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Running head: Visceral adiposity predicts post-op CD recurrence

Visceral Adiposity Predicts Post-Operative Crohn's Disease Recurrence

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Visceral adiposity predicts post-op CD recurrence

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Running title

Visceral adiposity predicts post-op CD recurrence

MeSH Key words

Crohn Disease, intra-abdominal fat, abdominal obesity, sarcopenia

Summary

Background

Excessive visceral adipose tissue has been associated with poorer outcomes in patients with inflammatory bowel disease.

Aim

We sought to determine whether body composition was associated with outcome in a prospective study of post-operative Crohn's disease patients.

Methods

The POCER study evaluated management strategies for prevention of post-operative Crohn's disease recurrence; subjects were enrolled after resection of all macroscopic Crohn's disease and were randomised to early endoscopy and possible treatment escalation, or standard care. The primary endpoint was endoscopic recurrence at 18 months. 44 subjects with cross-sectional abdominal imaging were studied, and body composition analysis performed using established techniques to measure visceral adipose tissue area, subcutaneous adipose tissue area, and skeletal muscle area.

Results

The body composition parameter with the greatest variance was visceral adipose tissue. Regardless of treatment, all subjects with visceral adipose tissue/height^2 > 1.5 times the gender-specific mean experienced endoscopic recurrence at 18 months, (compared to 47%) [relative risk 2.1, 95% CI 1.5-3.0, P = 0.012]. Waist circumference correlated strongly with visceral adipose tissue area (ρ = 0.840, P < 0.001). Low skeletal muscle was prevalent (41% of patients), but did not predict endoscopic recurrence; however appendicular skeletal muscle indices correlated inversely with faecal calprotectin (ρ = 0.560, P = 0.046)

Conclusions

Visceral adiposity was an independent risk factor for endoscopic recurrence of Crohn's disease after surgery. Sarcopenia correlated with inflammatory biomarkers. Measures of visceral adipose tissue may help to stratify risk in post-operative management strategies.

The POCER study was registered with ClinicalTrials.gov number NCT00989560.

Introduction

Visceral adipose tissue has distinct metabolic activity, cellular composition, inflammatory infiltrate and cytokine production[1]. In Crohn's disease, visceral adipose tissue has a different profile of adipocytokine expression than in healthy controls, and is the main source of serum TNF-α[2], which is a specific target of Crohn's disease treatment. Mesenteric "fat wrapping" of the intestine in Crohn's disease was recognised by Crohn as a feature of the condition[3], and is disease-specific, correlating with transmural inflammation[4]. Inflammatory activity in the submucosal and stromal tissues has been

implicated in post-operative Crohn's disease recurrence, with myenteric plexitis a described risk factor for recurrence[5-8].

There is considerable variation in the anatomical deposition of fat among individuals of the same body mass index and same total fat mass[9,10], with cross-sectional abdominal imaging providing accurate measurement of fat area and volume[10-13]. Patients with Crohn's disease are known to have a higher ratio of intra-abdominal to total abdominal fat, and higher visceral adipose tissue area, than controls[14,15]. Pro-inflammatory genes are up-regulated with increasing visceral adipose tissue volume[16]. In the obese state, visceral adipose tissue is infiltrated by inflammatory cells; adipose tissue macrophages can account for as much as 40 per cent of the cellular mass[17]. The pro-inflammatory milieu of an enlarged visceral adipose tissue compartment may predispose to recurrent Crohn's disease after surgery.

The majority of patients with Crohn's Disease will require surgery for the condition[18], and recurrence after surgery is common, with 48-93% of patients having endoscopic lesions at 1 year post operation[19]. Optimal post-operative management to prevent recurrence has been the focus of much research. Identification of risk factors for relapse and appropriate escalation of therapy appear to improve outcomes and resource utilisation[20-23].

Few patient-related factors have been identified as increasing risk of post-operative Crohn's disease recurrence; smoking status is the most recognised, conferring more than double the risk[19,20,22]. In this study, we sought to determine whether body composition is a predictor of, and relates to, post-operative Crohn's disease recurrence in a cohort of patients who had resection of all macroscopic Crohn's disease.

