ORIGINAL RESEARCH

Assessment of Computed Tomography-Defined Muscle and Adipose Tissue Features in Relation to Length of Hospital Stay and Recurrence of Hypertriglyceridemic Pancreatitis

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Background: Analytic morphometric assessment has recently been proposed to be applied to the study of acute pancreatitis (AP). However, the relationship between body composition and the outcomes of hypertriglyceridemic pancreatitis (HTGP) is still unclear. The aim of this study was to evaluate body composition in relation to the length of hospital stay (LOS) and recurrence of HTGP.

Methods: Patient characteristics, admission examination data, body composition parameters, LOS, and recurrence within 1 year were collected from the institutional pancreatitis database and follow-up records. Logistic regression analysis was used to identify risk factors for LOS and recurrence of HTGP.

Results: Of the 196 included patients, 158 (80.6%) were men and 53 (27.0%) were sarcopenic. The average LOS was 15.83±10.02 days. The recurrence rate of HTGP was 36.7%. Multivariate analysis with multiple linear regression suggested that subcutaneous adipose tissue (SAT) area (p=0.019) and high-density lipoprotein-cholesterol (HDL-C) (p=0.001) were independently associated with the LOS for HTGP after adjusting for age and sex. The multivariate adjusted hazard ratios for SAT area and HDL-C, with respect to the relationship between body parameters and LOS, were 1.008 (95% confidence interval [CI], 1.001–1.015) and 0.090 (95% CI, 0.022–0.361), respectively. No significant differences were observed between the AP and recurrent AP (RAP) groups in terms of characteristics, admission examination data, and body composition parameters.

Conclusion: SAT area and HDL-C are associated with LOS in patients with HTGP. The body composition of patients at the first symptom onset of HTGP cannot predict recurrence.

Keywords: hypertriglyceridemic pancreatitis, recurrent pancreatitis, length of hospital stay, body composition, subcutaneous adipose tissue

Introduction

Acute pancreatitis (AP), a common inflammatory disease, progresses to organ dysfunction in 10% to 20% of patients, with increasing incidence and a high mortality rate.[1–4] The most common etiologies of AP are gallstones and alcoholism.[2] Notably, hypertriglyceridemic pancreatitis (HTGP), which accounts for up to 10% of AP cases, occurs in the presence of hypertriglyceridemia with no signs of other causes.[5] Recent reports have indicated that the incidence of HTGP in Asia is increasing,[3,6] and is higher than that reported in Western countries,[7] which and ranked as the third leading cause for AP.[8]

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Most studies of AP did not classify the etiological patterns. Different etiologies have different pathophysiological mechanisms.[9] Gallstone induced pancreatitis is caused by duct obstruction by gallstone migration. Duct obstruction promotes pancreatitis by increasing duct pressure and subsequent unregulated activation of digestive enzymes.[10] While, it is generally believed that the pathophysiology of HTGP is that the free fatty acids' deposition, hydrolyzed by pancreatic lipase from TG, facilitates the occurrence of the disease. The fatty acids can be bound to serum albumin. Whereas, it would play a detergent-like role if exceeded, and attack platelets, vascular endothelium, and acinar cells.[7,11] Previous studies have shown that the prognosis and severity of AP seem to vary depending on etiology.[9] HTGP is associated with more complications, a longer and more severe disease, and a higher recurrence rate.[7,12,13] Therefore, it is important to distinguish the etiology of AP.

As we know, HTGP patients are usually associated with obesity and other metabolic complications, there is a higher chance for HTGP patients to have more fat tissue.[14] Obesity is a well-known risk factor for AP that can exacerbate inflammation.[4,15–20] A meta-analysis showed that obesity is associated with local complications, organ failure, and high mortality in patients with AP.[21] However, most studies did not distinguish between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). The study of fat distribution is crucial to understanding the metabolic implications of excess adiposity.[22–25] Computed tomography (CT) is a reliable method for the analysis of fat distribution and the measurement of adipose tissues.[26] The aim of the present study was to assess the impact of body composition on the length of hospital stay (LOS) and risk of recurrence of HTGP.

