Visceral Obesity Determined by CT As a Predictor of Short-term Postoperative Complications in Ovarian Cancer

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Research Article

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Abstract

Objective: To explore the association between visceral obesity and short-term postoperative complications in patients with advanced ovarian cancer undergoing cytoreductive surgery.

Methods: Medical records were reviewed for patients with ovarian cancer. Visceral fat area, subcutaneous fat area and total fat area were measured on a single slice at the level of L3/4 of a preoperative CT scan. Univariable and multivariable analyses were performed to investigate the correlation between visceral obesity and short-term complications and to analyze the risk factors for complications after surgery.

Results: Of the 130 patients, 53.8% (70/130) were presented visceral obesity. Patients with visceral obesity were older than those with nonvisceral obesity (58.3 years old vs. 52.3 years old, $p = 0.001$). The proportion of patients with hypertension was slightly higher (37.1% vs. 11.7%, $p = 0.001$). The total fat area and subcutaneous fat area were higher in patients with visceral obesity (296.9 ± 72.1 vs. 173.1 ± 67.3, $p < 0.001$; 168.8 ± 55.5 vs. 121.6 ± 54.3, $p < 0.001$). Compared with patients in the nonvisceral obese group, patients in the visceral obese group were more likely to have postoperative fever (21/70 30.0% vs. 8/60 1.25%, $p = 0.023$), leading to a longer length of hospital stay (21 days vs. 17 days, $p = 0.009$). Time from surgery to adjuvant chemotherapy for patients with visceral obesity has been delayed (24 days vs. 20 days, $p = 0.037$). Multivariate analysis showed that visceral obesity (OR 4.770, $p < 0.001$) and operation time (OR 1.008, $p < 0.001$) were independent predictors of postoperative complications.

Conclusion: Visceral obesity is an important risk factor for short-term postoperative complications in patients with advanced ovarian cancer undergoing cytoreductive surgery.

Introduction

Ovarian cancer is the most lethal gynecologic malignancies [1]. Cytoreductive surgery and chemotherapy are considered the standard treatments for advanced ovarian cancer. Removing all visible tumors during cytoreductive surgery provides the best survival outcome for patients [2]. However, patients with advanced ovarian cancer often have extensive metastases in the abdominal and pelvic cavity, including the omentum, intestine, peritoneum, appendix, liver, abdominal and pelvic lymph nodes [3]. Complete removal of tumors may only be achievable through more aggressive surgery, which may result in higher complication rates, including tissue damage, massive bleeding, prolonged operating time, etc [4]. Therefore, identifying risk factors that can predict short-term complications will provide value for the management of perioperative patients.

Hughes et al. recently reported a significant difference in the overall complication incidence of obese patients and nonobese patients after major abdominal surgery in gastric, rectal and liver cancers [5]. Apart from increasing difficulties during cytoreductive surgery, obesity may also contribute to more postoperative complications and higher costs [6]. Body mass index (BMI) is the most common indicator of obesity. However, it cannot be used to describe the distribution of abdominal fat. Recently, visceral fat area (VFA), total fat area (TFA) and subcutaneous fat area (SFA) have been proposed to assess fat distribution in obese patients [7]. Takeuchi et al. found that patients with high visceral fat areas were associated with postoperative complications in gastric cancer [8]. However, whether visceral obesity could predict short-term postoperative complications in patients with ovarian cancer remains unclear. Computed tomography (CT) scans are broadly used to assess the condition of patients with ovarian cancer and are more accurate and sensitive for assessing fat distribution [9-10].

Thus, the aim of this study was to determine the relationship between visceral obesity determined by CT scans and the short-term postoperative complications of ovarian cancer. Visceral obesity is an important predictor of short-term complications after cytoreductive surgery for advanced ovarian cancer.

Methods

Patients with ovarian cancer undergoing cytoreductive surgery between January 2018 and December 2020 in the First Affiliated Hospital of Nanjing Medical University were included, and a preoperative abdominal CT scan within 3 weeks was included. Those who had incomplete perioperative data or underwent any treatment after CT scan were excluded. All complications occurring within 30 days after surgery were included and classified according to the Clavien-Dindo classification (CDC) [11]. Grade I complications can be treated with antipyretics, diuretics, analgesics, and fluid replacement in the clinic, which were regarded as clinically meaningless complications. This study only analyzed complications of grade II and above. If one patient had multiple complications with different grades, the classification of complications was based on the highest complication rate. Extent and complexity of surgery was categorized using a previously described surgical complexity score (SCS) [12], which were defined as low, intermediate, and high (scores 1 to 3, 4 to 7, and ≥ 8, respectively). This study was approved by the Institutional Review Board at the First Affiliated Hospital of Nanjing Medical University.

