Original article

Attenuation around the gallbladder on plain abdominal computed tomography as a predictor of surgical difficulty in laparoscopic cholecystectomy

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Abstract

Purpose: This study examined whether abdominal plain computed tomography (CT) can predict surgical difficulty in acute cholecystitis.

Methods: We retrospectively analyzed 84 consecutive patients who underwent laparoscopic cholecystectomy for acute cholecystitis between January 2015 and December 2018. We distinguished three degrees of surgical difficulty based on the operative time and blood loss: difficult; both ≥120 min and ≥100 mL, respectively (n = 27), moderate; either ≥120 min or ≥100 mL, respectively (n = 30), and easy; both <120 min and <100 mL, respectively (n = 27). We calculated the attenuation around the gallbladder on CT before surgery and compared the values among the three groups.

Results: Mean age, albumin levels, C-reactive protein levels, and the CT attenuation around the gallbladder ($p < 0.001$) were significantly different between groups. The surgical difficulty was unrelated to the timing of surgery. The postoperative complications were more frequent in operations more than 72 hours after disease onset ($p = 0.04$) and with CT attenuation around the gallbladder of ≥ 1.4 ($p = 0.036$).

Conclusion: High attenuation around the gallbladder on plain CT predicted a high surgical difficulty of laparoscopic cholecystectomy. We recommend measuring the CT attenuation around the gallbladder in patients with acute cholecystitis.

Keywords: Computed tomography; Laparoscopic cholecystectomy; Surgical difficulty

Introduction

In 1998, the first randomized controlled trial to determine the optimal timing of laparoscopic cholecystectomy for acute cholecystitis was conducted. At the time, early laparoscopic cholecystectomy, meaning within 24 or 72 hours after the onset of acute cholecystitis, demonstrated better results in terms of the length of hospitalization and time to return to work than did delayed laparoscopic cholecystectomy performed after six to eight weeks.(1, 2) Since then, the ideal timing of laparoscopic cholecystectomy for acute cholecystitis has been examined in large numbers of patients at many facilities, also demonstrating a favorable prognosis for early-stage laparoscopic cholecystectomy.(3) However, not all hospitals can perform surgery within 72 hours after the onset of acute cholecystitis. For various reasons that include limited availability of surgeons and anesthesiologists and the lack of operating rooms, some hospitals cannot perform emergency operations. More recent reports have shown no significant differences in surgical safety, rate of postoperative complications, and length of hospitalization when surgery is performed before as compared to after 72 hours from the onset of acute cholecystitis.(4)

Based on these results, the Tokyo Guidelines 2018 (TG18), (5-7) the guidelines for the treatment of acute cholecystitis and cholangitis, recommend surgery within one week after disease onset. However, because the severity of acute cholecystitis varies among patients, an index that objectively predicts the surgical difficulty is required to time operations correctly.

In this study, we examined whether the measurement of attenuation around the gallbladder on the preoperative abdominal plain computed tomography (CT) can

predict 1) the surgical difficulty of laparoscopic cholecystectomy for acute cholecystitis and 2) postoperative complications.

Materials and Methods

In this study, we retrospectively reviewed the files of 84 consecutive patients undergoing laparoscopic cholecystectomy for acute cholecystitis, all performed by surgeons certified by the Japanese Society of Gastroenterological Surgery, at our institution between January 2015 and December 2018. During this period, three board certified surgeons performed the operations.

The surgical method and energy equipment used were the same for all surgeons. All cases were performed with four trocars. If maintaining the field of view was difficult, one additional trocar was allowed. The energy equipment used in all cases was a hook-type electric knife. An ultrasonic scalpel was added only when the surgery was difficult to complete with only an electric knife. The decision to convert to open surgery was left to the surgeons.

We recorded the preoperative white blood cell count (WBC) and platelet count, the hemoglobin, albumin, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), total bilirubin, and C-reactive protein (CRP) levels, as well as the estimated glomerular filtration rate (eGFR) in all patients.