Materials and Methods

The POCER study was a prospective, randomised controlled trial in post-operative Crohn's disease patients, examining the role of early endoscopic surveillance and treatment escalation for mucosal recurrence. This study has

been the source of a number of publications[20,21,23-28]. Patients were enrolled after surgery for Crohn's disease with resection of all macroscopic disease. All patients received 3 months of metronidazole (400mg orally twice-daily; dose reduced or discontinued if not tolerated). Patients with prior resections, smokers or those with perforating disease also received azathioprine (2mg/kg/day) or 6-mercaptopurine (1.5mg/kg/day) unless intolerant – in which case, adalimumab at standard induction and maintenance doses was used. Patients were randomised 2:1 to colonoscopy 6 months post-operatively (active care) or no colonoscopy (standard care). If patients were on corticosteroids at study enrolment, they were tapered and ceased by week 12. Patients with endoscopic recurrence (Rutgeerts score[29] ≥i2) at 6 months received treatment escalation: to thiopurine, thiopurine with fortnightly adalimumab, or weekly adalimumab as appropriate. The primary endpoint of the study was endoscopic recurrence at 18 months. Stool samples were collected at baseline (pre-operatively) and at 6, 12 and 18 months after surgery; markers of inflammation, including calprotectin, lactoferrin and S100A12 were assayed. Other clinical and biochemical data were collected at 6, 12 and 18-month time points. The study included 174 patients at 17 hospitals in Australia and New Zealand.

Subjects who had an abdominal CT or MRI within 12 months prior to enrolment at the primary POCER study site were identified by cross-reference with that site's radiology database. Scans had been performed as clinically appropriate and were not part of the study protocol, therefore only a subset of the POCER subjects were included in this analysis. Digital Imaging and Communications in Medicine images at L3 and L4-5 levels were imported and analysed for body composition using SliceOmatic 4.3 (TomoVision, Montreal, Canada) by a single experienced operator, who was blinded to study categories and treatments. An intra-observer coefficient of variation of 1.5% was recorded, consistent with ranges of 0.2%-3.4% cited in a validation study[30], which also found inter-investigator coefficient of variation 0.9%-4.8%. The data obtained were de-identified prior to further analysis. For CT images, Hounsfield unit (HU) ranges were used to differentiate between components of body composition; tissue from -30 to +150 HU was segmented as muscle.

Further correction and manual segmentation was performed according to tissue planes. For MRI scans, visual identification of tissue planes by the same operator was used to segment images. Analysis of this nature has been shown to provide similar results as CT analysis in the same subjects[31], using software providing results interchangeable with SliceOmatic[32]. Visceral adipose tissue area, subcutaneous adipose tissue area and skeletal muscle area were calculated for the relevant segments. Ratios between these variables and patient height were calculated. Using previously described formulae[33], estimations were made of appendicular skeletal muscle indices (ASMI), total body fat mass and fat-free mass. Waist circumference was measured from images using a recognised technique[34].

Statistical considerations

Values for body composition parameters were expressed as a proportion of the gender-specific mean value for the cohort. Endoscopic outcomes were assessed at 18 months. Modified intention-to-treat analysis included patients who withdrew prior to 18 months with exit colonoscopy findings carried forward; patients without colonoscopy were assigned a Rutgeerts score of i2 (endoscopic recurrence).

Data were analysed with Prism 6 (GraphPad Software, La Jolla, CA) and SPSS statistics 24 (IBM Corp, Armonk, NY). A P value <0.05 was considered significant. Spearman correlation coefficients were calculated for nonparametric correlations. Mann-Whitney tests were used to analyse differences between means for categorical data. Contingency analysis was performed with Fisher's exact test. Receiver operator characteristic (ROC) curves were used to identify cut-off values between outcome categories.

Ethical considerations

This analysis of the POCER study dataset and acquisition and analysis of previously performed imaging studies was approved by the Human Research Ethics Committee of St Vincent's Hospital Melbourne (approval LRR: 054/15),

as was the original POCER study (approval HREC-A 077/09). The POCER study was registered with ClinicalTrials.gov number NCT00989560.