Methods
Study Population
We retrospectively evaluated consecutive patients with HTGP who were admitted to our pancreatitis center between September 2016 and August 2019. The diagnosis of AP was made if at least two of the following three features were present: (1) acute abdominal pain, (2) serum amylase and/or lipase levels three or more times the upper limit of normal, and (3) evidence of pancreatitis on abdominal imaging.[27] The diagnosis of HTGP was confirmed if patients had AP with serum total triglyceride (TG) >11.3 mmol/L (1000 mg/dL), or a serum TG level of 5.65–11.3 mmol/L accompanied by chylous serum and

the absence of other risk factors for AP.[5] The exclusion criteria were (1) indication of biliary, alcoholic, autoimmune, drug-induced or pancreatic tumor-related etiology of AP; (2) poor CT imaging of the abdomen; (3) pregnancy. This study was performed with approval from the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (KY2019–011).

Clinical Data
Clinical data such as age, sex, body mass index (BMI), umbilical waist circumference (WC), pre-existing comorbidity (including hypertension, diabetes mellitus, and alcoholism), and admission laboratory test data (including Triglycerides [TG], total cholesterol, high-density lipoprotein-cholesterol [HDL-C], and low-density lipoprotein-cholesterol [LDL-C]) were retrospectively collected. The outcomes were LOS and recurrence (defined as hospital admission within 1 year after discharge).

Anthropometric Measurements by CT Image Analysis
All patients in this study underwent abdominal CT within 1 week of symptom onset for the quantitative assessment of body composition. CT scanning was performed by Aquilion ONE 320 Slice CT scanner (Toshiba, Japan) or 64-slice spiral CT scanner (Lightspeed VCT, GE Healthcare, USA). The slice thickness was 0.5 mm for the 320 Slice CT scanner (single-turn spiral time 0.5 s, 100 kV, 300 mA) and 0.625 mm for 64-slice spiral CT scanner (pitch 0.984, single-turn spiral time 0.5 s, 100 kV, 500 mA). For contrast-enhanced CT, 60mL of nonionic contrast agent (Ultravist 370; Bayer Schering Pharma, Berlin, Germany) was injected via the cubital vein with a high-pressure syringe at a rate of 4.0 mL/s; thereafter, 30 mL saline was administered at the same rate. The scanning was triggered intelligently by monitoring of the abdominal aorta, the arterial phase was delayed for 30–35 s, and the portal phase was delayed for 60–70s. Body composition parameters were measured based on the unenhanced CT scanning. Two experienced radiologists (with 5 years of imaging experience), who were blinded to the patients' clinical data, analyzed the CT images using a post processing station (GE Healthcare Advantage Workstation, version 4.6) with the axial image at the level of the L3 vertebra. Re-measurement took place when disagreement of the measurements occurred. The predetermined Hounsfield unit (HU) thresholds were −29 to 150 HU for abdominal muscle area,
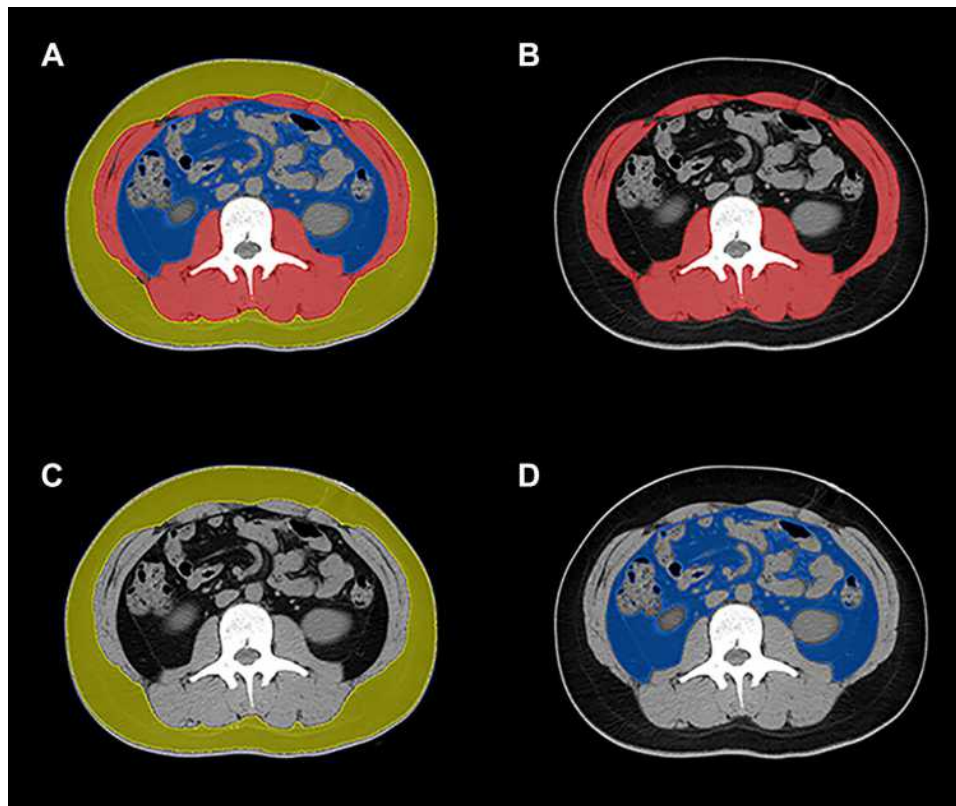
Figure 1 CT quantify body composition at the level of L3 vertebral (**A**). Abdominal muscle area is highlighted in red (**B**), SAT area in yellow (**C**), and VAT area in blue (**D**).