Surgical difficulty was classified according to the operative time and blood loss volume. It was determined by selecting values which were close to the median which were both easy to memorize and to apply clinically.

- difficult: both ≥120 min and ≥100 mL, respectively, n = 27 patients;

- moderate: either ≥120 min or ≥100 mL, respectively, n = 30 patients;
- easy: both <120 min and <100 mL, respectively, n = 27 patients.

The CT attenuation around the gallbladder was measured on a plain abdominal CT within three days before the operation. The attenuation around the gallbladder was defined as the ratio of the sum of the CT attenuation values of the two fat areas near the fundus and neck of the gallbladder to the sum of the CT attenuation values of the dorsal subcutaneous fat left and right of the third lumbar vertebra (Figure 1). Every region of interest (ROI) was set to about 100 mm^2, and the average CT attenuation value in each region was used. In this study, we excluded cases in which the ROIs could not be set to approximately 100 mm^2 due to low fat around the gallbladder because the patient was slender.

The severity of cholecystitis was classified using the TG18 acute cholecystitis severity classification.(8) We examined the timing of surgery within 72 hours after the onset of disease, conversion rate to open surgery, incidence of postoperative complications, and length of postoperative hospitalization. Postoperative complications were assessed using the Clavien-Dindo classification.(9, 10)

Perioperatively, antibiotics were administered as follows: A cephalosporin after induction of anesthesia and thereafter every three hours during the operation. The cephalosporin was given for two days after surgery. It was changed or continued based on the clinical course if necessary.

All variables were compared between the difficult, moderate, and easy groups. We also identified the predictive factors of difficult surgical cases and postoperative complication cases.

All procedures in this study conformed to the Declaration of Helsinki and its later amendments, and the protocol was approved by the ethics committee of our institution (R2020-078). Informed consent was obtained on an opt-out basis from all patients or their family members.

Statistical analyses

We described continuous variables as the mean ± standard deviation when normally distributed and as the median and interquartile range when not normally distributed. The three groups of surgical difficulty were compared using the chi-square test for nominal variables and the Kruskal-Wallis test for continuous variables. Multivariate logistic regression analysis was performed using the variables that had shown p-values of <0.05 in the univariate analysis. The continuous variables used in the univariate analysis were divided according to clinically intuitive values close to the cutoff value using a receiver-operating characteristic analysis. The level of statistical significance was set at a p-value < 0.05 for all analyses. All statistical analyses were performed with the statistical software R, version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria; https://cran.r-project.org/bin/macosx/).

Results

Patients' baseline and clinical characteristics are shown in Table 1. The mean age of the patients was 61.9 years in the easy group, 67.8 years in the moderate group, and 72.8 years in the difficult group (p = 0.015). There was no significant

difference in the sex ratio among the three groups. The WBCs were significantly higher in the moderate and difficult groups as compared to the easy group ($p = 0.002$). The albumin levels were 3.8, 3.5, and 3.3 g/dl in the easy, moderate, and difficult groups, respectively, which was significantly different ($p = 0.003$). No significant differences in the AST, ALT, ALP, and γ-GTP levels and the eGFR were found among the three groups, while the total bilirubin levels were significantly higher in the moderate and difficult groups as compared to the easy group ($p = 0.02$). The CRP values were significantly higher in the moderate and difficult groups as compared to the easy group ($p < 0.001$). The higher the TG18 severity classification of cholecystitis, the greater was the surgical difficulty ($p = 0.005$). The conversion rate to open surgery was 22.2% in the difficult group, which was significantly higher than that in the two other groups ($p = 0.006$). The rate of postoperative complications with a Clavien-Dindo classification grade ≥ II increased as the surgical difficulty increased, but this difference was not statistically significant. The postoperative hospitalization was significantly longer in the difficult group as compared to the two other groups ($p = 0.001$). The average attenuation values (Hounsfield unit; HU) of the two fat areas near the fundus and neck of the gallbladder were -100.63 HU in the easy group, -73.03 HU in the moderate group, and -50.64 HU in the difficult group ($p < 0.001$). Additionally, the average attenuation values of the left and right dorsal subcutaneous fat tissue of the third lumbar vertebra were similar among the three groups ($p = 0.786$). The CT attenuation around the gallbladder which was defined as the ratio of the average attenuation values around the gallbladder to the average attenuation values of dorsal subcutaneous fat tissue were 1.05, 1.45,

and 1.96 in the easy, moderate, and difficult groups, respectively, which was a significant difference ($p < 0.001$) (Table 1).