Image analysis was performed using ImageJ software (ImageJ; The National Institutes of Health, 105 Washington, MD, USA; version 1.47). Preoperative CT scan images of 130 patients with ovarian cancer at the level of L3-L4 were completely obtained. In this study, VFA, TFA and SFA were measured using a tissue attenuation range of -190 ~ -30 HU [13]. (Figure 1)

Statistical analysis: SPSS statistics v24 was used for all statistical analysis. The best cutoff value of VFA was determined by the Receiver Operating Characteristic curve (ROC curve). Patients were also classified according to BMI in three categories: normal BMI (< 25 kg/m^2), overweight (25-30 kg/m^2) and obese (≥30 kg/m^2). Continuous data are reported as the mean (± SD), and categorical data are reported as numbers (percentage). Comparisons between groups were made by Student's test or Mann–Whitney U test for continuous data and chi-squared test or Fisher's exact test for categorical variable data. The distribution between VFA and BMI was analyzed by linear regression. A *p*-value < 0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to explore the predictors of postoperative complications in patients with advanced ovarian cancer undergoing cytoreductive surgery. The variables with a *p*-value < 0.05 in the univariate analysis were evaluated in a multivariate logistic regression analysis.

Results

A total of 130 patients were included in this study. We first analyzed the correlation between BMI and VFA, and BMI and VFA were found to have a positive correlation (r = 0.606, $p < 0.001$) (Figure 2). BMI resulted to be lower than 25 kg/m^2 were in majority of patients (72.3%), between 25 and 30 kg/m^2 were in 21.5% and higher than 30 kg/m^2 were in 6.2%.

The clinicopathological characteristics of the 130 patients are summarized in Table 1. Their median age was 55 years (range, 24–80 years). There is a lack of visceral obesity standards for the Chinese population based on CT measurements. According to the ROC curve, 86.7 was determined to be the best cutoff value to divide patients into two groups, visceral obesity and nonvisceral obesity. Patients with visceral obesity were older than those with nonvisceral obesity (58.3 years old vs. 52.3 years old, p = 0.001) (Table 1). TFA and SFA were much higher in the visceral obesity group (296.9 ± 72.1 vs. 173.1 ± 67.3, $p < 0.001$; 168.8 ± 55.5 vs. 121.6 ± 54.3, $p < 0.001$) (Table 1). Patients with visceral obesity were more likely to have hypertension (37.1% vs. 11.7%, p = 0.001).

In patients with visceral obesity, high-density lipoprotein (HDL) and lipoprotein a (LPa) were low (p = 0.013, p = 0.001), while triglycerides (TG) (p = 0.000) were high. However, serum CA125 and HE4 levels were not significantly different between the two groups (Table 2).

Due to the large scope of cytoreductive surgery for advanced ovarian cancer, postoperative complications will increase. We found that 39% (51/130) of patients with advanced ovarian cancer had ≥ 2 postoperative complications. In addition, we analyzed the correlation between visceral obesity and postoperative complications in patients with stage III-IV disease, and the number of postoperative complications in patients with visceral obesity increased significantly ($p < 0.001$). Patients with visceral obese prolonged the time from surgery to adjuvant chemotherapy (p = 0.037). Patients in the visceral obese group were more likely to have postoperative fever (p = 0.023) (Table 3).

Considering BMI categories, no differences were detected for intra-operative, post-operative and short-term outcomes (Table S1).

Postoperative treatment and rehabilitation of Patients with fever were reported in Table 4. More types of antibiotics were used in patients with postoperative fever. And the using time of antibiotics and length of hospital stay prolonged significantly ($p < 0.001$, $p < 0.001$, p = 0.009) (Table 4).

To investigate whether the characteristics of patients with visceral obesity have independent predictive value for the occurrence of complications, univariate and multivariate logistic regression analyses were performed. Univariate analysis showed that operation time, intraoperative blood loss, intraoperative bowel resection and SCS were significantly associated with postoperative complications. In multivariate analysis, visceral obesity (OR 4.770, $p < 0.001$) and operation time (OR 1.008, $p < 0.001$) were independent predictors of postoperative complications (Table 5).