−30 to −190 HU for SAT, and −50 to 150 HU for VAT (Figure 1). Sarcopenia was defined using predetermined sex-specific abdominal muscle area cut-off values: 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women.[28]

Statistical Analyses

Statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA). We used the Kolmogorov–Smirnov test to assess whether the variables were normally distributed. Student's-test and the nonparametric Mann–Whitney U-test were used for comparisons of continuous variables. Categorical variables were analyzed using Pearson's chi-square and Fisher's exact tests. Continuous variables are expressed as mean± standard deviation, and categorical variables are presented as percentages. Logistic regression analysis was used to identify the risk factors. Probability values at $P < 0.05$ indicated statistical significance.

Results
Characteristics of Subjects

A total of 196 patients were considered eligible for the study (158 men and 38 women; mean age, 40.52±9.72 years). Men accounted for 80.6% of all patients. The average LOS was

15.83±10.02 days. The recurrence rate of HTGP was 36.7%. According to predefined sex-specific cutoff values,[28] 53 patients (27%) were sarcopenic. The baseline demographic characteristics, clinical characteristics, and body composition of patients with HTGP are summarized in Table 1.

Comparisons of Characteristics According to LOS

The LOS was dichotomized at 14 days, based on the median LOS of the entire population. Patients in the short LOS group (≤14 days) and those in the long LOS group (>14 days) were compared to evaluate the association between LOS and demographic characteristics, clinical characteristics, and body composition (Table 2). The short and long LOS groups comprised 94 and 102 patients, respectively. No statistical difference was observed with respect to age, sex, BMI, and pre-existing comorbidity (hypertension, diabetes mellitus, or alcoholism) between the two groups (all p>0.05). Patients in the long LOS group presented higher total cholesterol (11.15±7.00 vs 9.36±5.66 mmol/L, p=0.043) and TG (24.76±27.20 vs 17.87±22.5 mmol/L, p=0.021). The mean HDL-C level of patients with long LOS was

Table 1 Baseline Demographic and Characteristics of 196 Patients Who Underwent CT for HTGP

Parameter	Datum
Age (y)	40.52±9.72
Sex	
Women	38 (19.4%)
Men	158 (80.6)
Body mass index (kg/m²)	25.83±3.31
< 18.5	1 (0.5%)
18.5–24.9	79 (39.9%)
25.0–29.9	96 (48.5%)
≥ 30.0	20 (10.1%)
Pre-existing comorbidity	
Hypertension	63 (32.1%)
Diabetes	123 (62.1%)
Alcoholism	89 (45.4%)
Laboratory test at diagnosis	
Triglycerides (mmol/L)	21.46±25.04
Total cholesterol (mmol/L)	10.29±6.44
HDL-C (mmol/L)	0.64±0.25
LDL-C (mmol/L)	2.32±1.17
Body composition at diagnosis	
Abdominal muscle area, cm²	155.58±33.46
Subcutaneous adipose tissue area (SAT area), cm²	132.64±51.11
Visceral adipose tissue area (VAT area), cm²	174.00±107.83
Total adipose tissue area (TAT area), cm²	307.65±124.18
Umbilical waist circumference (WC), cm	88.20±9.09
Sarcopenia	53 (27%)
Outcomes investigated	
LOS (days)	15.83±10.02
Recurrence	72 (36.7%)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOS, length of hospital stay.

lower than that of patients with short LOS (0.57±0.24 vs 0.72±0.24 mmol/L, p < 0.001) (Figure 2A). A significant association between LOS and individual SAT area was observed. SAT area was significantly higher in the long LOS group than in the short LOS group (142.77±50.57 vs 121.64±49.65 p=0.001) (Figure 2B). Other body composition parameters, including abdominal muscle area, VAT, Total adipose tissue area (TAT area), Umbilical waist circumference (WC), and sarcopenia, were also similar between the two groups (all p>0.05). Multivariate analysis with multiple linear regression suggested that SAT area (p=0.019) and HDL-C (p=0.001) were independently associated with the LOS for HTGP after adjusting for age and sex (Table 3).

