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Intra peritoneal abdominal fat area measured from computed tomography is an independent factor of severe acute pancreatitis

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Acute pancreatitis;
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Abstract

Purpose: The purpose of this study was to search for a possible relationship between acute pancreatitis (AP) severity and visceral fat (VF) surface on contrast-enhanced computed tomography (CECT).

Material and method: A total of 112 patients with AP who underwent CECT within 2 to 3 days after the beginning of AP were included. There were 68 mean and 44 women, with a mean age of 56.3 ± 21.6 (SD) years (range: 19—98 years). AP was regarded as mild for patients with an hospital stay up to 5 days and severe for those with an hospital stay greater than 5 days. VF surface was measured on CECT at the level of L4-L5 and of the umbilicus. Association between AP severity and VF surface, computed tomography severity index (CTSI), modified CTSI (mCTSI) and other variables were searched for using uni- and multivariate analysis.

Results: At univariate analysis, the VF surface at the level of L4 was greater in patients with severe AP (129.3 ± 68.6 [SD] cm^2; range: 21.8-355.8 cm^2) than in patients with mild AP (100.1 ± 68.4 [SD] cm^2; range:13.2—333 cm^2) (P = 0.006). Similarly, the VF surface at the umbilicus was greater in patients with severe AP (161.1 ± 76.1 [SD] cm^2; range: 31.3—376.7 cm^2) than in those with mild AP (128.4 ± 74.3 cm2; range: 12.8-323.1 cm2) (P = 0.024). CTSI and mCTSI were also associated to AP severity. At multivariate analysis, only VF surface either measured at the umbilical or at the L4-L5 level was associated with AP severity (P = 0.017 and 0.006, respectively).

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Conclusion: VF surface at the level of L4—L5 on CECT is an independent factor of AP severity. VF surface at the level of L4—L5 on CECT is an independent factor of AP severity. These results are in line with recent data on the role of abdominal fat in the genesis of inflammatory response, which is associated with severe forms of AP.

Acute pancreatitis (AP) is one of the causes of acute abdominal pain and has high potential for life-threatening complications [1,2]. Approximately 10—20% of patients with AP develop severe local and systemic complications, associated with high morbidity and mortality [3]. Early recognition of severe AP is a critical issue for early and appropriate triage and targeted treatment. Currently, contrast-enhanced computed tomography (CECT) is used as the reference standard for both diagnosis and severity assessment of AP. In this regard, CT severity index (CTSI) and its modified version (mCTSI) are the most commonly used imaging methods for AP severity assessment [3]. However, the roles of these indexes have been questioned because relevant morphologic changes are more appropriately imaged at 5—7 days after admission or may be not present on a too early CECT examination [4]. In addition, reproducibility of its measurements remains low [5]. The extra-pancreatic inflammation on CT criteria (EPIC) has been recently proposed gathering different extra-pancreatic signs of inflammation, yielding 81% sensitivity and 63% specificity in the diagnosis of organ failure [6]. However, the EPIC criteria cannot predict the severity of AP. Meanwhile, other indexes have been tested; among numerous variables, a persistent systemic inflammatory response syndrome (SIRS) seems associated with a poor prognosis [1,3]. In combination with other clinical variables, the pancreatitis activity scoring system has been recently proposed and helps discriminate between different profiles of disease activity according to hospital stay duration [3]. To date, no laboratory test is practically available or consistently accurate to predict AP severity [7]. Hence, more sensitive and reliable methods are required for severity assessment during the early stage of AP.

A meta-analysis has individualized obesity as a risk factor of morbidity and mortality in AP [8]. Probably more than obesity, fat distribution could be an important variable in the development of complications of AP, because visceral fat inflammation produces different bioactive substances such as leptin and interleukin [6], which can contribute to a pro-inflammatory state and SIRS [9]. In the same way, it has been recently demonstrated that more than pancreatic necrosis, peri-pancreatic fat necrosis worsens the prognosis of AP [10] Three studies have demonstrated a strong association between the quantity of abdominal fat on CT and AP severity [11,12,13] although another study did not show any association [14].

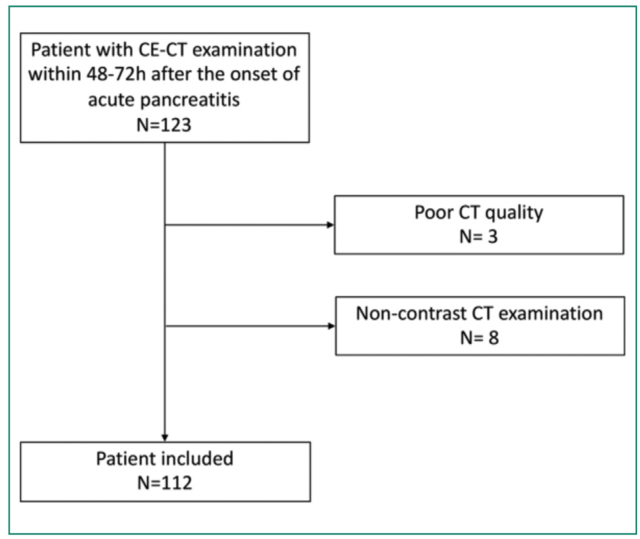

Figure 1. Diagram shows study flowchart.