Results

Of the 66 subjects enrolled at the primary study site, 44 patients (67%) had imaging performed at that site, with available electronic images, prior to study entry. Of these, 33 had been assigned to active care, and 11 to standard care, with 10 patients withdrawing before 18 months (figure 1). Characteristics of the subjects are described in table 1. The median time between abdominal imaging and surgery was 56 days (IQR 22-127 days prior to surgery); 25 studies were CT scans and 19 were MRI. There was no difference in rates of endoscopic recurrence in groups divided according to indication for scan (P = 0.928). There were no differences in any anthropometric or body composition parameter between the high risk and low risk groups, nor between those randomised to endoscopy or standard care. In the endoscopy group, there was no statistically significant difference in body composition parameters between 8 patients who stepped up therapy and those who did not. Steroid use in the preoperative period was not associated with a difference in mean values of any body composition measurement or derivative, but was associated with a significantly smaller change in faecal calprotectin from baseline to 18 month measurements (mean change -173µg/g ± 964 vs. -1958µg/g ± 1202, P = 0.013). Preoperative steroid use (within 2 weeks of surgery) was also associated with a "high risk" categorisation (P = 0.003) and initial treatment with adalimumab (P = 0.008). The use of steroids was not different between those who had endoscopic recurrence (11/25) and those who did not (8/19, P = 1.000).

Relationships with adipose tissue

Mean values of body composition measurements are shown in table 2. The parameters with the greatest variance were the visceral adipose tissue area at L3 [expressed as a proportion of gender mean, with SD 0.909] and this value divided by height squared ("visceral adipose tissue/height index" [VHI]

[expressed as a proportion of gender mean, with SD 0.937]). Both exhibited an asymmetric distribution: there was significant rightwards skew (VHI 2.14) and excessive kurtosis. Other body composition parameters, such as BMI, did not demonstrate such variability or departure from a normal distribution (figure 2). Of this cohort of IBD patients, 29.5% had a BMI in the overweight or obese range, compared with 63.4% in the general Australian population[35].

Area under the ROC curve analysis showed VHI/gender mean was more sensitive and specific than visceral adipose tissue area, or visceral adipose tissue area/height^2, for detecting endoscopic remission, although this only became a discriminant at higher than mean values. A cut-off value of 1.5 times the mean was identified. All patients with visceral adipose tissue area, or VHI, >1.5 times the gender-specific mean were assigned endoscopic recurrence at 18 months (figure 2), whereas 47% of those with VHI ≤1.5 × (gender mean) had recurrence (relative risk 2.1 [CI 1.5-3.0], P = 0.012). Three subjects with VHI >1.5 × (gender mean) did not undergo endoscopy at the 18-month endpoint – all experienced clinical recurrence prior (at 4.7 months, 15.1 months and 17.3 months respectively). High/low risk status, randomisation outcomes, and drug treatments including step-up therapy were not significantly different between these patients and the remainder of the cohort. Early withdrawal rate did not vary significantly between these groups (P = 0.322).

Contingency analysis found that VHI >1.5 × (gender mean) was highly specific for endoscopic recurrence (100% [82%-100%]) with sensitivity of 29% (12%-51%). Positive predictive value was 1.00 (0.59-1.00) and negative predictive value 0.53 (0.35-0.70). Above a cut-off visceral adipose tissue area/height^2 value of 51cm^2/m^2, all 8 patients had endoscopic recurrence (figure 2).

There was no relationship between other body composition parameters and outcome measures, disease activity indices or biochemical markers such as C-reactive protein or faecal calprotectin. There was no significant difference in

the mean CDAI at 18 months between those with VHI greater than or less than 1.5 times the gender mean (117.6 vs. 85.0, P = 0.341). 43% of those with VHI >1.5 × (gender mean) had taken steroids at the time of surgery, this was the same proportion as those with VHI ≤1.5 × (gender mean) [P = 0.938]. The mean VHI was not different between those who had not taken steroids and those who had (30.99 cm^2/m^2 vs 35.60, P = 0.884).
From chi-square analysis, the relative risk of recurrence in patients with excessive visceral adiposity (2.1) was similar to that of smokers in the sample selected in this analysis (RR 2.1 [1.2-3.6], P = 0.015).

Waist circumference (WC) strongly correlated with fat area measurements, in particular visceral adipose tissue area (ρ = 0.840, P < 0.001); however, in patients with visceral adipose tissue area >1.5 times the gender mean, this correlation between visceral adipose tissue area and waist circumference was not significant. The range of WC measurements was much smaller than the range of VHI, with a more symmetrical distribution (skewness 0.93 vs. 2.35) and less kurtosis. The range of WC values as a proportion of gender mean was 0.77-1.38 (IQR 0.89-1.10), whereas the VHI range was 0.12-4.81 (IQR 0.37-1.28). This smaller variation and symmetrical distribution from the mean diminished the discriminative value of waist circumference in comparison to VHI, although all 4 patients with a waist circumference >1.3 times the gender mean had endoscopic recurrence. Gender-specific WC cut-off values for prediction of recurrence could not be identified, but all 5 (3 female, 2 male) patients with WC > 105cm experienced recurrence (P = 0.060).

