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ORIGINAL RESEARCH

Can Radiological Visceral Adiposity Analysis in Acute Pancreatitis Aid in Identifying Underlying Etiology? Assessing the Clinical Potential of Quantitative Radiological Analyses of Visceral Adiposity

Michael Sala[1], Mina Guirgis*[1,2,3], Philip Misur[4], Ruwan Wijesuriya[1]

1. Department of General Surgery, St. John of God Midland Hospital, Midland, Western Australia, Australia
2. Department of Upper GI Surgery, St. George Hospital, Sydney, New South Wales, Australia
3. School of Medicine, University of Otago Christchurch, Christchurch, New Zealand
4. Department of Radiology, Royal Perth Hospital, Wellington Street, Perth, Western Australia, Australia

* **Corresponding author.** Contact: drminaguirgis@gmail.com

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Abstract

Purpose: This study aims to investigate the relationship between visceral adiposity and the possible etiologies of acute pancreatitis. Obesity creates low-grade inflammation and evidence supports an association between obesity and inflammatory conditions such as pancreatitis. CT imaging is utilized in assessing pancreatitis severity and complications but also offers the chance to quantitatively measure visceral fat area (VFA) and subcutaneous fat area (SFA). Given the metabolic role that fat plays, we hypothesized that different body fat distributions, as measured by these areas, may be associated with different etiologies. Further, this also allows us to explore a relationship between severity, etiology, and the fat distributions in patients with acute pancreatitis.

Method: Retrospective observational cohort study of all patients admitted to a single center. The VFA, SFA, their ratio (VFA/SFA) and total fat area (TFA) were calculated using a semi-automatic algorithm.

Results: 518 patients were admitted with acute pancreatitis over a three-year period. 177 patients underwent CT imaging. Gallstone pancreatitis patients had higher VFA and TFA measurements while alcoholic pancreatitis patients had lower measurements. Patients with pancreatitis with no clear cause had the lowest VFA/SFA ratio. Increasing VFA was associated with increasing severity in a univariate logistic regression model ($p = 0.01$) but this association diminished in a multivariate model accounting for etiology ($p = 0.09$).

Conclusion: The pattern of fat distribution differs amongst the etiologies of acute pancreatitis, as this likely reflects multiple contributing pathogenic mechanisms. Patients with gallstone pancreatitis had disproportionately more visceral fat, alcohol had the least overall fat, and those without a clear cause had the lowest VFA/SFA ratio. Etiology is strongly associated with body fat distribution. Severity is associated with increased visceral fat, but much less so when etiology is controlled for. The radiological assessment of fat distribution thus can give clues to associated etiology.

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Introduction

Acute pancreatitis is a common and significant acute inflammatory disease, and its incidence continues to increase worldwide (1,2). Further, it can often be an unpredictable disease process that can be difficult to classify. Most patients will have a mild episode of acute pancreatitis that usually resolves without complications within one week. However, 20% of patients will have a moderate or severe episode (3-5). This is associated with significant morbidity that presents as an array of many different complications including pancreatic necrosis, infection, organ failure and diabetes. Severe episodes of pancreatitis can have a mortality rate of up to 40% (6). Such heterogeneity in presenting complications and end outcomes — from very mild to severe disease — has sparked much interest in developing scoring and classification systems to aid in prognostication and management over the past three decades (3). The revised Atlanta classification from 2013 was a landmark step in helping categorize the disease to clarify treatment (5). Since then, there has been increasing evidence to suggest the first 24 hours are most crucial for identifying high-risk patients who may benefit from more aggressive monitoring and therapy. Many laboratory markers and peptides have been investigated to assist in stratifying patients with acute pancreatitis, but despite such intense interest, mortality rates have not improved (7,8). This is because the disease process is the result of multiple and interrelated pathological processes that can be difficult to characterize in a clinical assessment. Therefore, it is worthwhile to continue to explore relationships between measurable clinical, biochemical and radiological parameters that are risk factors for pancreatitis, along with the various associated mechanisms that influence disease progression, so that we may better be able to judge a patient's clinical trajectory.