The purpose of this study was to search for a possible relationship between AP severity and abdominal fat content on CECT.

Materials and Methods

Patients

All patients admitted between 2010 and 2015 with a diagnosis of AP were retrospectively identified from the local clinical database. Diagnostic of AP was based on the presence of at least two of the three following items:

- a serum amylase three times the limit of normal;
- radiological evidence of AP;
- characteristic pancreatic upper abdominal pain.

A total of 123 patients with AP who underwent CECT examination within 48—72 hours following the onset of symptoms were initially included. After exclusion of 11 patients, the study population consisted of 112 patients. There were 68 mean and 44 women, with a mean age of 56.3 ± 21.6 (SD) years (range: 19—98 years). Fig. 1 is a flow chart of patients who were considered for this study.

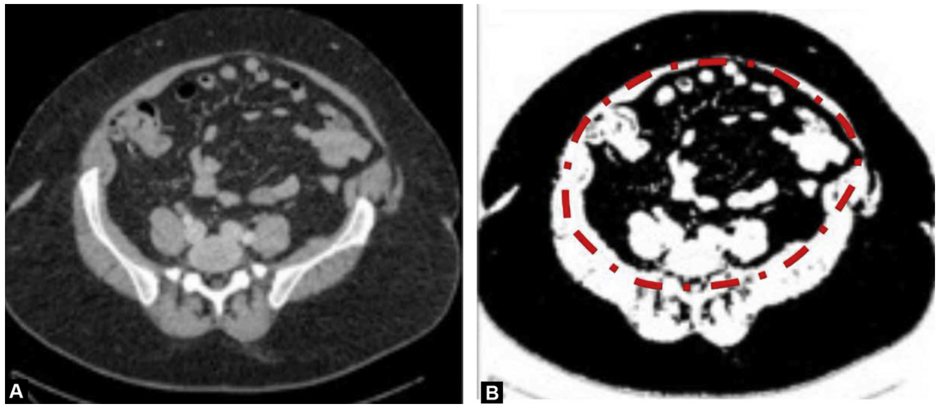

Figure 2. A. Figure shows CT image in the axial plane at the level of the fifth lumbar vertebra (L4) and at the level of the umbilicus. B. Figure shows automatic segmentation according to the density of the fat area.

Baseline demographics and biological data including age, body mass index (BMI) and lipase serum level were collected for all patients. For this study, the severity of AP was assessed by a hospitalisation stay longer than 5 days (or death occurring before 5 days) [15]. Considering the retrospective study design, institutional review board approval was exempted.

Image analysis

Visceral fat (VF) measurements were made using a semi-automatic process. An open source image analysis software (Image J, National Institute of Health), which is a Java-based image processing program was used to calculate VF from CECT images by segmentation of abdominal tissues based on Hounsfield unit (HU) value. An attenuation range of −190 to −30 HU was used [12]. Measurements were performed on CECT image obtained in the axial plane passing by the fourth or fifth lumbar vertebrae (L4/L5) and at the level of the umbilicus (Fig. 2). The regions of interest (ROIs) automatically drawn by the segmentation software were corrected manually when needed. The software then calculated the cross-sectional area of the VF. All CECT examinations were retrieved from the local picture archiving and communication system and studied under a DICOM format.

For each patient, the CTSI and mCTSI [5,16,17] scores were computed separately during two different reading sessions spaced by at least 15 days from each other, and performed by one reader without knowledge of the previous scoring results.

Statistical analysis

SAS release 9.4 analysis software (SAS Institute) was used for statistical analysis. Quantitative data were expressed as mean ± standard deviation (SD) or median and range. Univariate comparisons according to AP severity as defined above were made using the Mann-Whitney test. Multivariate logistic regression analysis was performed to identify independent variables associated with AP severity. Due to a skewed distribution, VF areas were log-transformed before fitting the logistic model. Correlation between variables were searched for using Spearman rank correlation coefficient. A two-sided P-value < 0.05 was regarded as significant.

Results

Baseline demographic data of the study population are presented in Table 1. Twenty patients (17.9%) required admission to the intensive care unit. The mean hospital stay was 7.5 ± 6.5 (SD) days (median, 5 days; range: 2—38 days). There were no readmissions within 30 days following discharge.