Discussion

Epidemiological evidence confirms that obesity is a risk factor for the onset of a variety of cancers [14-15]. To determine obesity, BMI is typically used, and patients with a BMI of ≥30 kg/m² are defined as obese. However, BMI does not reflect the whole-body fat distribution [16]. Traditionally, intra-abdominal fat is indirectly measured by waist circumference, hip circumference or waist-to-hip ratio [17]. Whereas, these parameters do not reflect the distribution of body fat either. In the present study, CT was used to measure the visceral fat area directly. Our results showed that patients could have visceral obesity even with a normal BMI. Nevertheless, an appropriate range of CT values for adipose tissue segmentation has not yet been determined. In a recent study, visceral obesity in females was defined as > 80.1 cm², using metabolic syndrome (MetSyn) as an indicator of obesity-associated dysmetabolism in obesity-associated cancer [18-19]. Heus et al. found that the visceral fat area threshold was 100 cm² and 130 cm², and 100 cm² had a better correlation with postoperative complications [20]. In the present study, We use ROC curve to define the best cutoff value. The incidence of complications after cytoreductive surgery increased significantly in patients with visceral obesity. This suggests that providers should design strategies to reduce complications and be more aware of the possibility of complications.

The occurrence of postoperative complications is an important unfavorable factor for the rapid recovery of patients [21]. It is particularly critical to identify the factors predicting postoperative complications. Severe complications can be the result of complex procedures. These complications can result in delays of the start of adjuvant therapy, which can worsen the condition. In a study of 369 patients who had an abdominal or laparoscopic procedure for proven or suspected gynecological cancer, Kondalsamy-Chennakesavan et al. demonstrated that surgical complexity was one of the independently predictive factors of an adverse events [22]. In our study, the complexity of the operation was scored by SCS. Univariate analysis also showed that SCS weas significantly associated with postoperative complications, while result of multivariate analysis was not. The reason for this inconsistency may be due to small size of enrolled patients.

Whether visceral obesity can be used to predict postoperative complications in patients has been controversial. C. Heus et al. found that patients with visceral obesity had an increased risk of postoperative complications [23]. In contrast, the study by Rutten et al. showed that there was no correlation between visceral obesity and postoperative complications [24]. It is worth noting that the characteristics of the patients included in these two studies were not consistent. Moreover, the operation period was also inconsistent, and the selected CT scan images and method of measurement were also different. In this study, VFA was manually traced on a single transverse slice at the level of L3–L4. Importantly, visceral obesity defined as a VFA of ≥ 86.7 cm^2 was identified as an independent prognostic factor associated with postoperative complications. In addition, Boutin et al. found that there was no significant relationship between adipose tissue distribution and postoperative complications in patients with soft tissue sarcoma [25]. The results from three studies on complications of radical resection of gastrointestinal tumors revealed that an increase in visceral fat could lead to a prolonged operation time, poor recovery and postoperative complications [26-28]. These studies suggest that visceral obesity may only have predictive value in certain types of tumors.

Postoperative fever is common in patients undergoing cytoreductive surgery. A postoperative body temperature rise (<38.0 °C) does not require special treatment [29]. In this study, we found that patients with visceral obesity were more likely to have postoperative fever and a postoperative body temperature ≥38.0 °C. Adipose tissue is the primary site for storing and mobilizing lipids: it is also associated with endocrine and metabolic functions and contains multiple immune cells [30]. Weisberg et al. demonstrated that the number of macrophages increases during obesity, and the expression of TNF-α and IL-6 are induced, which activate the inflammatory pathway [31]. Similarly, the low levels of adiponectin in obese patients may increase postoperative insulin resistance and induce inflammation [32]. Therefore, the increase in postoperative fever in patients with visceral obesity may be related to the greater release of these inflammatory factors, but this needs further study.

In this study, preoperative CT images were used to assess the incidence of postoperative complications. Visceral obesity was defined as > 86.7 cm^2, which improved the applicability in clinical practice. Our study confirmed that BMI is a weak indicator for short-term surgical and recovery outcomes after cytoreductive surgery. However, this study also has some limitations. First, it was a single-center and retrospective study that produced inherent and unavoidable biases. Second, In China, due to the lack of rehabilitation institutions to assist in the management of postoperative patients, most patients need to recover in the hospital after surgery, which leading to a relatively long hospital stay. At the same time, the length of hospital stay is prolonged also because of the immediate postoperative chemotherapy. Meanwhile, it may help us observe mild complications. Last, the sample size was small. The number of samples needs to be increased to further prove that visceral obesity is an independent predictor of short-term complications of cytoreductive surgery for ovarian cancer.