Table 2 shows the predictive factors of difficult surgical cases (patients of difficult group). In the univariate analysis, significant differences were observed in the patients with an albumin level <3.5 g/dL, CRP level ≥5 mg/dL, moderate (grade II) or severe (grade III) acute cholecystitis according to the TG18 classification, and the CT attenuation around the gallbladder ≥1.4. In the multivariate analysis, CRP levels of ≥5 mg/dL and the CT attenuation around the gallbladder of ≥1.4 were identified as independent predictive factors of difficult surgical cases (Table 2).

Table 3 shows the predictive factors of postoperative complications with a Clavien-Dindo grade ≥ II. The univariate analysis revealed significant differences in patients with ALT levels of ≥30 IU/L, patients who underwent surgery ≥72 hours after the onset of cholecystitis, and patients with the CT attenuation around the gallbladder of ≥1.4. The multivariate analysis demonstrated that surgery more than 72 hours after the onset of cholecystitis and the CT attenuation around the gallbladder of ≥1.4 were independent risk factors of postoperative complications (Table 3).

Discussion

This study used CT attenuation around the gallbladder to quantify the severity of inflammation in patients with acute cholecystitis and relate it to the surgical difficulty. We established that the CT attenuation around the gallbladder was related to both the severity of cholecystitis and surgical difficulty, but the latter

was not related to the timing of surgery. Postoperative complications were more frequent in operations performed more than 72 hours after disease onset and in patients with a CT attenuation around the gallbladder of ≥1.4.

Acute cholecystitis is a common disease that is treated with cholecystectomy in hospitals worldwide, but the optimal timing of surgery remains controversial. Early surgery after the onset of cholecystitis results in more severe systemic inflammation than delayed surgery. Meanwhile, delayed operations can often be technically challenging owing to adhesions and thickening of the tissue around the gallbladder, even when systemic inflammation is mitigated.

Previous reports indicated similar complication rates for both early and delayed cholecystectomy, while early cholecystectomy resulted in longer operative time but shorter hospitalization.(1, 2) Since then, numerous studies have examined various factors, including medical expenses and quality-adjusted life-years, indicating advantages for early cholecystectomy.(4, 11-18)

The superiority of early surgery was confirmed in studies of cholecystectomies after both the treatment of choledocholithiasis with endoscopic retrograde cholangiopancreatography and acute pancreatitis.(19-23) Consequently, surgery is recommended within 72 hours from the onset of acute cholecystitis.

The TG18 for acute cholecystitis recommend surgery within one week after disease onset in all patients who can tolerate the operation because the short-term results were similar for surgery within 24 or 72 hours and one week after disease onset in a meta-analysis.(7)

Regardless, it remains unclear whether early surgery is recommended for all patients because the severity of cholecystitis varies considerably. In this study,

we used CT attenuation around the gallbladder to quantify the degree of cholecystitis in each patient and examined whether it correlates with the surgical difficulty and severity of postoperative complications. In general, because CT attenuation is related to tissue inflammation, a high CT attenuation around the gallbladder indicates more severe inflammation around the gallbladder.

