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A thesis of the Degree of Master of Philosophy

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The amount of visceral adipose tissue (VAT) quantitatively measured by abdominal computed tomography is dose-dependently associated with mortality in sepsis

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ABSTRACT

Introduction: Adipose tissue is recognized as not only an energy reservoir, but also an endocrine organ producing proinflammatory cytokines. An impact of visceral adipose tissue in critical illnesses has been proposed, but research regarding the association between visceral adipose tissue and sepsis is scant, and visceral adipose tissue has not been quantitatively measured.

Methods: In this retrospective cohort study, we enrolled patients admitted to our intensive care unit with sepsis who had abdominal computed tomography within 1 month of occurrence of sepsis. Age, sex, anthropometric values, comorbidities, Acute Physiology and Chronic Health Evaluation II score, source of infection, and appropriateness of antibiotics were reviewed. The areas of visceral adipose tissue and total adipose tissue on the section of abdominal computed tomography image of the umbilicus or L4-5 level were measured by calculating pixels presenting fat density.

Results: Among 310 patients admitted because of sepsis, 178 patients were finally included in this study. Median age was 65 years and 59.0% were men. In-hospital mortality rate was 59.0%. Women had more total and subcutaneous adipose tissue and a lower visceral/total adipose tissue ratio compared with men. The amount of visceral adipose tissue and the visceral/total adipose tissue ratio were higher in the in-hospital mortality group than in the group of survivors (92.00 cm^2 vs. 60.82 cm^2 and 45.88% vs. 32.79%, $P < 0.001$ and <0.001, respectively). After adjusting for age, sex, comorbidities, Acute Physiology and Chronic Health Evaluation II score, source of infection, and appropriateness of antibiotics, a multiple logistic regression analysis revealed that the amount of visceral adipose tissue and visceral/total adipose tissue ratio were independent prognostic factors of sepsis with an obvious dose-dependent relationship (visceral adipose tissue/total adipose tissue ratio quartile 3: odds ratio 8.529, $P < 0.001$ and quartile 4: odds ratio 35.772, $P < 0.001$, compared with quartile 1, respectively).

Conclusions: The amount of visceral adipose tissue and visceral adipose tissue/total adipose tissue ratio quantitatively measured by abdominal computed tomography were positively correlated with mortality in sepsis, and this association was dose dependent. Visceral obesity should be considered as the poor prognostic factor of sepsis.

Keywords: visceral adipose tissue; sepsis; abdominal computed tomography
Student number: 2013-22594

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LIST OF ABBREVIATIONS

TNF-α: tumor necrosis factor-alpha
IL: interleukin
VAT: visceral adipose tissue
TAT: total adipose tissue
SAT: subcutaneous adipose tissue
BMI: body mass index
SAD: sagittal abdominal diameter
A-CT: abdominal computed tomography
APACHE II score: acute physiology and chronic health evaluation II score
CRP: C-reactive protein
ARDS: acute respiratory distress syndrome
AKI: acute kidney injury
RRT: renal replacement therapy
DM: diabetes mellitus
LC: liver cirrhosis
HU: Hounsfield unit
ROC: receiver-operating characteristic
AUC: area under curve

INTRODUCTION

Sepsis is a major health-care problem with significant mortality, affecting hundreds of thousands of patients annually in the United States, and its incidence has increased during recent decades (1). Although development of sepsis treatments including 'bundle management' has been accomplished following the introduction of early goal-directed therapy (2), sepsis outcomes have not improved. Severe sepsis-related mortality increased from 1993 to 2003 (3), and sepsis incidence was recently reported to be increasing (4).

Historically the pathogenesis of sepsis is thought to be mediated mainly by an uncontrolled hyperinflammatory response to pathogens by their host, but currently it is accepted that the processes of immunosuppression start simultaneously with the hyperinflammatory response in the early phase of sepsis (5). Proinflammatory cytokines such as tumor necrosis factor-alpha (TNFα), and anti-inflammatory cytokines such as interleukin (IL)-10 increase during early sepsis, and both result in worse sepsis outcomes (6, 7). Because of the mixed pattern of pro- and anti-inflammatory processes in sepsis, clinical trials of specific agents focusing on the interruption of the initial cytokine cascade have failed to improve the sepsis outcomes (8-10). However, a recent cohort study revealed that early corticosteroid administration during refractory septic shock was associated with improved survival with decreased level of TNFα, which suggests a beneficial role of corticosteroid with anti-inflammatory activities (11).