Declarations

Author contributions

Xianglin Nie, Lin Zhang, Wenjun Cheng made substantial contributions to the project administration, visualization, writing of original draft, review and editing of the manuscript. Xianglin Nie, Huangyang Meng and Yi Zhong made substantial contributions to patient selection and clinical data. Yi Jiang made substantial contributions to review the records. Ting chen made substantial contributions to the usage of CT and ImageJ. All authors approved this final version of the manuscript.

Declaration of Competing Interest

The authors declare no relevant conflicts of interest.

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Tables

Table 1. Clinicopathological characteristics

Characteristics	Obesity	Non-obesity	*P*-value
	N=70	N=60	
Age (years)	58.3(9.1)	52.3(10.9)	**0.001**
Abdominal surgery times n (%)			
≥ 2 times	7(10.0)	10(16.7)	0.261
< 2 times	63(90.0)	50(83.3)	
Hypertension n (%)	26(37.1)	7(11.7)	**0.001**
Diabetes n (%)	5(7.1)	1(1.7)	0.287*
Ascites n (%)			
≥3000 ml	22(31.4)	19(31.4)	0.977
< 3000 ml	48(68.6)	41(68.3)	
ASA n (%)			
ASA1	35(50.0)	38(63.3)	0.304*
ASA2	33(47.1)	21(35.0)	
ASA3	2(2.9)	1(1.7)	
FIGO stage n (%)			
III	57(81.4)	58(96.7)	0.700
IV	13(18.6)	2(3.3)	
Histology n (%)			
Serous	65(92.9)	54(90.0)	0.560
Non-Serous	5(7.1)	6(10.0)	
Neoadjuvant chemotherapy			
Yes	38(54.3)	29(43.3)	0.498
No	32(45.7)	31(51.7)	
SFA	168.8 ± 55.5	121.6 ± 54.3	**0.000**
TFA	296.9 ± 72.1	173.1 ± 67.3	**0.000**

*, Fisher’s exact test. BMI, Body mass index. ASA, American Society of Anesthesiologists. SFA, subcutaneous fat area. TFA, total fat area.

Table 2. Preoperative serological test results

Characteristics	Obesity	Non-obesity	*P*-value
	N=70	N=60	
PT	11.0 ± 1.0	11.2 ± 0.9	0.127
APTT	26.6 ± 2.3	27.2 ± 2.4	0.126
D-dimer	1.9 ± 2.2	1.9 ± 2.5	0.878
ALT	18.8 ± 12.7	19.1 ± 15.6	0.891
AST	23.6 ± 10.7	23.2 ± 10.7	0.803
LDH	236.4 ± 129.7	233.5 ± 133.8	0.879
HDL	1.1 ± 0.3	1.2 ± 0.3	**0.013**
LDL	2.9 ± 0.7	2.9 ± 0.7	0.916
Lpa	197.2 ± 200.4	320.9 ± 296.7	**0.001**
TC	4.6 ± 0.9	4.7 ± 1.0	0.699
TG	1.7 ± 1.0	1.2 ± 0.5	**0.000**
ALB	3.9 ± 3.4	3.8 ± 4.2	0.385
CA125	548.2 ± 978.7	551.0 ± 961.7	0.984
HE4	274.5 ± 346.9	253.8 ± 286.2	0.651

PT, Prothrombin time. APTT, activated partial thromboplastin time. ALT, alanine aminotransferase. AST, aspartate aminotransferase. LDH, lactate dehydrogenase. HDL, high-density lipoprotein. LDL, low-density lipoprotein. Lpa, Lipoprotein(a) . TC, Serum total cholesterol. TG, Triglyceride. ALB, Serum Albumin. Hb, Hemoglobin. TLC, total lymphocyte count.