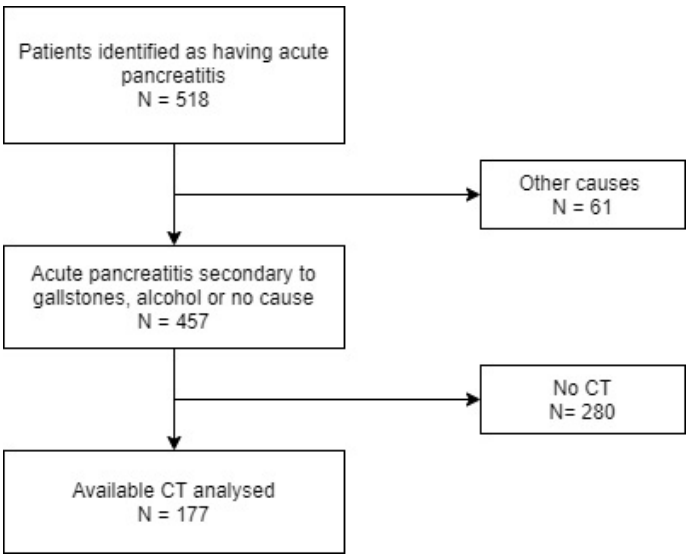
One independent risk factor for pancreatitis severity is obesity. The rise in pancreatitis incidence has at least been partly attributed to the rise in obesity for the last four decades (9). Similarly, obesity (a state of chronic inflammation) can also be associated with other inflammatory diseases such as diverticulitis (10). Importantly, however, it is the visceral fat distribution that can be shown to produce proinflammatory cytokines that propagate inflammatory states (11). Given the ease of availability and common use of CT imaging in acute surgical conditions, there has been growing research focusing on quantitative radiological analyses to ascertain whether certain fat distribution patterns can aid in prognostication (12,13). In addition to prognostication, identifying the underlying etiology of pancreatitis is crucial as it allows for possible interventions to reduce the risk of recurrent pancreatitis. However, identification of etiology can be difficult, and up to one third of patients may have no initial cause found. There is also evidence to suggest that current diagnostic tools may miss occult biliary disease, as some patients with recurrent "idiopathic" pancreatitis may benefit from cholecystectomy (14). It is also well known that alcohol is a risk factor for pancreatitis and alters fat metabolic pathways (15) and so this also suggests alcoholic patients may be prone to having a predilection for a certain fat distribution. The metabolic role that fat plays in the pathogenesis of disease, and the uncertainty in establishing the etiology and prognosis of acute pancreatitis in many patients, prompted us to explore the relationship between measurable fat parameters, etiology and severity. This may then ultimately influence clinical judgement and management decisions.

Methods and materials

Patient selection

A retrospective cohort study was performed in a single metropolitan center with 24-hour acute general surgery and radiology services. All patients presenting with an admission code of acute pancreatitis were identified between July 2016 and August 2019. Patients were identified as having mild, moderate, or a severe admission of acute pancreatitis according to the revised Atlanta classification. Patients were then subgrouped according to the etiology of their admitting episode. Patients were classified as having no clear cause for their pancreatitis if investigations failed to find an attributable etiology. They were not classified as idiopathic, as not all patients underwent cross-sectional and endoscopic imaging and adjunctive blood tests to look for rarer causes. Patients who had an etiology other than gallstones, alcohol or no cause were not included in this analysis because the conditions were too sparse to form a broad judgement on the fat distribution. Patients that had a CT scan within one year of admission were included in the study, as summarized in Figure 1. Demographic data collected included sex, age and an updated Charlson's comorbidity index and score. Ethics approval was obtained from the St. John of God Health Care Human Research and Ethics Committee (Ref: #1765).