Well-known risk factors for sepsis are chronic diseases such as cancer, acquired immunodeficiency syndrome, and usage of immunosuppressive agents, and several studies have indicated the relationship between obesity and critical illness. Adipose tissue is in fact an endocrine organ that secrets various cytokines influencing many pathological processes (12), especially proinflammatory cytokines like TNFα, IL-6, IL-1, and leptin, forming a proinflammatory milieu (13). Visceral adipose tissue (VAT) is more specifically associated with systemic inflammation with increased IL-6 level than subcutaneous adipose tissue (SAT) (14-17).

General obesity measured using the body mass index (BMI) does not seem to be significantly correlated with the mortality of critical illnesses (18). An inverse association between BMI and mortality in critical illnesses has been reported (19). But visceral obesity measured by waist circumference was positively correlated with the outcomes of systemic inflammatory diseases like acute pancreatitis (20). Furthermore, visceral obesity measured by sagittal abdominal diameter

(SAD) was superior to BMI in predicting the outcomes of medical intensive care unit (MICU) mortality of critical illnesses (21), and SAD was positively associated with increased mortality in a recent study of sepsis (22). However, indices such as waist circumference or SAD cannot be considered as accurate measurements of VAT, which leaves the possibility of interruption of other confounding factors such as ileus, ascites, and fluid therapy. Therefore, we sought to determine whether VAT, as quantitatively measured by abdominal computed tomography (A-CT), may predict sepsis outcomes.

MATERIALS AND METHODS

1. Participants

Among the patients admitted in the MICU between January 2013 and June 2014 at Seoul National University Hospital (SNUH), we retrospectively analyzed the patients clinically diagnosed with sepsis at the time of admission to MICU using previously described criteria (23). Our total MICU bed capacity was 22. Patients younger than 19 years were excluded and patients who were examined with A-CT within 1 month based on the date of diagnosis of sepsis were included for the final analysis. This study was approved and individual patient consent was waived by the SNUH institutional review board.

2. Data collection

Patient data was extracted from medical records, including age, sex, comorbidities (diabetes mellitus, liver cirrhosis, solid tumor, hematologic malignancy, and immunocompromised state), BMI (calculated as weight (kg)/height $(m)^2$), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, serum lactate level, and serum C-reactive protein (CRP) level at the time of diagnosis of sepsis. Acute lung injury (ALI) with PaO_2/FiO_2 <250 mmHg without pneumonia or <200 mmHg with pneumonia, renal dysfunction presenting urine output <0.5 mL/kg/h for more than 2 h or serum creatinine >2.0 mg/dL, coagulopathy (prothrombin time-international normalized ratio >1.5), platelet count <100,000/mcL, and hyperbilirubinemia (total bilirubin >2 mg/dL) were defined as the organ failure variables for the diagnosis of severe sepsis according to recent guidelines (24), and septic shock was diagnosed as arterial hypotension requiring vasopressors despite adequate fluid resuscitation (23).

The appropriateness of antimicrobial therapy was determined by following two a priori criteria. First, effective intravenous antimicrobials should be administered within the first hour of recognition of severe sepsis or septic shock (24), which is the critical determinant of survival in patients with sepsis (25-27). Second, an antimicrobial agent with in vitro microbiologic activity against an isolated pathogen should be administered. In the cases of culture-negative infections, the antimicrobial therapy should be appropriate for the clinical infection, defined by the recommendations of the *Sanford Guide to Antimicrobial Therapy* (43rd edition). An antimicrobial therapy was deemed appropriate if it satisfied both criteria.

The cause of MICU admission, putative source of infection causing sepsis, suspected primary microbiological pathogens, need for renal replacement therapy (RRT), length of stay in MICU and hospital, and in-hospital mortality were also collected.

3. Radiologic evaluation

To evaluate the amount of VAT quantitatively, we used an A-CT image cut.

Patients enrolled in this study had their index A-CT in a supine position assessed by Brilliance 64 (Philips, Cleveland, OH, USA), Somatom Definition (Siemens, Forchheim, Germany), Discovery CT750 HD, LightSpeed Ultra (GE Healthcare, Milwaukee, WI, USA), or Aquilion ONE (Toshiba, Otawara, Japan) systems. We selected a cross-sectional image cut at the umbilicus level from the cuts of index A-CTs. A cross-sectional image cut at the umbilicus level is a valid predictor of TAT (28).