Four deaths were observed (3.6%); these patients were included in the severe AP group whatever the duration of the hospital stay. Fifty-five patients (49.1%) presented a severe form of AP according to our criteria.

At univariate analysis, the VF surface at the level of L4—L5 was greater in patients with severe AP (129.3 ± 68.6 [SD] cm^2) than in those with mild AP (100.1 ± 68.4 [SD] cm^2) (P = 0.006) (Table 2). At the level of the umbilicus, VF was 161.1 ± 76.1 (SD) cm^2 in patients with severe AP and 128.4 ± 74.3 (SD) cm^2 in patients with mild AP. The VF measured at the umbilicus or at L4—L5 strongly correlated with each other ($r_S = 0.91$; $P < 0.001$) and with BMI ($r_S = 0.57$; $P < 0.001$). There was also a significant difference according to AP severity for CTSI ($P = 0.004$) and mCTSI ($P = 0.005$). These two CT scores strongly correlated with each other ($r_S = 0.93$; $P < 0.001$). VF surface did not correlate with CT scores CTSI ($r_S = 0.06$, $P = 0.54$ for L4; $r_S = 0.12$, $P = 0.20$ for umbilicus) neither with mCTSI ($r_S = -0.02$, $P = 0.82$ for L4; $r_S = 0.03$, $P = 0.73$ for umbilicus). BMI poorly and negatively correlated with mCTSI score ($r_S = -0.23$; $P = 0.018$) but not significantly with CTSI ($r_S = -0.18$, $P = 0.065$). Age differed greatly between AP severity groups: 65.9 ± 18.8 (SD) years in severe forms against 47.0 ± 20.2 (SD) years in mild forms ($P < 0.001$). Age increased with VF at L4-L5 ($r_S = 0.53$; $P < 0.001$) and with VF at the umbilicus ($r_S = 0.44$; $P < 0.001$). Multivariate logistic regression analysis conveyed contrasted results whether age was included or not in the statistical model. At first, age was not included in the logistic model, resulting in significant associations of AP severity with VF surface at L4—L5 ($P = 0.006$) and VF surface at the umbilicus ($P = 0.017$) independently of CTSI and mCTSI scores. When included in the model, age remained as the single

Table 1 Characteristics of the study population ($N = 112$).

Parameter	*N* (%)	Mean ± SD	Range
Gender			
Male	68 (60.7)		
Female	44 (39.3)		
Age (years)		56.3 ± 21.6	[19—98]
CT delay (hour)			
48 hours	55 (49.1)		
72 hours	57 (50.9)		
Deaths (number)	4 (3.6)		
Hospitalisation stay (days)			
Medecine bed		6.9 ± 5.3	[0—33]
ICU		0.6 ± 3.4	[0—30]
Total		7.5 ± 6.5	[2—38]
BMI (m/cm^2)		26.3 ± 6.9	[18—51]
< 18.49	5 (4.6)		
18.5—24.9	53 (48.6)		
25—29.9	30 (27.5)		
> 30	21 (19.3)		
CTSI score		2.7 ± 2.6	[0—10]
mCTSI score		4.0 ± 3.1	[0—10]
Lipase serum level (UI/L)		2826 ± 6076	[109—59267]

ICU:ntensive care unit; CTSI:computed tomography severity index; mCTSI:modified computed tomography severity index.

Table 2 Relation between AP severity (assessed by hospital stay over 5 days or death) and the variables studied.

Variables mean ± SD, [range]	Severe AP (hospital stay > 5 days) $N = 55$	Mild AP (hospital stay up to 5 days) $N = 57$	Univariate *P*-value	L4—L5 Multivariate *P*-value	Umbilicus Multivariate *P*-value
Total hospitalisation stay (days)	11.3 ± 7.5 [5—38]	3.8 ± 0.9 [2—4]			
L4-L5 area (cm^2)	129.3 ± 68.6 [21.8—355.9]	100.1 ± 68.4 [13.2—333.0]	0.006	0.006	—
Umbilicus fat area (cm^2)	161.1 ± 76.1 [31.3—376.7]	128.4 ± 74.3 [12.8—323.1]	0.024	—	0.017
CTSI	3.5 ± 3.0 [0—10]	2.0 ± 2.1 [0—7]	0.004	0.990	0.986
mCTSI	4.8 ± 3.1 [0—10]	3.2 ± 2.8 [0—10]	0.005	0.297	0.316
BMI (m/cm^2)	26.7 ± 6.8 [17.7—50.8]	25.8 ± 7.0 [17.9—50.3]	0.303	—	—
Age (years)	65.9 ± 18.8 [22.2—98.7]	47.0 ± 20.2 [19.4—86.8]	< 0.001	—	—
Lipase (UI/L)	2578 ± 2976 [213—11901]	3065 ± 8032 [109—59267]	0.287	—	—

Numbers are expressed as mean ± standard deviation. Numbers in brackets are ranges.

independent variable while VF was no longer significant. The results of uni- and multivariate analyses are given in Table 1.