Figure 1. Patient selection pathway.



Imaging analysis

Using custom-designed software, the cross-sectional area of visceral and subcutaneous adipose tissue was semi-automatically segmented based on HU intensity, frequency and spatial analysis at the L4/L5 intervertebral disc. The software made the process of computing the fat area relatively easy and quick to do. The L4/L5 disc was done as it is easily reproducible and minimizes cross-sectional imaging of bone and other visceral organs. The algorithm semi-automatically labelled the Visceral Fat Area (VFA) and Subcutaneous Fat Area (SFA) regions of interest. All regions of interest were manually inspected, and mislabeled pixels were manually reassigned. Patient's fat regions that exceeded the image frame of the scan were included by manually estimating the shape and size of the abdomen (Figures 2a-d).

Statistical analysis

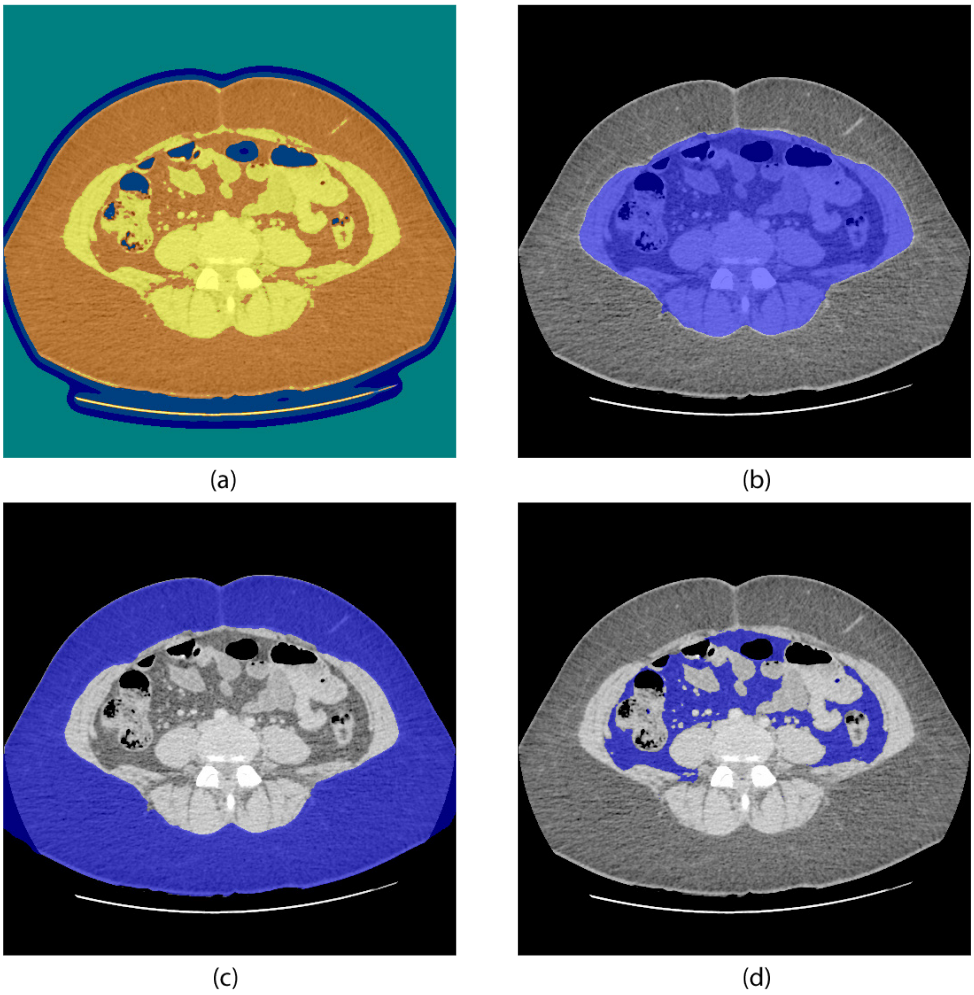
Analysis was performed in MATLAB with a statistical test of $p < 0.05$ considered significant.

