)	0.06
Height (cm)	175	(161-180)	163	(158-169)	0.05
Preoperative weight (kg)	75.2	(61.5-83.4)	88.5	(80.4-95.4)	0.015
Preoperative BMI (kg/m^2)	24.3	(22.7-27.3)	31.7	(30.0-36.1)	<0.001
Preoperative PG-SGA score	4.0	(1.5-10.5)	3.0	(2.0-4.0)	0.298
Preoperative PG-SGA					0.216
• A (well nourished)	15	(60%)	8	(88.9%)	
• B/C (malnourished)	10	(40%)	1	(11.1%)	
Preoperative HGS (% predicted)	82.8	(76.2-106.4)	84.8	(74.5-107.1)	0.759
Preoperative SMI (cm^2m^2)	43.6	(35.2-50.9)	57.4	(46.8-61.7)	0.001
Preoperative sarcopenia	21	(84%)	4	(16%)	<0.001
Surgical resection					0.163
• Complete	17	(68%)	9	(100%)	
• Partial	8	(32%)	0	(0%)	
Type of cancer					0.397
• Primary rectal	7	(28%)	1	(11%)	
• Rectal recurrence	12	(48%)	5	(56%)	
• Primary other	2	(8%)	1	(11%)	
• Recurrent other	4	(16%)	2	(22%)	
Rectal or other cancer					0.701
• Rectal	19	(76%)	6	(67%)	
• Other	6	(24%)	3	(33%)	

BMI: Body Mass Index; PG-SGA: Patient-Generated Subjective Global Assessment; HGS: Handgrip Strength; SMI: Skeletal Muscle Index.

III Postoperative Mortality and Complications

There was no difference in mortality between patients that were sarcopenic and non-sarcopenic after surgery, as overall mortality was 0%. As outlined in (Table 5), there was no difference in postoperative length of stay (PO-S 29, IQR 29-46 vs PO-NS 28, 24-59; p=0.489). Additionally, there was no difference in any postoperative complications.

Table 5: Postoperative survival and complications.

	Postoperative sarcopenic patients (n=25)		**Postoperative non-sarcopenic patients (n=9)**		**p-value**
30 day mortality	0	(0%)	0	(0%)	1.000
Postoperative length of stay (days)	29	(29-46)	28	(24-59)	0.489
Total complications	3	(1.0-4.0)	6	(1.5-6.5)	0.072
Postoperative sepsis	11	(44%)	7	(78%)	0.14
Wound complications	12	(48%)	6	(67%)	0.163
Respiratory complications	7	(28%)	6	(67%)	0.120
Gastrointestinal complications	18	(72%)	6	(67%)	0.489
Urological complications	1	(4%)	1	(11%)	0.759
Cardiovascular complications	5	(20%)	3	(33%)	0.645

IV Postoperative Nutrition Related Outcomes

Postoperative BMI and weight were unsurprisingly lower in the sarcopenic population, however as demonstrated in Table 6, there was a greater percent loss of weight in the postoperative non-sarcopenic group. The difference was initially not significant at 7 then 14 days but diverged over time and was significantly different at 21 days (PO-S 3% vs PO-NS 7%, p=0.016) and 3 months (PO-S 7% vs PO-NS 17%, p=0.016) [1-19]. Both PG-SGA and HGS did not correlate with sarcopenia in the postoperative period.

Table 6: Postoperative nutrition related outcomes.

	Postop Sarcopenic Patients (n = 25)		**Postoperative Non-Sarcopenic Patients (n = 9)**		**p-value**
Postoperative SMI	39.2	(34.1-47.9)	54.2	(46.2-61.2)	<0.001
7 day postoperative weight change (%)	-1.34	(-4.6 - +3.8)	-1.4	(-6 - -0.1)	0.471
7 day postoperative BMI (kg/m^2)	24.1	(21.3-27.5)	31.1	(29.9-35.1)	0.001
7 day postoperative PG-SGA					0.618
• A (well-nourished)	11	(44%)	5	(55.6%)	
• B, C (malnourished)	14	(56%)	4	(44.4%)	
7 day postoperative HGS (% predicted)	80.2	(64.2-95)	62.1	(46.1-84.2)	0.102
14 day postoperative weight change (%)	-3	(-6.1 - +4.5)	-5.9	(-8.4 - -3.5)	0.097
14 day postoperative BMI (kg/m^2)	23.4	(20-27.9)	30.4	(28.5-30.4)	0.001
14 day postoperative HGS (% predicted)	81.5	(70.9-92.5)	88.3	(75.1-101.1)	0.324
21 day postoperative weight change (%)	-3	(-7.2 - -0.8)	-7	(-14.6 - -5.6)	0.016
21 day postoperative BMI (kg/m^2)	23.6	(19.9-26)	28.2	(27.5-32.9)	0.001
3 month postoperative weight change (%)	-7.3	(-12.7 - -3.5)	-16.5	(-18.9 - -11.4)	0.016