The CT attenuation value is defined with water as 0 Hounsfield units (HU) and air as the lowest value, -1000 HU; -1000 HU of air is set to display in black on the CT image. The higher the density of the substance, that is, the X-ray absorption value, the higher the CT value. Generally, bone is +1000 HU and normal fat tissue is 0 to -100 HU. When inflammation occurs in a relatively soft tissue due to infection, the vascular permeability is enhanced and exudate is generated from the tissue. Exudate is a plasma component containing proteins such as water, globulin, albumin, and fibrinogen, and is useful for tissue repair. Therefore, when the inflammation of cholecystitis spreads beyond the gallbladder wall to the surrounding fat tissue, the fat tissue is filled with a large amount of exudate and becomes edematous. As described above, the CT attenuation value of normal fat tissue is under 0 HU, but the exudate containing blood protein has a concentration higher than that of water, so the attenuation value of the exudate exceeds 0 HU. Therefore, the more severe the inflammation, the more exudate is mixed in the fat tissue, and the higher the CT attenuation value.

The rationale of this study was based on the fact that the degree of inflammation around the gallbladder influences surgical difficulty in laparoscopic cholecystectomy. Previous studies that evaluated the severity of cholecystitis on CT images all used contrast CT.(24-26) However, contrast CT cannot be used in

all patients because some may have allergies or reduced renal function. Some hospitals may be unable to use contrast CT in an emergency at night. Additionally, plain CT can be used in all patients and is likely to be performed as part of the routine diagnostic workup in acute cholecystitis. This is considered to be an advantage of our study over the previous studies.

We found a high degree of surgical difficulty more frequently in elderly patients and patients with high preoperative WBC, bilirubin, and CRP levels and low albumin levels. The CT attenuation around the gallbladder and the severity of cholecystitis according to the TG was related to surgical difficulty. However, no correlation was observed between surgical difficulty and surgery within 72 hours after the onset of cholecystitis. The predictive factors of surgical difficulty were a CRP level of ≥ 5 mg/dL and CT attenuation around the gallbladder of ≥1.4. Moreover, the predictive factors for postoperative complications (Clavien-Dindo grades > II) were a delay of surgery for more than 72 hours after disease onset and CT attenuation around the gallbladder of ≥1.4.

Consequently, we recommend aiming for an early operation within 72 hours of disease onset whenever possible. However, because the surgical difficulty may vary considerably, the CRP level and CT attenuation around the gallbladder should be considered to identify patients suitable for early operation. If surgery can only be performed after more than 72 hours, the CT attenuation around the gallbladder may also provide guidance in that the operation should be delayed until the attenuation level has dropped in cases with high levels. The exact level needs to be determined in future studies.

The limitations of this study include its retrospective design and that it collected data from a single facility in a small number of patients. We also defined the classification of surgical difficulty uniquely. At this time, there is no international standard criteria of difficulty in laparoscopic cholecystectomy. Therefore, we selected the operative time and blood loss volume obtained from the database we used. In addition, while all surgeons in this study were board certified by the Japanese Society of Gastroenterological Surgery, the operators differed among patients. Prospective studies with a large number of cases are needed to validate our results.

In conclusion, CT attenuation around the gallbladder and CRP levels were confirmed as predictors for the surgical difficulty of laparoscopic cholecystectomy in acute cholecystitis. Factors contributing to postoperative complications were CT attenuation around the gallbladder and a delay of surgery for more than 72 hours after disease onset. We recommend measuring the CT attenuation around the gallbladder in all patients with acute cholecystitis on the plain abdominal CT that is often routinely performed.

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Ethical approval

The study protocol conformed to the Clinical Research Guidelines and was

approved by the ethical committee of our institution (approval number: R2020-078).

Consent to participate / Consent for publication

Informed consent was obtained on an opt-out basis from all patients or their family members.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable

Author Contributions

HI designed the research and analyzed the patient data. HI, HM, HM, HK, AT, KT, MK, SK, TM, and MT performed data collection. HI drafted the manuscript. All authors read and approved the final version of the manuscript.