For categorical data where the normal distribution could approximate the binomial distribution, the Chi-squared test statistic was used to determine group differences. When this was not the case Fisher's exact test was used.

Untransformed and log transformed histograms of the fat areas were inspected and the Shapiro-Wilk test used to assess for normality. When distributions were found to lack normality, non-parametric analysis of the data was conducted.

The median of each fat group is reported, and the confidence interval of the sample median was calculated by the bootstrap method. This was to demonstrate sample variance within the subgroup only (as data was heterogenous and skewed), so it is important to note that this cannot be used to determine between group differences.

To compare between group differences; analysis of the variance (ANOVA) of the VFA, SFA, TFA, and VFA/SFA ratios among subgroups by etiology, sex and severity



Figures 2a-d. Image segmentation algorithm identifying regions of interest. (a) Algorithm creates an array of spatial, intensity and texture information that then uses k-means clustering to segment the images. (b) Spatial information is checked by the user to ensure the border of the abdominal wall is correctly drawn. (c) Subcutaneous region of interest is drawn with the user manually labelling a region extending beyond the limits captured by the CT image. (d) Visceral region of interest is drawn and mislabeled pixels in the lumen of the intestines are corrected for.

was conducted. One-way ANOVA of age and Charlson's comorbidity scores were also compared among subgroups by etiology.

The Kruskal-Wallis one-way ANOVA was used to test for distribution differences where normality did not hold. Post-hoc comparisons using the Dunn–Šidák correction were used to determine subgroup differences.

A univariate and multivariate logistic regression was conducted to explore the relationship between etiology, visceral fat, and severity.

Results

518 patients with a diagnosis of acute pancreatitis were admitted to this single center over a three-year period. 167 patients (32%) were identified as having gallstones pancreatitis, 120 patients (23%) identified as having alcohol-related pancreatitis, and 169 patients (33%) did not have an identifiable underlying cause of pancreatitis. 61 patients (12%) had other causes of pancreatitis and were not included for study. 177 patients had a CT scan, and the groups are summarized in Table 1. There was no detectable difference between patients having a CT and etiology ($p = 0.62$). While the proportion of those with moderate or severe episodes of acute pancreatitis secondary to alcohol and gall stones were 19% and 17%, respectively, higher than those without a clear cause at 6%, this was not found to be statistically significant, $p=0.13$ (see Table 1). The aggregated median VFA was 159 cm^2, SFA 285 cm^2, TFA 472 cm^2 and VFA/SFA Ratio 0.57.

Demographics

Patients with gallstones were statistically more likely to be older, have ischemic heart disease, congestive cardiac failure, liver disease (typically fatty liver) and diabetes with an end-organ complication. The mean Charlson comorbidity score did not demonstrate significant differences between etiology groups. These results are summarized in Table 2.

Males were over-represented in the sample and were heterogeneously distributed between groups. Males were found to have disproportionately more visceral fat, with the median measured at 172 cm^2 compared to females at 150 cm^2 (Ratio of 0.52 vs 0.82). Females were found to have more subcutaneous and overall total fat, with the median measured at 347 cm^2 and 485 cm^2 compared to males at 253 cm^2 and 461 cm^2. All these findings were statistically significant ($p < 0.05$).

Severity

An association between increasing VFA and the VFA/SFA ratio was found with increasing severity. The cohort was only sufficiently powered to find a statistically significant difference between mild pancreatitis and a combined group of moderate or severe pancreatitis (see Table 3). SFA and TFA did not appear to significantly influence severity.

Patients with gallstones or alcohol etiologies were more likely to experience a severe episode than those with no clear cause.

Etiology

Fat distribution by etiology is summarized in Table 4 and the boxplot in Figure 3.

Patients with gallstone pancreatitis had disproportionately more visceral, subcutaneous and total fat than those with alcoholic or pancreatitis of no clear cause.