Relationships with skeletal muscle

Low muscle mass was prevalent: 41% of patients had a calculated ASMI consistent with sarcopenia as defined by an appendicular skeletal muscle index less than two standard deviations below a young adult mean measured by whole body dual-energy X-ray absorptiometry[36,37]. No patient had the combination of low muscle mass and obesity (“sarcopenic obesity”). Skeletal muscle area did not predict endoscopic outcomes. There was a moderate

inverse correlation between skeletal muscle area and faecal inflammatory markers (calprotectin, lactoferrin and S100A12) at baseline. Calculated ASMI also showed inverse correlation with faecal markers (ρ = -0.564, P = 0.005 for calprotectin; correlation coefficients and P values similar for other faecal markers [figure 3]). This relationship was consistent across the study duration, with an inverse correlation between ASMI and the change in calprotectin from baseline to 18 months (ρ = 0.560, P = 0.046) suggesting that increased muscle mass was associated with reduced intestinal inflammation regardless of treatment effects (figure 3). The mean baseline faecal calprotectin was significantly higher in patients with sarcopenia (2570µg/g ± 879 vs. 1095µg/g ± 1074, P = 0.003).

Discussion

Identifying excessive visceral adipose tissue as a risk factor for post-operative Crohn's disease recurrence, regardless of treatment, in the setting of a prospective randomised study is a novel finding. As a proof of concept study, we chose an arbitrary measure of visceral adiposity with internal reference to describe the poorer outcomes experienced by subjects with a corrected visceral adipose tissue significantly higher than the median. The large range of values of VHI compared with anthropometric measures such as waist circumference allowed identification of statistically significant predictors of outcome within a small dataset. In the POCER study, smoking was identified as a risk for endoscopic recurrence with a relative risk of 2.8[20]. Excessive visceral adiposity conferred a similar increase in relative risk in our analysis.

Lifetime steroid exposure was not assessed in this study, and the effect of steroid use on body composition parameters in the short term is not well-defined in patients with inflammatory diseases, with visceral adipose tissue accumulation being described as a characteristic of Crohn's disease, independent of steroid use[14,38-40].

The prevalence of sarcopenia in this cohort of patients requiring surgery for complicated Crohn's disease was an expected finding, however, the association between low skeletal muscle mass and faecal calprotectin has not previously been described.

Successful risk stratification and appropriate perioperative management are key to preventing postoperative recurrence of Crohn's disease[41], with previous studies associating increased hazard with patient and surgical parameters such as smoking, disease behaviour, resection length and history of previous resection[19], serology[28,42] and microbial factors[26]. Prior steroid use has been associated with a reduced risk of post-operative recurrence in a meta-analysis[43]. Individualised post-operative medical care based on risk factors, with early monitoring for recurrence and escalation of therapy if necessary, allows cost-effective management[20-22,44,45].

This study is limited by the post-hoc analysis of a sample of the entire study, with sample size preventing more rigorous subgroup regression analysis, including the role of body composition in drug efficacy and therapeutic monitoring. Although randomisation to active treatment, smoking status and excessive visceral adiposity were identified as variables contributing to risk of Crohn's disease recurrence, larger patient numbers and more data regarding prior therapy and surgical findings may have allowed more robust analysis of the interaction between these and other possibly contributory factors such as corticosteroid use, disease duration and extent of resection. Abdominal imaging was not part of the study protocol, and there was variation in the time between scan and surgery. However, we have previously shown that a strong correlation existed between body composition analysis using abdominal imaging obtained as part of routine clinical care, compared with dedicated whole body dual energy X-ray absorptiometry (DXA) studies performed at a different time in Crohn's disease patients; with scans performed a median 21 days (IQR 0-135 days) apart. Notably, there was no correlation between time between scans and difference between the values[33] suggesting that despite active intestinal inflammation or symptoms, body composition parameters remained stable over this period. Nevertheless, the strengths of a prospective

trial support the data obtained, with all subjects having no macroscopic disease at induction, defined follow-up and predetermined end points.