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Figure legends

Figure 1. Calculation of the CT attenuation around the gallbladder

The computed tomography (CT) attenuation around the gallbladder is calculated by adding the CT attenuation values near the fundus of the gallbladder (*FGB*) and near the neck of the gallbladder (*NGB*), and dividing that sum by the sum of the CT attenuation values of the dorsal subcutaneous fat tissue right and left of the third lumbar vertebra (*RDL* and *LDL*) as follows: [(*FGB*) + (*NGB*)/(*RDL*) + (*LDL*)].

a) Example of low CT attenuation around the gallbladder

b) Example of high CT attenuation around the gallbladder

Table 1. Comparison of background factors, operative factors and CT attenuation around the gallbladder among groups classified by surgical difficulty

		Easy group (n=27)	Moderate group (n=30)	Difficult group (n=27)	p-value
Age (years)		61.9 ± 14.3	67.8 ± 15.1	72.8 ± 10.4	0.015
Gender (%)	Woman	11 (40.7)	11 (36.7)	9 (33.3)	0.852
	Man	16 (59.3)	19 (63.3)	18 (66.7)	
Hemoglobin (g/dL)		12.9 [11.9, 14.0]	13.0 [11.3, 13.9]	12.6 [11.6, 13.8]	0.97
WBC (x1000^3/μL)		7.0 [6.3, 9.6]	13.6 [8.90, 16.7]	11.3 [8.3, 17.3]	0.002
PLT (x1000^3/μL)		230 [190, 273]	202 [159, 281]	211 [183, 262]	0.715
Albumin (g/dL)		3.8 [3.4, 4.0]	3.5 [2.9, 3.7]	3.3 [2.9, 3.5]	0.003
AST (IU/L)		20 [16, 30]	24 [16, 47]	27 [22, 36]	0.093
ALT (IU/L)		20 [16, 32]	25 [13, 55]	24 [20, 39]	0.499
ALP (IU/L)		228 [180, 276]	242 [194, 317]	255 [200, 472]	0.362
γ-GTP (IU/L)		35 [25, 64]	46 [17, 229]	55 [33, 79]	0.183
Total bilirubin (mg/dL)		0.87 [0.67, 1.12]	1.18 [0.98, 1.45]	1.11 [0.75, 1.35]	0.02
eGFR (mL/min/1.73m^2)		74.6 [60.1, 91.5]	68.0 [55.8, 80.0]	64.6 [58.4, 80.4]	0.512
CRP (mg/dL)		0.52 [0.20, 1.06]	7.23 [2.79, 15.7]	9.92 [5.58, 16.8]	<0.001

TG 18 grade (%)	Mild (I)	20 (74.1)	15 (50.0)	6 (22.2)	0.005
	Moderate (II)	6 (22.2)	13 (43.3)	19 (70.4)	
	Severe (III)	1 (3.7)	2 (6.7)	2 (7.4)	
Operation within 72 hours from symptom (%)		17 (63.0)	24 (80.0)	15 (55.6)	0.131
Conversion to open surgery (%)		0 (0)	1 (3.3)	6 (22.2)	0.006
Complications (CD grade ≥II) (%)		2 (7.4)	4 (13.3)	7 (25.9)	0.157
Hospitalization (days)		5 [3, 6]	5 [4, 9]	9 [6, 13]	0.001
Average attenuation value around the gallbladder (HU)		-100.63 [-106.03, -91.10]	-73.03 [-100.71, -49.84]	-50.64 [-71.33, -34.67]	<0.001
Average attenuation value of the dorsal subcutaneous fat (HU)		-107.46 [-112.82, -101.99]	-107.94 [-112.67, -103.87]	-107.61 [-112.08, -95.38]	0.786
CT attenuation around the gallbladder		1.05 [1.02, 1.15]	1.45 [1.11, 2.13]	1.96 [1.49, 3.02]	<0.001

Abbreviations: WBC, white blood count; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline Phosphatase; γ-GTP, γ-glutamyl transpeptidase; eGFR, estimated glemerular filtration rate; CRP, C-reactive protein; TG, Tokyo guidelines; CD, Clavien-Dindo classification; HU, Hounsfield unit

Age is expressed as mean ± standard deviation

Other continuous variables are expressed as median [25percentile, 75percentile]

Table 2. Univariate and multivariate analysis to identify factors predicting difficult surgical cases