Comparisons of Characteristics According to AP Recurrence

No significant differences were observed between the AP and RAP groups in age, sex, BMI, and pre-existing comorbidity (hypertension, diabetes mellitus, or alcoholism). The laboratory test values for TG, total cholesterol, HDL-C, and LDL-C were not significantly different between the two groups. The body composition parameters abdominal muscle area, SAT, VAT and TAT, as well as WC and sarcopenia, were not significantly different between the two groups (all p>0.05) (Table 4).

Discussion

AP is a common disease of the abdomen necessitating emergency department visits.[3,29,30] Biliary tract stones and alcoholism are the most common etiologies of AP.[2] Recent reports have indicated an increasing prevalence of HTGP in Asia.[3,6] Jin et al showed that from 2001 to 2016, the prevalence of HTGP increased from 14.0% to 34.0%.[3] These changes may be related to caloric intake and an increasing incidence of diabetes.[31] Notably, HTGP now ranked as the third leading cause for AP.[8] The treatment of HTGP diagnosed as mild acute pancreatitis is mainly fasting, acid inhibition, enzyme inhibition and fluid replacement. Fluid replacement only needs to supplement daily physiological requirements, generally no enteral nutrition is needed, and fenofibrate capsules can be taken at the same time to regulate blood lipids. For moderately severe acute pancreatitis and severe acute pancreatitis diagnosed, it is necessary to maintain organ function, use inhibitors to inhibit pancreatic exocrine and pancreatin, early enteral nutrition, rational use of antibiotics, treatment of local and systemic complications, and analgesia.[32] At the same time, intensive insulin therapy or plasma exchange therapy can reduce blood lipid for hyperlipidemia. The patients discharged from hospital should take fenofibrate capsules and pancreatin enteric-coated capsules for a long time, and regularly monitor blood lipid and hematuria amylase.[33]

A plethora of clinical and experimental data have identified obesity as a risk factor for AP.[4,15–20] Hansen et al studied 118,000 patients with AP, and confirmed that BMI is an independent factor of AP.[16] Blaszczak et al reported that class III obesity seems to have an adverse mortality effect in patients with AP.[18] A recent study by Thavamani et al suggested that morbid obesity is an independent risk factor for clinical outcomes in pediatric AP.[19] However, most studies did not distinguish between

Table 2 Comparison of Baseline Characteristics Between Short LOS (≤14 Days) and Long LOS (>14 Days) Groups

| Parameter	Short LOS (≤14 Days) (n=94)	Long LOS (>14 Days) (n=102)	P value
Age (y)	41.45±8.8	39.67±10.4	0.201
Sex			0.244
Women	15 (16.0%)	23 (22.5%)	
Men	79 (84.0%)	79 (77.5%)	
Body mass index (kg/m^2)	25.73 (3.00)	25.92 (3.58)	0.685
< 18.5	0 (0.0%)	1 (1.0%)	
18.5–24.9	36 (38.3%)	43 (42.2%)	
25.0–29.9	50 (53.2%)	46 (45.1%)	
≥ 30.0	8 (8.5%)	12 (11.8%)	
Pre-existing comorbidity			
Hypertension	26 (27.7%)	37 (36.3%)	0.197
Diabetes	25 (26.6%)	29 (28.4%)	0.774
Alcoholism	41 (43.6%)	48 (47.1%)	0.629
Laboratory test at diagnosis			
Triglycerides (mmol/L)	17.87±22.5	24.76±27.20	0.021*
Total cholesterol (mmol/L)	9.36±5.66	11.15±7.00	0.043*
HDL-C (mmol/L)	0.72±0.24	0.57±0.24	<0.001*
LDL- C (mmol/L)	2.43±1.26	2.23±1.08	0.243
Body composition at diagnosis			
Abdominal muscle area, cm^2	158.25±32.48	153.12±34.31	0.285
Subcutaneous adipose tissue area (SAT area), cm^2	121.64±49.65	142.77±50.57	0.001*
Visceral adipose tissue area (VAT area), cm^2	171.77±67.47	178.00±134.20	0.579
Total adipose tissue area (TAT area), cm^2	293.42±94.94	320.78±145.30	0.200
Umbilical waist circumference (WC), cm	89.26±9.03	87.24±9.08	0.120
Sarcopenia	24 (25.5%)	29 (28.4%)	0.648

Note: *P< 0.05.
Abbreviation: LOS, length of hospital stay.