Table 3. Intra- and post-operative characteristics

Characteristics	Obesity	Non-obesity	P-value
	N=70	N=60	
Blood loss volume	958.6 ± 1101.9	755.0 ± 593.1	0.203
Operation time (min)	333.9 ± 145.8	302.8 ± 120.3	
< 300	43(58.9)	30(41.1)	0.190
≥ 300	27(47.4)	30(52.6)	
Surgical approach n(%)			0.202
Open abdomen	59(85.9)	55(89.4)	
Laparoscopy to open abdomen	11(15.7)	5 (8.3)	
Scope of operation n(%)			
Bowel resection	18(25.7)	13(21.7)	0.589
Lymph node dissection/biopsy	32(45.7)	28(46.7)	0.914
Liver resection	2(2.9)	0(0)	0.545*
Diaphragmectomy	10(14.3)	13(21.7)	0.272
Ureteral stent implantation	8(11.4)	6(10.0)	0.793
SCS			
1(low)	6(28.6)	7(11.7)	
2(intermediate)	53(75.7)	45(75.0)	0.804
3(high)	11(15.7)	8(13.3)	
R0/R1			
R0	56(80.0)	49(81.7)	0.810
R1	14(20.0)	11(18.3)	
CDC	50(71.4)	22(36.7)	**0.000**
CDC1	19(27.1)	2(3.3)	0.079
CDC2	25(35.7)	17(28.3)	**0.004**
CDC3	1(1.4)	1(1.7)	0.383*
CDC4	5(7.1)	2(3.3)	0.343*
Complications			

Fever	21(30.0)	8(13.3)	**0.023**
Incision infection or bleeding	0(0)	1(1.7)	0.938*
Abnormal liver function	11(15.7)	6(10.0)	0.335
Intestinal obstruction	2(2.9)	0(0)	0.187*
Infection or sepsis	9(12.9)	7(11.7)	0.837
Thromboembolism	4(5.7)	2(3.3)	0.519*
Blood transfusion rate	12(17.1)	10(16.7)	0.942
Intestinal fistula	1(1.4)	0(0)	0.353*
Pleural effusion	9(12.9)	2(3.3)	0.052*
Antibiotic using time	9(5.1)	8(3.1)	0.371
Time to chemotherapy	24(13.9)	19(7.2)	**0.037**
ICU admission n(%)	5(7.1)	2(3.3)	0.569*
Length of hospital stay	18.2(7.5)	18.6(7.4)	0.758

*, Fisher's exact test. CDC, Clavien–Dindo classification. SCS, surgery complexity score.

Table 4. Postoperative treatment and rehabilitation of Patients with high fever

Characteristics	High fever	Non-high fever	P-value
	N=29	N=101	
Length of hospital stay	21.6(17.5)	17.5(6.3)	**0.009**
Antibiotic using time	11(7.3)	7(2.8)	**0.000**
Types of antibiotics	3(0.8)	2(0.5)	**0.000**
Time to chemotherapy	24.9(19.9)	21.5(7.4)	0.148

Table 5. Univariate and Multivariate Logistic Regression Analysis

	Univariate Logistic Regression Analysis	*P*-value	Multivariate Logistic Regression Analysis	*P*-value
	OR(95%CI)		OR(95%CI)	
Age (years)	1.009(0.975 - 1.044)	0.604		
Abdominal surgery times				
≥ 2 times	0.794 (0.274 - 2.300)	0.671		
< 2 times				
Hypertension	0.967(0.431 - 2.168)	0.934		
Diabetes	0.286(0.032 - 2.524)	0.260		
BMI				
< 25	1	0.431		
25-30	1.281 (0.692 - 2.371)			
≥ 30	-			
SFA	1.001(0.995 - 1.007)	0.698		
TFA	1.003(0.999 - 1.007)	0.092		
VO	4.365(2.063 - 9.236)	**0.000**	4.770(2.080-10.943)	**0.000**
HDL	0.672(0.179 - 2.532)	0.557		
Lpa	1.000(0.999 - 1.002)	0.539		
LDL	1.334(0.787 - 2.261)	0.285		
TG	1.421(0.855 - 2.363)	0.175		
ALB				
< 4	1.152(0.552-2.401)	0.707		
≥ 4				
ASA				
ASA1	1			
ASA2	2.424(0.210 - 27.933)	0.198		
ASA3	4.353(0.369 - 51.370)			
Neoadjuvant	0.857(0.424 - 1.731)	0.667		