	Univariate analysis		Multivariate analysis	
	Risk ratio	p-value	Risk ratio	p-value
Age ≥70 years old	2.64 (0.99-7.00)	0.051		
Male patients	1.26 (0.48-3.29)	0.64		
Presence of anemia	0.77 (0.31-1.94)	0.58		
WBC ≥10000 /μL	1.73 (0.69-4.39)	0.24		
PLT ≥150000 /μL	1.39 (0.41-4.74)	0.6		
Albumin <3.5 g/dL	2.70 (1.05-6.96)	0.039	1.08 (0.33-3.48)	0.9
AST ≥30 IU/L	1.48 (0.58-3.77)	0.41		
ALT ≥30 IU/L	1.09 (0.42-2.82)	0.86		
ALP ≥300 IU/L	1.60 (0.63-4.09)	0.33		
γ-GTP ≥50 IU/L	1.85 (0.73-4.66)	0.19		
Total bilirubin ≥1.0 mg/dL	1.05 (0.42-2.63)	0.92		
eGFR <60 mL/min/1.73m^2	1.18 (0.44-3.14)	0.74		
CRP ≥5.0 mg/dL	8.14 (2.67-24.80)	0.00022	3.91 (1.10-13.90)	0.035
Moderate or severe of TG18 grade	5.57 (1.94-16.00)	0.0014	2.53 (0.74-8.68)	0.14
Operation within 72 hours from symptom	2.05 (0.79-5.32)	0.14		
High CT attenuation around the gallbladder	11.50 (3.48-38.00)	0.000063	5.00 (1.33-18.70)	0.017

Abbreviations: WBC, white blood count; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline Phosphatase; γ-GTP, γ-glutamyl transpeptidase; eGFR, estimated glemerular filtration rate; CRP, C-reactive protein; TG, Tokyo guidelines
Presence of anemia is defined as hemoglobin level of <13 g/dL for men and <12 g/dL for women
High CT attenuation around the gallbladder is defined as ≥1.4

Table 3. Univariate and multivariate analysis to identify factors predicting postoperative complications

	Univariate analysis		Multivariate analysis	
	Risk ratio	p-value	Risk ratio	p-value
Age ≥70 years old	3.24 (0.82-12.80)	0.093		
Male patients	0.63 (0.19-2.09)	0.46		
Presence of anemia	0.88 (0.27-2.89)	0.84		
WBC ≥10000 /μL	0.83 (0.26-2.73)	0.76		
PLT ≥150000 /μL	0.41 (0.05-3.46)	0.41		
Alb <3.5 g/dL	3.07 (0.87-10.90)	0.083		
AST ≥30 IU/L	2.15 (0.65-7.09)	0.21		
ALT ≥30 IU/L	3.56 (1.05-12.10)	0.042	1.91 (0.48-7.56)	0.36
ALP ≥300 IU/L	2.59 (0.73-9.20)	0.14		
γ-GTP ≥50 IU/L	1.51 (0.46-4.93)	0.5		
Total bilirubin ≥1.0 mg/dL	2.07 (0.58-7.34)	0.26		
eGFR <60 mL/min/1.73m^2	0.99 (0.28-3.56)	0.99		
CRP ≥5.0 mg/dL	1.74 (0.52-5.84)	0.37		
Moderate or severe of TG18 grade	1.65 (0.49-5.52)	0.42		
Operation within 72 hours from symptom	4.08 (1.19-14.00)	0.025	4.39 (1.07-18.00)	0.04
High CT attenuation around the gallbladder	4.06 (1.03-16.00)	0.045	4.90 (1.10-21.70)	0.036

Abbreviations: WBC, white blood count; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline Phosphatase; γ-GTP, γ-glutamyl transpeptidase; eGFR, estimated glemerular filtration rate; CRP, C-reactive protein; TG, Tokyo guidelines
Presence of anemia is defined as hemoglobin level of <13 g/dL for men and <12 g/dL for women
High CT attenuation around the gallbladder is defined as ≥1.4