Patients without a clear cause for their pancreatitis had the lowest ratio of visceral to subcutaneous fat; 0.48 vs 0.58 for alcohol ($p = 0.03$) and 0.68 for gallstones ($p < 0.001$).

Patients with alcoholic pancreatitis had the least amount of fat overall at 351 cm^2, compared with pancreatitis of no clear cause at 462 cm^2 ($p = 0.14$) and gallstones at 530 cm^2 ($p < 0.001$).

Multivariate analysis

Using a univariate logistic regression model, an association between log(VFA) and severity ($p = 0.01$) was confirmed, but when combined in a multivariate model to account for etiology this association became non-significant ($p = 0.09$). This can be accounted for the well-known relationship between gallstones and obesity that would contribute to

Table 1. Patients identified as having acute pancreatitis within the time period.

	No Clear Cause		Alcohol		Gallstones		p value
Total patients	169	33%	120	23%	167	32%	
Mild cases	159	94%	97	81%	139	83%	0.13*
Moderate or severe cases	10	6%	23	19%	28	17%	0.13*
Total patients with a CT	69	41%	48	40%	60	36%	0.62†

** Chi-square test of severity between all etiology groups.*
† Test between those with and without a CT between etiology groups.

Table 2. Demographic data of included patients, categories are expressed as frequencies and a proportion of the sample.

	No Clear Cause		Alcohol		Gallstones		p value
Median age years (IQR*)	61	(45-70)	51	(39-66)	68	(45-79)	<0.001
Male	40	58%	40	83%	42	70%	0.01
Female	29	42%	8	17%	18	30%	0.01
Ischemic heart disease	8	12%	7	15%	18	30%	0.02
Congestive cardiac failure	5	7%	4	8%	13	22%	0.03
Peripheral vascular disease	3	4%	3	6%	5	8%	0.65
Cerebral vascular event	3	4%	2	4%	2	3%	1.00
Dementia	1	1%	1	2%	1	2%	1.00
Connective tissue disorder	4	6%	3	6%	2	3%	0.76
Liver disease (mild)	25	36%	3	6%	2	3%	0.29
Liver disease (moderate/severe)	0	0%	5	10%	1	2%	0.004
Diabetes with no complications	13	19%	7	15%	18	30%	0.12
Diabetes with end-organ complication	0	0%	0	0%	6	10%	0.002
Chronic pulmonary disease	12	17%	7	15%	13	22%	0.63
Peptic ulcer disease	1	1%	3	6%	2	3%	0.38
Hemiplegia	0	0%	1	2%	0	0%	0.27
Moderate or severe CKD	3	4%	1	2%	4	7%	0.54
Solid tumor	2	3%	3	6%	3	5%	0.67
Metastatic tumor	3	4%	0	0%	0	0%	0.11
Leukemia	1	1%	1	2%	1	2%	1.00
Lymphoma	0	0%	1	2%	0	0%	0.27
AIDS	0	0%	0	0%	0	0%	0.81
Mean score	1.6	(1.2-2.0)	1.7	(1.2-2.6)	2	(1.6-2.5)	0.22
Total patients	69	39%	48	27%	60	34%	