Our paper adds to a small, but growing, body of literature regarding the role of body composition in inflammatory diseases. Crohn's disease patients in clinical remission have been found three times more likely than healthy controls to have sarcopenia[46], with a recent systematic review[47] finding that body composition parameters often varied from population norms, including lower bone mineral density[48], lower body mass index (BMI) and lower fat-free mass[49,50]. Expansion of the visceral adipose tissue compartment in Crohn's disease is also described, with a four-fold increase in adipocyte number compared to controls[51] and an increased volume of visceral adipose tissue[15,38,52].

Measures of visceral adipose tissue have been associated with the likelihood of Crohn's disease recurrence in a retrospective cohort analysis of post-surgical patients[53], The current study validates those findings in a prospective study and in another ethnic population, their subjects exclusively being Han Chinese. In that study, a higher ratio of visceral adipose tissue to subcutaneous adipose tissue (mesenteric fat index) correlated with recurrence, consistent with another small retrospective study which demonstrated a higher incidence of penetrating or stricturing disease in patients with a higher mesenteric fat index[54]. Visceral adiposity - but not BMI - was a risk factor for longer operative times, more blood loss, longer intestinal resection, more post-operative ileus and more complications overall in another retrospective cohort study using pre-operative CT scan to perform body composition analysis[39]. We do not have data regarding these surgical factors in our study. An observational cohort study found that penetrating or stricturing Crohn's disease was associated with an increased visceral adipose tissue/fat mass ratio, and that a high visceral adipose tissue/fat mass ratio was associated with increased disease activity at followup[15]. High mesenteric fat index, but not BMI nor abdominal circumference, was associated with 30-day morbidity in a retrospective cohort of 143 patients[55]. Conversely, a lower mesenteric fat index has been associated with more post-operative infectious

complications in Crohn's disease[56]. The mesenteric fat index or visceral adipose tissue/fat mass ratio were not associated with any of the outcome measures in our study.

Increased visceral adipose tissue is associated with alterations in gut microbial population ratios[57], with similar alterations present in inflammatory bowel disease[58,59]. This interplay between an altered microbiota and host immune system is another possible mechanism of visceral adiposity being associated with Crohn's disease recurrence.

We found that inflammatory biomarkers showed an inverse correlation with skeletal muscle mass; although this has not previously been described with faecal calprotectin, in patients undergoing colorectal surgery for malignancy, low muscle mass was associated with higher serum calprotectin[60]. While this association may be explained by the fact that inflammation and cachexia are catabolic states, causing reduced muscle mass, there may be a bidirectional influence. Skeletal muscle has been shown to exert an anti-inflammatory effect in inflammatory diseases through the action of myokines such as IL-6, IL-7 and IL-15[61,62].

In this analysis of a set of patients from a prospective interventional study, excessive visceral adiposity was an independent risk factor for endoscopic recurrence of Crohn's disease after surgery. Sarcopenia also correlated with elevations in faecal calprotectin. Further research may lead to validation of these findings and the integration of measures of visceral adipose tissue into post-operative management strategies.

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Authorship statement

Darcy Holt is the guarantor of this article. All authors devised the study. DH, AH, MK and PDC collected the data. DH performed the analysis and drafted the manuscript. All authors contributed to the critical review and revision of the manuscript. All authors approved the final version of the article, including the authorship list.

Conflicts of interest and sources of funding

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Tables

Table 1 Characteristics of study participants

Female, n	24	54.5%
Age, y ± SD	37.8±14.2	
Disease duration (mean ± SD)	5.5±4.0	
BMI, kg/m^2 (mean ± SD)	23.5±4.9	
Initial post-operative drug therapy		
Metronidazole only	8 (17.8%)	
Thiopurine	26 (57.8%)	
Adalimumab	10 (22.2%)	
Steroid use, n	20	45.5%
Days between scan and surgery	56 (22-127)	

(median ± IQR)		
Indication for scan, n		
	Active disease/inflammation	14
	Obstructive/stricture	14
	Penetrating/fistulising	6
	Perianal disease	1
	Information unavailable	9