Firstly, a line separating the body from the airspace was drawn using a cursor around the skin surface. The area of total adipose tissue (TAT) within the selected range was defined as the sum of the pixels within the range of –150 to –50 Hounsfield units (HUs), commonly used to define the density of fat tissue in the CT image (29). Secondly, the border delineating the area of VAT was drawn using a cursor around the inner layer of the abdominal wall musculature, separating the VAT from the SAT as described previously (29, 30). The area of VAT within the selected range was defined as the sum of the pixels appearing fat density, and the area of SAT as subtracting VAT from TAT. The ratio of VAT to TAT was calculated to evaluate the comparative degree of visceral obesity (28).

4. Statistical analysis

The amount of VAT and the ratio of VAT to TAT (VAT/TAT) were analyzed as independent variables to determine whether they were associated with sepsis outcomes. First, we compared BMI, VAT, and VAT/TAT in terms of in-hospital mortality, and in-ICU or 28-day mortality, and other sepsis outcomes such as presence of organ dysfunction, severe sepsis, septic shock, or need for RRT using a paired *t* test. We also analyzed the association between CRP level at the time of diagnosis of sepsis and VAT/TAT using Pearson's partial correlation analysis. To evaluate the dose-dependent relationship of visceral obesity and sepsis mortality, the whole participants were divided into four quartile groups according to the amount of VAT and VAT/TAT, respectively, and the association between quartile groups of VAT and VAT/TAT and sepsis mortality was analyzed by linear association.

To determine the independent effect of VAT and VAT/TAT predicting mortality from sepsis, multiple logistic regression analysis was performed by adjusting for age, sex, BMI, comorbidities, and APACHE II score, source of infection, and appropriateness of antibiotics. Two models were selected for VAT and VAT/TAT, respectively.

To evaluate the power of prediction of visceral adiposity for sepsis mortality, receiver-operating characteristic (ROC) curves of APACHE II score, VAT, and VAT/TAT were depicted; they were compared according to the area under correlated ROC curves (AUC). After the best cut-off value of VAT/TAT predicting sepsis mortality was found, we divided the participants into two groups according to the cut-off value. Ninety-day survival of these groups were assessed by Kaplan–Meier survival analysis, and compared by log-rank test.

Statistical analysis was performed in using SPSS software (version 21.0 for Windows; IBM SPSS Inc., Armonk, NY, USA), except the analysis of ROC

curves using MedCalc software (version 13.3.3; MedCalc Software, Ostend, Belgium). Numerical variables are expressed as mean ± standard deviation. All statistical tests were two-sided, and differences were considered statistically significant at $P < 0.05$.

RESULTS

1. Participants

During the study period, 846 patients admitted to MICU were screened, and 310 patients were diagnosed as having sepsis. Among these, 178 patients underwent A-CT within 1 month of the diagnosis of sepsis and were enrolled for the final analysis (Figure 1). Baseline characteristics of patients with A-CT were similar to those of patients without A-CT, but those who were examined by A-CT had more intra-abdominal and soft tissue infections and less respiratory infections compared with those who were not examined by A-CT (Table 1). The mean APACHE II score was 29.36, which represents the severity of this retrospective sepsis cohort.

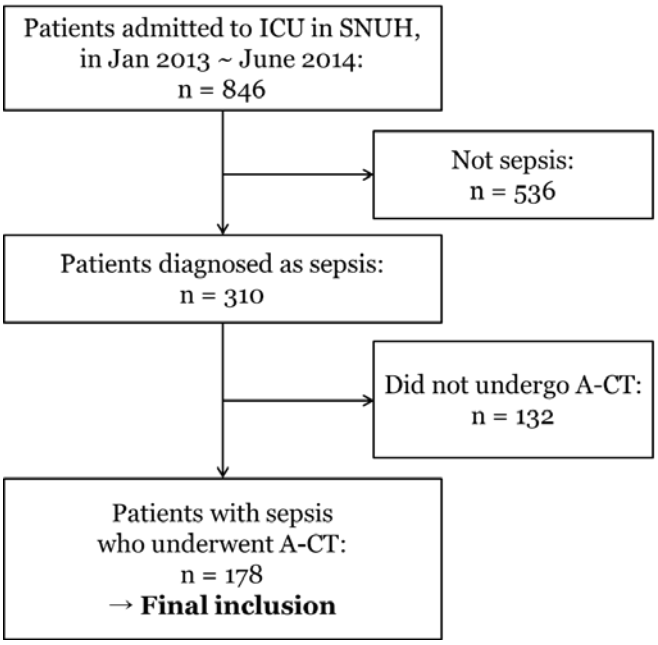


Figure 1. Inclusion flow chart.