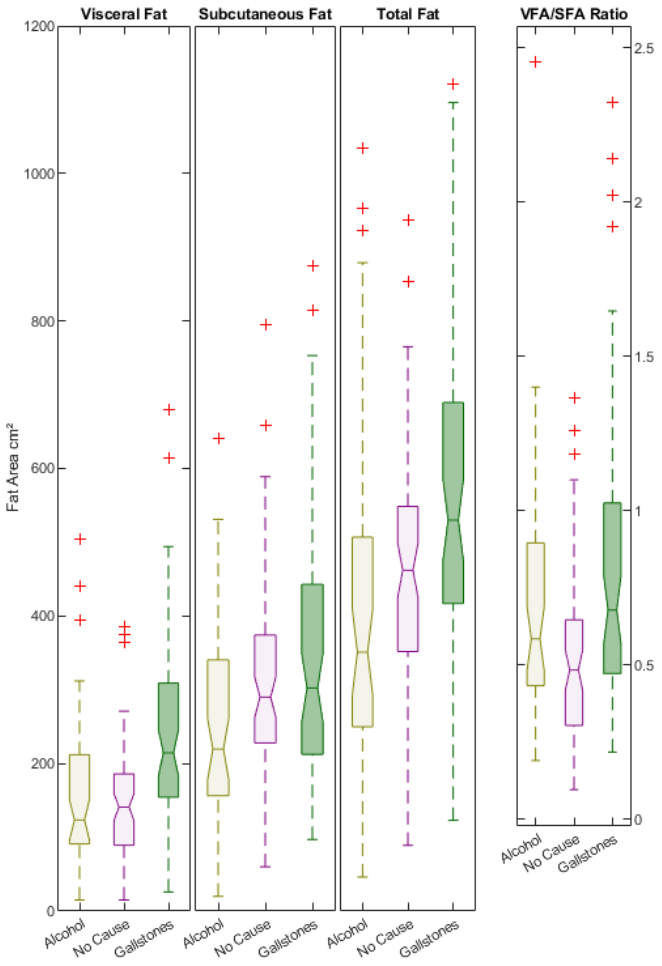
* *Interquartile range*

Table 3. Median fat areas by severity (95% confidence interval using bootstrap method).

	Mild (CI)		Moderate or severe (CI)		
Patients	121		56		p value
VFA* (cm^2)	145	(128-160)	190	(180-225)	0.002
SFA† (cm^2)	276	(237-302)	294	(283-372)	0.24
VFA/SFA‡	0.51	(0.47-0.61)	0.67	(0.66-0.89)	0.01
TFA§ (cm^2)	438	(376-474)	507	(472-582)	0.17

* *Visceral fat area*
† *Subcutaneous fat area*
‡ *Visceral fat area to subcutaneous fat area ratio*
§ *Total fat area*

Figure 3. Boxplot distribution of fat distribution between subgroups of patients with acute pancreatitis demonstrating median, quartiles and outliers.



Using a univariate logistic regression model, an association between log(VFA) and severity (p = 0.01) was confirmed. When using a multivariate model that incorporates only VFA and etiology subgroups, the most significant variables in the univariate analysis, this association became non-significant (p = 0.09). Other models incorporating all terms and interaction effects do not change the test of significance and so only the simplified multivariate analysis is presented in Table 4.

Discussion

The results demonstrate that patients with different causes of pancreatitis have different fat distributions. To our knowledge, this is the first study to quantitatively demonstrate this association. Most studies have previously focused on the association between increasing severity and visceral fat (11,16-18). We also confirmed this finding, but when we account for etiology in a logistic regression model the strength of the association between visceral fat and severity became nonsignificant. We attribute this to the well-known association between gallstones and obesity. We suspect if this study had a higher power, a multivariate model would probably have found a significant result, as visceral fat also affects other pathological mechanisms that contribute to severity. Most importantly. however, it is the strong association between increasing VFA and gallstones that is established in this study. Alcoholic patients were found to have the least over all fat, which is probably attributable to patients presenting with malnutrition or in chronic caloric deficits. As the disease process is heterogenous, it is no surprise that distinct phenotypical fat distributions between different etiologies emerged, owing to the multiple pathogenic mechanisms involved in the development of pancreatitis and the metabolic role of fat.

Historical accounts of fat necrosis dating to the turn of the twentieth century implicated fat in the disease process (19). Over time, the association between obesity and pancreatitis has become more clearly linked and demonstrated (20). Evidence suggests that obesity is a low-grade inflammatory state, with visceral fat felt to be more metabolically active and a larger driver of this process (21,22). Visceral fat contributes to impaired immune function by increasing levels of interleukin-6, tumor necrosis factor-α, and reducing adiponectin (an anti-inflammatory adipokine), amongst other adipocyte cytokines that are also implicated in dysregulation of the systemic inflammatory response syndrome (SIRS) (23-25).