SMI: Skeletal Muscle Index; BMI: Body Mass Index; PG-SGA: Patient-Generated Subjective Global Assessment; HGS: Handgrip Strength.

Discussion

Although the sample size was not large enough to demonstrate a significant rise in sarcopenia from the pre to postoperative period for pelvic exenteration, the results showed that median SMI significantly decreased from 47.9cm^{2}m^2 (IQR 36.1-54.9) to 43.4cm^{2}m^2 (IQR 35.7-51.1) (p=0.008). It was demonstrated that the most significant preoperative risk factors for postoperative sarcopenia were preoperative sarcopenia, low BMI, weight, and SMI. There was no difference in postoperative complications between those that were sarcopenic and not

in the postoperative period. There was no difference in mortality whether patients were sarcopenic or not, as all patients survived to discharge and at 3 months on follow-up. The increase in the incidence of sarcopenia from the pre to postoperative period reflects the muscle wastage that pelvic exenteration undoubtedly induces. This is reinforced by the significant reduction in SMI across the whole cohort. Furthermore, SMI was significantly reduced even in patients who were non-sarcopenic postoperatively, suggesting that the surgical insult leads to a reduction in muscle mass in all patients.

The high incidence of sarcopenia post-surgery is a multifaceted issue, and poor nutrition intake alone is unlikely the sole determinant. Protein requirements are higher post pelvic exenteration surgery due to the pathophysiologic demands of wound healing, combating potential infections, and an overall systemic inflammatory response [19]. Pelvic exenteration surgery is a major surgical insult and the magnitude of the surgery is reflected in rates of prolonged postoperative recovery and complications [20]. Furthermore, with the majority of patients indicated for surgery due to recurrence, preoperative irradiation and/or chemotherapy would have likely impacted their recovery [21]. Protein losses are also increased due to catabolism and its associated metabolic changes, resulting in lean tissue loss [19, 22]. These catabolic changes may be minimised but are not entirely preventable [23]. It is likely a combination of decreased nutritional intake, increased protein needs and altered protein metabolism that results in the increase of sarcopenia after pelvic exenteration surgery, as was observed in this study.

Oncology patients of higher weights and BMI have been shown in the literature to have lower rates of sarcopenia [24, 25]. Kalantar-Zadeh reported on what they described as the "risk-factor paradox", where high body weight and obesity are found to be protective in wasting diseases such as cancer and its associated cachexia [26]. It has been suggested that this survival advantage is due to the greater energy stores available, able to be drawn on throughout the negative energy balance experienced during the disease state [18]. The cohort in this study demonstrated the same result, with median (preoperative) weight and BMI of postoperatively sarcopenic patients significantly lower than non-sarcopenic patients.

In this study, patients that were non-sarcopenic postoperatively had a significantly higher percentage of weight loss at 3 weeks and 3 months post-surgery than the postoperative sarcopenic patients. This may seem counter-intuitive but likely reflects the great need for energy stores to be utilised in times of high metabolic demand. In cases of sarcopenia, these stores are overall already diminished or unavailable. These energy stores being drawn on during the times of increased nutritional need post-surgery may explain the greater weight loss at 3 months post operation seen in our postoperative non-sarcopenic patients. Although not significant at the 1-week postoperative period, the loss of weight gradually increased over time to become significant at 3 weeks and 3 months thereafter, reflecting the gradual temporal catabolic nature that pelvic exenteration can induce. This suggests longer follow-up to monitor the progress of weight loss and identify at-risk patients is needed. As outlined in Bauer position paper on sarcopenia, patients may benefit from a resistance exercise programme and protein-rich diet postoperatively [27]. Furthermore, prehabilitation is an emerging field showing promise to improving postoperative recovery. In the cardiac surgery population, it has been shown to reduce the length of stay and improve reported quality of life compared with the control populations [28]. Similarly, functional capacity was shown to have improved in the colorectal surgical population [29].