Discussion

The present study suggests that fat distribution, and VF in particular, strongly correlates with the development of severe AP as there is a significant relationship between VF surface measured on CECT and the severity of the AP. This variable is easily and quickly measurable and could thus be used in daily practice to distinguish mild from severe AP.

We used hospitalisation stay as an indicator of severity. According to Wu et al., hospitalisation duration can be considered as a sign of severity [15]. Indeed, these researchers have demonstrated from a cohort of 3215 patients that patients with self-limited AP tended to experience a rapid decline in activity scores. Meanwhile patients with prolonged illness demonstrated on average a high level of disease activity throughout early course of illness. One other option could have been to grade severity of AP according to the new version of Atlanta classification [18]. A report by Natu et al. has already shown a strong relationship between VF and AP severity and local complications from a large cohort of patients [13]. However, it has been recently demonstrated that the diagnosis of abnormalities related to AP, according to Atlanta classification was mildly reproducible with low kappa values for CT diagnosis of extra pancreatic necrosis, type of pancreatitis, characteristics of collections, and appropriate term of collections of 0.326, 0.370, 0.408 and 0.356, respectively [19].

In this study, VF surface was used rather than a volumetric measure. Indeed, previous studies showed that tVF surface measured on a single level strongly correlates with fat volume [20]. Some authors used an umbilical reference mark [20,21] although others used a reference bony mark [22,23]. However, the level of analysis has little impact on the measure. In this regard, Lee et al. showed that the measurements of VF and sub-cutaneous fat performed at the level of L4—L5, L4—L5 + 5 cm and L3—L4 present very few differences [23]. However, in AP, fat measurement should be ideally performed at distance from the pancreatic gland since measures obtained at the level of L4—L5 are more strongly associated with AP severity ($P = 0.006$) than measurements obtained at the umbilical level ($P = 0.017$). This could be explained by the diffusion of the inflammation around the pancreas; modifying the fat density, these phenomena could then undervalue the fat measurement that is obtained by attenuation-based segmentation. In the same way, early measurement, before inflammation diffusion in the abdominal cavity, could be more precise. This assumption however, needs to be confirmed by further studies.

Several studies have shown a relationship between obesity and severity of AP [24,25]. Our study shows that more than obesity (BMI was not related with the severity of AP), distribution of this fat seems to be the most important parameter. Two other studies have already shown this relationship [11,12]. On the contrary, Hall et al. did not show any relationship between VF and AP severity [14]. However, these researchers performed CT examinations at varying time points (median time 15 days) from the initial diagnosis of AP, which could have altered the fat measurements considering the diffusion of the inflammatory process [14]. Secondly, patients with high BMI were over-represented, which may have skewed the results [14]. To confirm our results, there are some theoretical points in favor of a relation between VF and severity of AP. First, VF produces several inflammatory bioactive substances such as leptin and interleukin-6, which can contribute to metabolic syndrome through a pro-inflammatory state [9]. Second, it has been shown that extra pancreatic inflammation evaluated from CECT (EPIC score) is an early predictor of organ failure in AP as defined by the revised Atlanta classification [6]. Third, peri pancreatic fat necrosis worsens AP independently of pancreatic necrosis via unsaturated fatty acids, which are associated with more severe diseases [10].

Our study has some limitations. First, our study population represents a skewed population since it contains only patients who required CECT for the diagnosis of AP. Second, age was strongly associated with severe forms of AP and also with VF surface so that it is therefore possible that age might have acted as a confounding factor. Third, CECT was performed within 48—72 h after the onset of symptoms and this might have distorted measurements of VF as discussed before. However, this timing is in accordance with most guidelines on AP [5,7,26]. Fourth, intra- and inter-observer reproducibility of the measures were not evaluated but a recent study demonstrated the excellent reproducibility and repeatability of the VF measurements [27].

In conclusion, VF measurement at the level of L4—L5 on CECT is an independent factor of AP severity. These results are consistent with recent biological or imaging data on the role of abdominal fat in the genesis of inflammatory response leading to severe forms of AP. Further prospective study with more patients is necessary in order to establish an acute threshold forecast of AP.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients included in the article. The authors also confirm that the personal details of the patients have been removed.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Disclosure of interest

The authors declare that they have no competing interest.

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