VAT and SAT depots. The study of fat distribution is crucial to understanding the metabolic implications of excess adiposity. More and more researchers have realized that the study of fat distribution is important in obesity research.[22–25] CT imaging is a reliable method for the analysis of fat distribution and the measurement of adipose tissues.[26] The axial CT image at L3 is known to represent muscle tissues and fat distribution.[26,34] Pankaj Gupta et al have combined modified CT severity index (MCTSI) with adipose tissue features to propose a fat-modified CT severity index (FMCTSI) and have found that FMCTSI is a better CT index than MCTSI for predicting the severity and clinical outcomes of AP and FMCTSI based on TAT or VAT has different efficacy.[35] Blaszczak et al conducted a study in 68,158 individuals, among whom 424 developed AP, and demonstrated that greater abdominal adiposity is associated with a higher

severity of AP.[36] However, many studies have suggested that VAT is not significantly associated with AP.[37–39] Duarte-Rojo et al have shown that both SAT and VAT independently predict a severe outcome of AP.[40] The differences in results across different studies may be explained by several factors. First, the studies involved a heterogeneous population of patients, including those from Southeast Asia, Europe, and North America. Second, different software programs were used to analyze body composition, which may be an additional confounding factor. Third, most studies did not classify the etiological patterns of AP, which may be mainly because of the different proportions of the etiological patterns in previous studies. Therefore, studies on the etiologies of AP are needed. To our knowledge, this is the first study on the impact of body composition on LOS and recurrence in patients with HTGP.
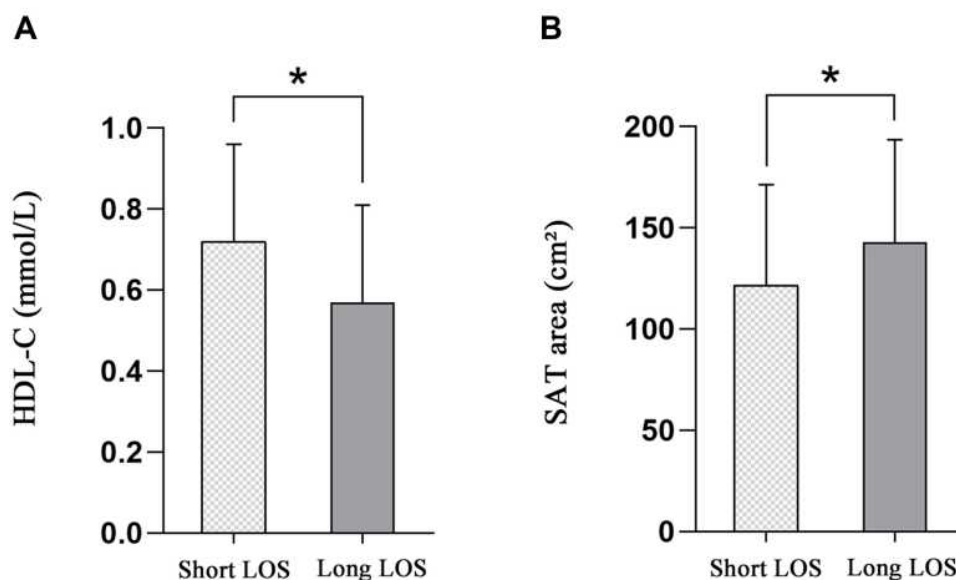
Figure 2 HDL-C is significantly lower in the long LOS group compared to the short LOS group(**A**). SAT area is significantly higher in the long LOS group compared to the short LOS group (**B**).*P< 0.05.

Our results revealed that SAT area and HDL-C were independent predictors of LOS. Patients in the long LOS group (>14 days), based on the median LOS of the entire sample, had higher SAT area than patients in the short LOS group (≤14 days). Previous studies have also determined that patients with LOS >14 days have more severe pancreatitis.[36] Szentesi et al studied 1257 individuals with AP, and reported that obese patients had longer LOS than non-obese patients.[41] Murata et al showed a similar finding in pediatric AP.[42] However, they did not conduct further analysis on fat distribution and etiological classification. Fujisawa et al suggested that SAT may be an especially important factor related to the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis;[43] however, they did not investigate its

relationship with LOS. Many studies have found that adiponectin, secreted by adipose tissue, is play an important role in exerting anti-inflammatory effect through the inhibition of proinflammatory signaling and NF-kappa B, which is decreased in obesity. The serum adiponectin level correlates with SAT and obesity might decrease adiponectin from SAT that could affect inflammatory effect of AP[43–47].