Table 2 Mean values of body composition parameters (BMI: body mass index, VAT: visceral adipose tissue area, SAT: subcutaneous tissue area, IMAT: intermuscular adipose tissue area, SM: skeletal muscle area)

	Gender			*Endoscopic outcome*		
	Male	Female	P	Remission	Recurrence	P
	n = 20	n = 24		n = 19	n = 25	
Weight, kg (mean ± SD)	76.9 ± 13.0	65.1 ± 18.6	0.019	72.8 ± 14.8	68.8 ± 18.9	0.451
Height, m (mean ± SD)	1.80 ± 0.07	1.66 ± 0.08	<0.001	1.77 ± 8.39	1.70 ± 0.11	0.019
BMI, kg/m^2 (mean ± SD)	23.66 ± 3.54	23.39 ± 5.87	0.855	23.12 ± 3.29	23.84 ± 5.89	0.614
Waist circumference, cm (mean ± SD)	89.0 ± 12.7	87.1 ± 15.0	0.65	87.9 ± 9.8	87.9 ±16.5	0.995
VAT, cm^2 (mean ± SD)	126.7 ± 106.0	75.2 ± 73.9	0.076	88.7 ± 49.5	106.1 ± 115.6	0.504
SAT, cm^2 (mean ± SD)	122.5 ± 76.7	170.2 ± 132.4	0.144	149.9 ± 79.4	147.5 ± 133.2	0.942
IMAT, cm^2 (mean ± SD)	6.7 ± 4.2	4.5 ± 3.2	0.056	6.2 ± 3.9	5.0 ± 3.8	0.310
SM, cm^2 (mean ± SD)	155.4 ± 28.2	104.9 ± 20.7	<0.001	138.1 ± 37.1	120.0 ± 31.9	0.096

Figure legends

Figure 1 Trial profile and patient disposition

Figure 2 (A) Values for BMI (body mass index) were clustered around the gender-specific mean. VHI (visceral adipose tissue area/height^2) exhibited a

greater range, with all subjects with VHI >1.5 times the gender mean demonstrating endoscopic recurrence; (B) All subjects with visceral adipose tissue area/height^2 (VHI) >51cm^2/m^2 had endoscopic recurrence

Figure 3 (A) A negative association between calculated appendicular skeletal muscle index (ASMI) and faecal calprotectin existed, and (B) was consistent across the study period

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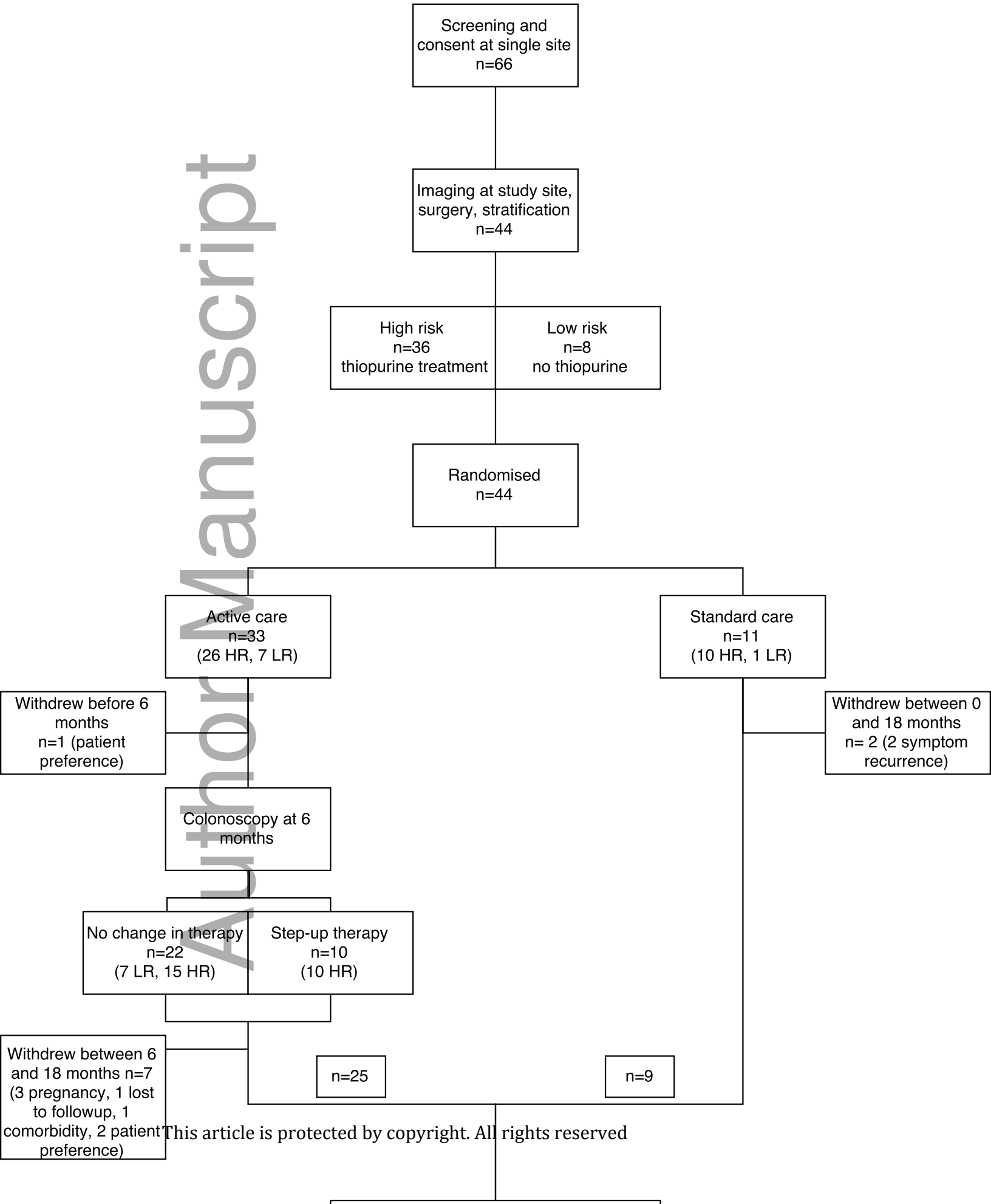