chemotherapy				
Blood loss volume	1.001（1.000 - 1.002）	**0.001**		
Operation time (min)				
< 300	1.007（1.004 - 1.011）	**0.000**	1.008（1.004 - 1.011）	**0.000**
≥ 300				
Surgical approach	1.193(0.415 - 3.431)	0.744		
Scope of operation				
Bowel resection	0.350（0.138-0.887）	**0.027**		
Lymphnode dissection/biopsy	0.879（0.435-1.777）	0.720		
Diaphragmectomy	2.137（0.781-5.845）	0.139		
Ureteral stent implantation	2.682（0.710-10.126）	0.146		
SCS				
1（low）	1			
2（intermediate）	0.137（0.022-0.853）	**0.042**		
3（high）	0.144（0.032-0.659）			
R0/R1	1.226（0.508-2.962）	0.650		
FIGO stage				
III	0.723（0.232-2.535）	0.576		
IV				

BMI, Body mass index. SFA, subcutaneous fat area. TFA, total fat area. VO, visceral obesity. HDL, high-density lipoprotein. Lpa, Lipoprotein(a) . TG, Triglyceride. ALB, Serum Albumin. PNI： prognostic nutritional index.

Figures

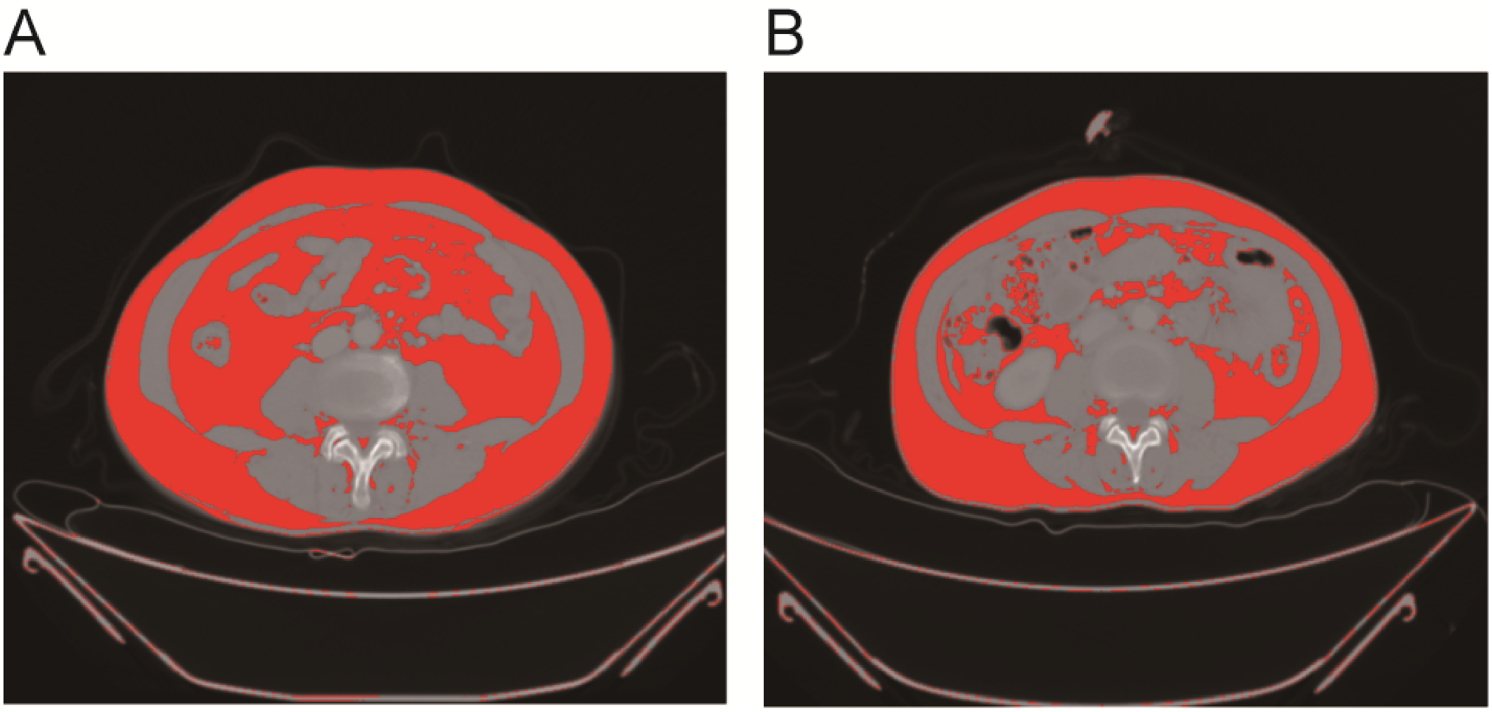

Figure 1

Visceral fat area, subcutaneous fat area and total fat area were measured on a single slice at the level of L3/4 of a preoperative CT scan. a. Visceral obesity. b. Nonvisceral obesity