Few studies have been conducted on the correlation between obesity and the recurrence of pancreatitis. Shimonov et al found that higher amounts of VAT and abdominal muscle area were significantly associated with a lower recurrence rate of AP in 158 patients;[48] however, in our study, there was no significant association between body composition and the recurrence of

Table 3 Multivariate Analyses of Risk Factors for LOS of HTGP

Parameter	OR	P value
Age (y)	0.999 (0.967–1.031)	0.937
Sex	0.793 (0.355–1.773)	0.572
Triglycerides (mmol/L)	0.996 (0.973–1.020)	0.767
Total cholesterol (mmol/L)	1.041 (0.953–1.137)	0.375
HDL-C (mmol/L)	0.090 (0.022–0.361)	0.001*
Subcutaneous adipose tissue area (SAT area), cm^2	1.008 (1.001–1.015)	0.019*

Note: *P< 0.05.

Table 4 Comparison of Baseline Characteristics Between AP and RAP Groups

Parameter	AP (n=124)	RAP (n=72)	P value
Age (y)	41.39±9.92	39.03±9.25	0.891
Sex			0.719
Women	25 (20.2%)	13 (18.1%)	
Men	99 (79.8%)	59 (81.9%)	
Body mass index (kg/m^2)	26.14±3.45	25.28±3.00	0.079
< 18.5	0 (0.0%)	1 (1.4%)	
18.5–24.9	47 (37.9%)	32 (44.4%)	
25.0–29.9	60 (48.4%)	36 (50.0%)	
≥ 30.0	17 (13.7%)	3 (4.2%)	
Pre-existing co-morbidity			
Hypertension	40 (32.3%)	23 (31.9%)	0.964
Diabetes	34 (27.4%)	21 (29.2%)	0.793
Alcoholism	60 (48.4%)	29 (40.3%)	0.272
Laboratory test at diagnosis			
Triglycerides (mmol/L)	18.21±18.82	27.04±32.52	0.143
Total cholesterol (mmol/L)	9.86±5.10	11.03±8.25	0.894
HDL-C (mmol/L)	0.64±0.24	0.65±0.28	0.978
LDL- C (mmol/L)	2.37±1.04	2.25±1.38	0.147
Body composition at diagnosis			
Abdominal muscle area, cm^2	155.36±33.81	155.97±33.07	0.903
Subcutaneous adipose tissue area (SAT area), cm^2	137.98±52.82	123.44±46.98	0.054
Visceral adipose tissue area (VAT area), cm^2	180.41±126.55	162.95±63.21	0.359
Total adipose tissue area (TAT area), cm^2	320.00±140.33	286.40±86.68	0.097
Umbilical waist circumference (WC), cm	87.95±9.25	88.63±8.86	0.615
Sarcopenia	34 (27.4%)	19 (26.4%)	0.876

Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

HTGP. HTGP may be different from other etiologies of pancreatitis in terms of the effect of body composition. The doctor's medical advice for TG control after discharge may be another reason because the body composition of the patients after 1 year may be different from that at the first hospitalization. Dynamic changes in body composition may be the direction of future research. In addition, many studies have shown that alcoholism, cigarette smoking, hypertriglyceridemia, and local complications are risk factors for recurrent pancreatitis.[49,50] However, our study showed no significant association between hypertriglyceridemia and recurrence of HTGP.

This study had some limitations. First, the number of patients with HTGP within categories by pancreatitis type was small; thus, studies with larger sample sizes are required. Second, as our study results were derived from a retrospective single-center analysis, further prospective and multicenter studies should be conducted in the future. Finally, the outcome of recurrence was assessed within 1 year after discharge, which may not reflect the long-term outcome of patients.

Conclusion

In the present study, we found that SAT area and HDL-C are associated with LOS in patients with HTGP. The CT-defined body composition may help identify patients at a high risk of long-term hospitalization and assist in treatment decision making. In addition, we found that the body composition of patients at the first symptom onset of HTGP cannot predict the recurrence of the disease. Future studies should investigate strategies focusing on dynamic change in body composition.

Ethics Approval and Consent to Participate

Funding

Disclosure

The authors have no conflicts of interest to declare.

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