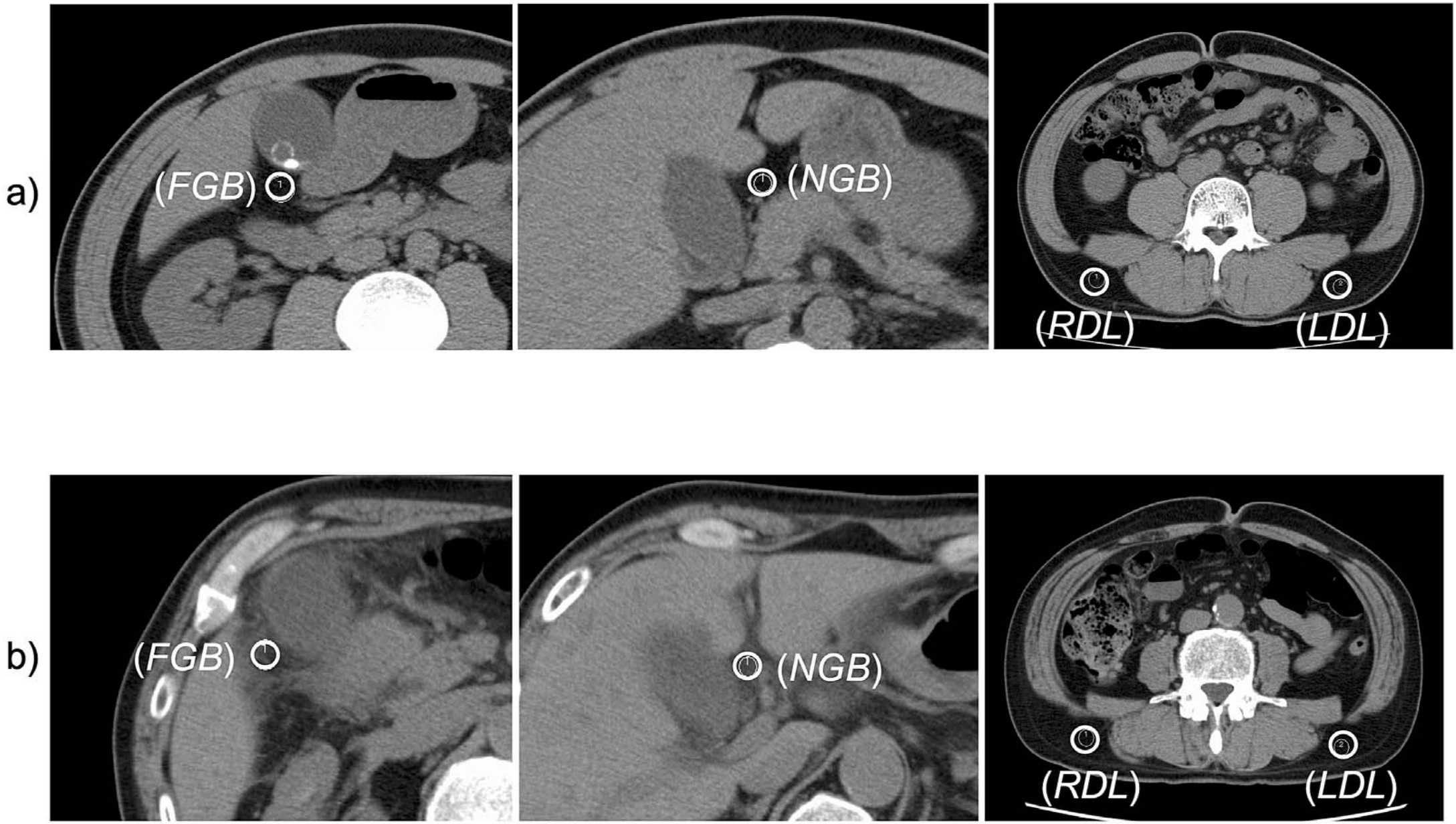

Figure 1