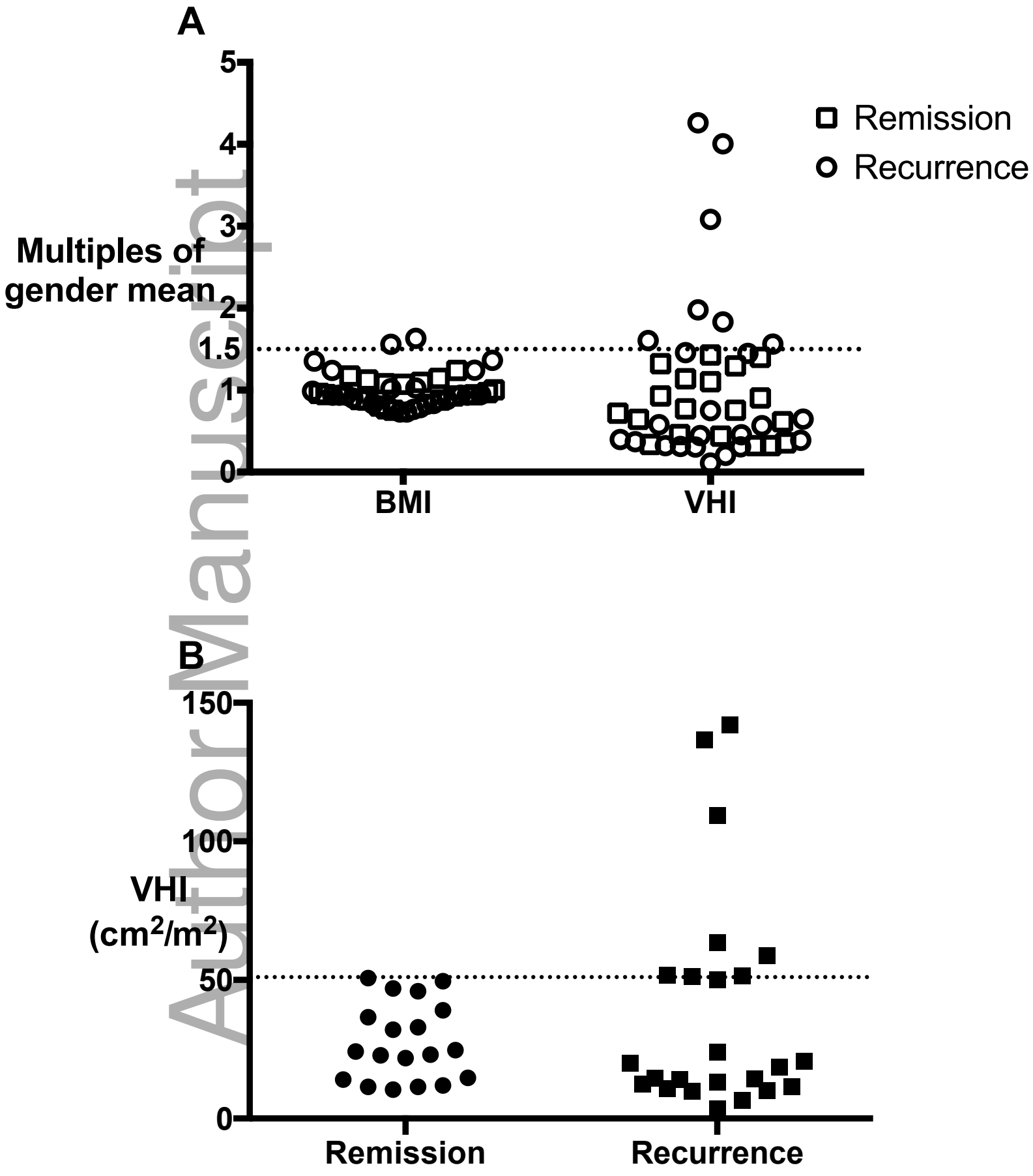

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