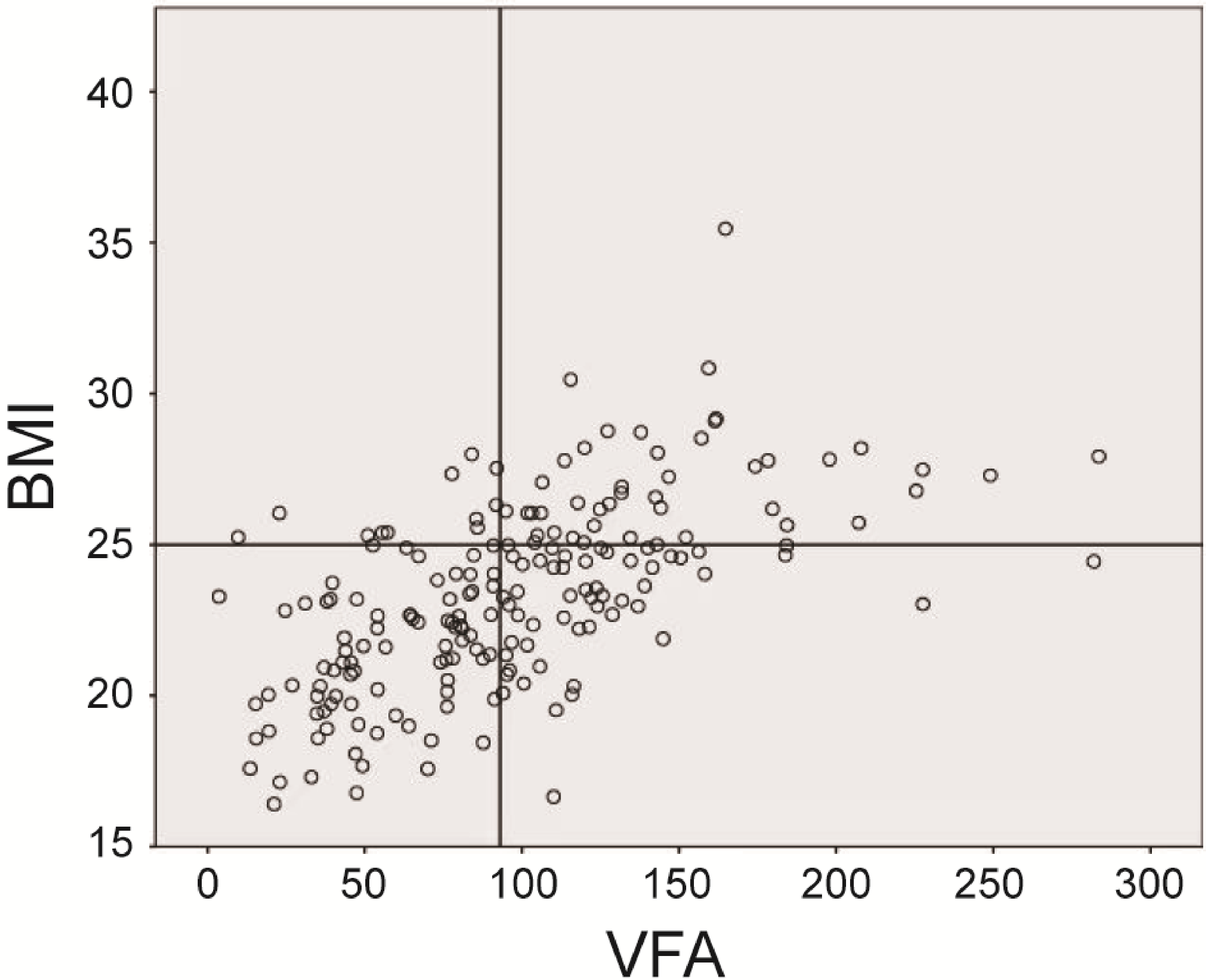

Figure 2

Correlation between BMI and VFA. BMI, Body mass index. Visceral fat area.

Supplementary Files

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- supplementaltable.docx