Table 4. Median fat areas by etiology (95% confidence interval using bootstrap method).

	No Clear Cause (CI)		Alcohol (CI)		Gallstones (CI)		p value
VFA* (cm^2)	141	(131-168)	124	(130-195)	214	(210-273)	< 0.001
SFA† (cm^2)	290	(266-331)	219	(194-255)	302	(252-353)	0.004
VFA/SFA‡	0.48	(0.39-0.70)	0.58	(0.48-0.70)	0.68	(0.60-0.82)	< 0.001
TFA (cm^2)§	462	(426-486)	351	(315-432)	530	(478-606)	< 0.001

* *Visceral fat area*
† *Subcutaneous fat area*
‡ *Visceral fat area to subcutaneous fat area ratio*
§ *Total fat area*

Further, peri-pancreatic fat lipolysis and subsequent necrosis, independent from pancreatic parenchymal necrosis, also contribute to widespread toxicity and more severe pancreatitis (26,27). This releases systemic unsaturated fatty acids that inhibit mitochondrial complexes, contributing to multi-organ dysfunction (26). These findings demonstrate the important role that visceral fat independently plays in the pathogenesis and severity of the disease course.

In their meta-analysis, Martínez et al. noted that obesity has a relationship with the etiology of pancreatitis, and noted that this may be a confounder in determining the association between severity and obesity. Martínez et al. directly questioned whether the relationship between the severity of acute pancreatitis and obesity was due to biliary pancreatitis being associated with obesity (16,28-30) and now we have quantitatively demonstrated this as a confounding effect. In our univariate model, we noted that VFA was associated with increasing severity (p=0.01), but when combined in our multivariate model accounting for etiology the effect was not statistically significant (p=0.09). This can be accounted for by the well-known relationship between gallstones and obesity that would contribute to multicollinearity in the model. While this would be in support of Martinez's suggestion, we believe VFA would also be contributing to additional pathological mechanisms, as described, suggesting that VFA also has important effects independent of etiology. Therefore, we suspect that a higher-powered study may find a statistically significant effect in such a model.

It is worth noting this is a retrospective cohort series and we were unable to consistently control for patient selection bias. Though the number of patients having scans between groups was not statistically significant, 61% of patients (280) did not have a CT. We may assume that less severe patients may have been less likely to have had a scan. While this is many patients to omit, it is neither necessary, ethical, nor frugal for these patients to be subjected to CT radiation. Therefore, our findings may only be valid for patients with whom clinicians felt necessary to scan, though this is becoming more liberal. Our model also relies on the approximation that the log of the fat areas was normal. Therefore, our modelling may only be a loose exploration of the relationship between fat, etiology and severity. Given the previously known associations between obesity and gallstones, as well as the independent pathological mechanisms that visceral fat plays, we still feel the model quantitively demonstrates the end result of biological and clinical observations noted in the literature.

As previously said, the strongest conclusion of this study is that patients with gallstone pancreatitis are disproportionately affected by visceral adiposity. This reconfirms Sekine's quantitative findings that visceral fat is a better predictor of gallstone disease than BMI (31). As visceral fat is associated with the metabolic syndrome and insulin resistance, cholecystokinin pathways become altered and gallbladder motility can become dysfunctional. Further, hydroxymethyl glutaryl CoA reductase is activated leading to cholesterol supersaturation and subsequent risk of crystallization (31-33). So we conclude that our observations and model show that increased visceral adiposity increases the risk of gallstones while simultaneously being pro-inflammatory.