Of note, the PG-SGA was not predictive of sarcopenia in the postoperative period. There are several reasons that may be attributed in part or collectively to this phenomenon. The definition of sarcopenia is highly debated and inconsistently agreed-upon, likely contributing to differences in outcomes across studies utilising HGS as a marker of sarcopenia [30]. Souza reported on a significant correlation between PG-SGA and sarcopenia; however, it is important to note the differences between the two cohorts to explain this aberrancy and why this study did not come to the same conclusion [31]. Although most of the patients in this study suffered from colorectal cancer, Souza's study was reporting on primarily non-surgical patients with more advanced disease. Furthermore, the changes in PG-SGA that would have been reported by this study's postoperative cohort were likely to be similar whether sarcopenic or not. Looking at the four components of the PG-SGA it is clear to see why this method of assessment is likely to be highly confounded by surgical interventions. With regards to change in diet, that would have likely been driven primarily by postoperative surgeons' orders and the anatomical area resected, rather than any sarcopenia-related factors.

Similarly, the physical symptoms would likely have been induced by a surgical intervention such as pelvic exenteration and postoperative pain management. In fact, all three components of the diet, physical symptoms, and activities and function would have deteriorated across the board for both postoperative sarcopenic and non-sarcopenic patients independent of their nutritional status. Furthermore, the weight loss component is confounded by the fact that non-sarcopenic patients lost more weight than sarcopenic patients, as discussed earlier. Hence, it is indicative that the PG-SGA may not be a superior assessment to identify at-risk patients in the postoperative period, being less sensitive and specific than other body-composition measures.

Sarcopenia can have a large effect on the quality of life, functional status and clinical outcomes, even being an independent predictor of disease-free survival in cancer patients [11, 23]. CT scan technology allows sensitive body composition analysis that is more accurate than current methods at identifying sarcopenia in an increasingly obese population [8, 32]. This study has shown an increase in sarcopenia prevalence after patients undergo pelvic exenteration surgery. This muscle wastage needs to be minimised in order to reduce adverse outcomes associated with sarcopenia. Thus, an accurate body composition tool using CT scans could allow for targeted dietetic interventions to those most at risk, resulting in improved patient outcomes. As CT scans are performed routinely in this patient group, their use for accurate body composition analysis is not unreasonable. However, analysis of the scans is a time-consuming process, and therefore more practical strategies are required. A potential method is to identify patients at the highest risk of postoperative sarcopenia, i.e. those at the lower end of normal BMI and/or weight (with their appropriate age, height and gender bracket).

A limitation of our study was the small sample size. Our study was a retrospective cohort study and thus, a limitation was the uniformity of

time to a postoperative CT. A larger prospective study with dedicated CT protocols and timing postoperatively would provide more consistency and accuracy (in particular at 3 weeks and 3 months postoperatively), although they should only be performed where clinically indicated in view of the radiation risk. Furthermore, this cohort of pelvic exenteration patients represents a population undergoing major surgical insult with significant tumor burden, and thus these results cannot be generalised to other postoperative groups.

Conclusion

This study has demonstrated that pelvic exenteration surgery leads to muscle wastage, which will likely lead to an increase in the incidence of sarcopenia in larger studies. This is established by a reduction in SMI from the pre to postoperative period. Multiple factors may be attributed to this change, including preoperative clinical condition, extensive surgery, poor nutritional intake post-surgery, increased protein needs and altered protein metabolism. The practical use of CT scans to sensitively and accurately recognise sarcopenia can allow for the identification of patients requiring further follow-up and monitoring of long-term outcomes. Optimisation of nutritional intake and prehabilitation may demonstrate a long-term improvement in outcomes studied in the future.

Data Availability

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Conflicts of Interest

None.

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