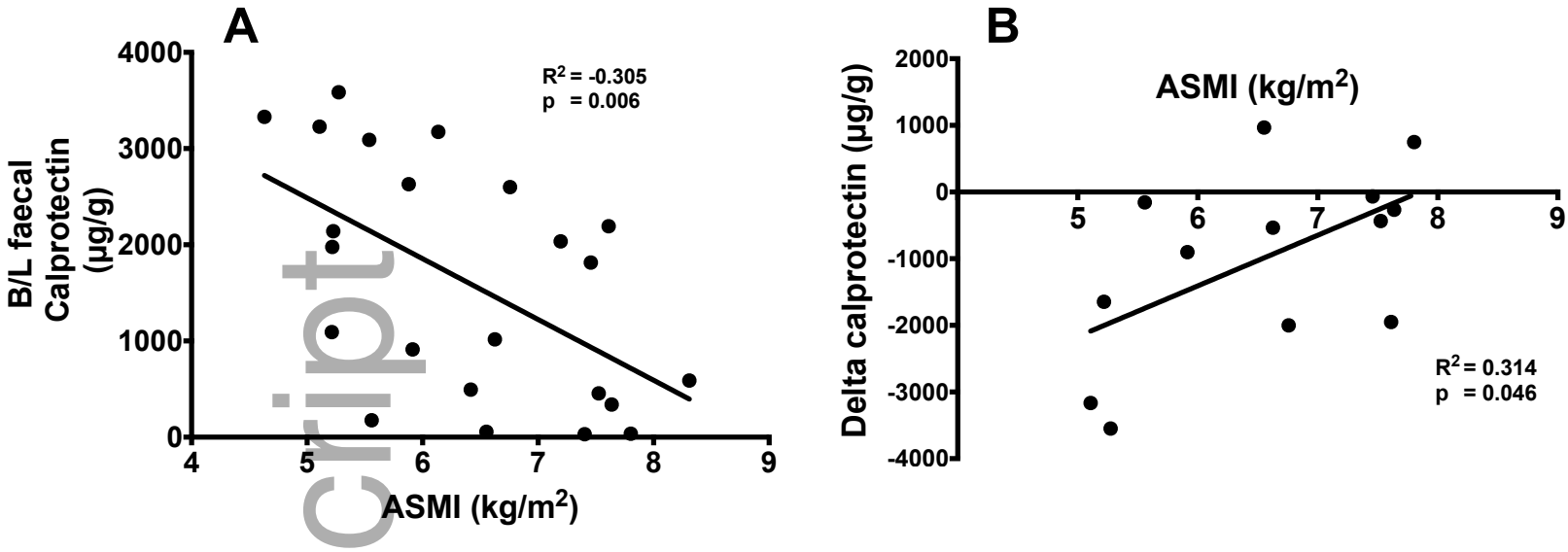

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