In comparison to the other groups, it is interesting to note that the alcohol group in this study population had the lowest VFA at 124 cm^2. Previous evidence shows increasing alcohol intake is associated with disproportionate increases in visceral fat (34, 35). Though these epidemiological surveys were not done on patients with acute pancreatitis, Kim, in South Korea, reported an adjusted mean VFA of approximately 140 cm^2 and Sumi, in Japan, a mean of approximately 128 cm^2 in patients with excess alcohol use (34, 35). Kuan reported multiple averages of VFA

Table 5. Logistic regression modelling to assess risk of severity.

	Univariate analysis			Multivariate analysis*		
	OR (95% CI)		p value	Adjusted OR (95% CI)		p value
log(VFA)	2.0	(1.2-3.4)	0.01	1.6	(0.92-2.9)	0.09
log(SFA)	1.2	(0.68-2.2)	0.52			
Alcohol	4.4	(1.7-11)	0.001	4.5	(1.8-11)	0.001
Gallstones	5.8	(2.4-14)	0.0001	4.7	(1.9-12)	0.0007
Male	1.5	(0.75-3.2)	0.24			
Age	1.0	(0.98-1.1)	0.73			

** Limited multivariate model accounting for visceral fat and etiology only*

of patients with acute pancreatitis in their metanalysis ranging from 100–252 cm^2, but with a skew biased towards 140 cm^2 (22). Sekine measured the mean VFA of patients with symptomatic gallstones in Japan at 136 cm^2 (31). Our gallstone population had a much higher median VFA of 214 cm^2. Our overall patient population had a median VFA of 159 cm^2, which is in line with our entire population being disproportionately obese if taken as a surrogate measure of BMI (36). Our alcoholic patients were the "least" obese with the lowest VFA, which we suspect is from malnourished patients in this group that would have brought down this measure.

The aggregate of patients with no clear cause for their pancreatitis had the lowest VFA/SFA ratio as described in Table 5. While many of these patients underwent thorough investigations including repeated ultrasound, magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) on select occasions, this was not routine. We therefore did not define this population as having idiopathic pancreatitis, though it can approximate such a group. We could not suggest that microlithiasis is indeed a precipitant in this group. The re-admission rate for this group was 13% over the study period and there was only one false negative ultrasound within the group, suggesting that the clinical management was appropriate. The group also had the lowest chance of developing a severe episode. In contrast to the lowest VFA/SFA ratio, a high proportion of fatty liver was observed in this group. This rate was similar to those with gallstone pancreatitis, but the relevance of this is not certain. Why do these patients have less visceral obesity, but just as much fatty liver? What other molecular and metabolic pathways are involved? These are just some questions that may worth exploring.

The measurement of visceral fat is straightforward. It can easily be done by drawing a region of interest manually or with automated software. It can also be qualitatively done by paying attention to the distribution of fat to form an opinion about the patients nutritional and metabolic background. With the ongoing development of automatic segmentation, this may also present an ongoing opportunity to quantitatively assess patient risk by inferring associated pathological processes and etiologies when certain fat distributions are recognized, as we have shown.

Conclusion

There were significant differences in the fat distribution among patients presenting with acute pancreatitis of differing etiology. As the metabolic syndrome contributes to the development of gallstones, it was consistent that we found patients with gallstone pancreatitis are disproportionately affected by the highest levels of visceral adiposity. Alcoholic patients in general were less obese than those with no clear cause or gallstone pancreatitis. Patients without a clear cause for their pancreatitis also had a unique distribution of fat, sitting somewhere in between but with lowest VFA/SFA ratio. In our modelling, etiology is more strongly associated with body fat distribution than severity.

Given a growing obesity pandemic (2,9), the pathophysiological effects of visceral fat become more important. New and objective investigations into visceral adiposity will continue to uncover clinically relevant information that can be associated with various pathologies. This study showed that quantitative radiological profiling of visceral adiposity is distinctly associated with fat phenotypes that can be linked to different etiologies in acute pancreatitis.

Conflicts of interest

The authors report no conflicts of interest.

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