	Total	With A-CT	Without A-CT	P value
Number	310	178	132	
Age (year)	62.83 ± 15.63	62.63 ± 15.35	63.31 ± 15.96	0.707
Comorbidities				
Diabetes mellitus (%)	77 (24.8%)	50 (28.1%)	27 (20.6%)	0.145
Liver cirrhosis (%)	42 (13.5%)	32 (18.0%)	10 (7.6%)	0.011
Solid tumor (%)	98 (31.6%)	63 (35.4%)	35 (26.7%)	0.110
Hematologic malignancy (%)	87 (28.1%)	44 (24.7%)	43 (32.8%)	0.126
Immunocompromised (%)	113 (36.5%)	57 (32.0%)	56 (42.7%)	0.057
Height (cm)	162.58 ± 8.96	162.15 ± 9.12	163.28 ± 8.72	0.275
Weight (kg)	58.04 ± 11.57	58.69 ± 11.34	57.19 ± 11.80	0.258
BMI (kg/m^2)	21.96 ± 4.03	22.30 ± 3.82	21.50 ± 4.25	0.084
APACHE II score	29.36 ± 10.52	28.70 ± 10.55	30.33 ± 10.43	0.178
Source of infection				
Respiratory infection	185 (59.7%)	79 (44.4%)	106 (80.3%)	< 0.001
Intraabdominal infection	53 (17.1%)	48 (27.0%)	5 (3.8%)	< 0.001
Soft tissue infection	23 (7.4%)	20 (11.2%)	3 (2.3%)	0.003
Primary bloodstream infection	15 (4.8%)	10 (5.6%)	5 (3.8%)	
Urinary tract infection	14 (4.5%)	10 (5.6%)	4 (3.0%)	
Intravascular catheter infection	7 (2.3%)	3 (1.7%)	4 (3.0%)	
Central nervous system infection	1 (0.3%)	1 (0.6%)	0 (0.0%)	
Other infection	12 (3.9%)	7 (3.9%)	5 (3.8%)	

Table 1. Comparison of characteristics of participants with and without A-CT in the cohort.

Among the patients with A-CT, male patients had more severe disease presenting as a higher APACHE II score and lower BMI than female patients. Seventy-nine patients (44.4%) had respiratory infection and 48 patients (27.0%) had intra-abdominal infection. As suspected, primary microbiologic pathogens such as gram-negative organisms (70 patients, 39.3%) were the most common, followed by gram-positive organisms (33 patients, 18.5%) and fungi (11 patients, 6.2%). According to the analysis of adipose tissue in A-CT, male patients had a similar amount of VAT compared with female patients, but less SAT, which resulted in a higher ratio of VAT/TAT in male patients than in female patients (Table 2).

Most of the participants enrolled had severe sepsis (94.9%), and 74.2% progressed to septic shock (Table 3). The in-hospital mortality of the cohort was 59.0%, which was slightly low considering the high mean APACHE II score.

	Total	Male	Female	P value
Number	178	105	73	
Age (year)	62.63 ± 15.35	63.79 ± 15.13	60.97 ± 15.61	0.229
Comorbidities				
Diabetes mellitus (%)	50 (28.1%)	32 (30.5%)	18 (24.7%)	0.396
Liver cirrhosis (%)	32 (18.0%)	18 (17.1%)	14 (19.2%)	0.728
Solid tumor (%)	63 (35.4%)	43 (41.0%)	20 (27.4%)	0.063
Hematologic malignancy (%)	44 (24.7%)	25 (23.8%)	19 (26.0%)	0.736
Immunocompromised (%)	57 (32.0%)	32 (30.5%)	25 (34.2%)	0.596
Height (cm)	162.15 ± 9.12	167.47 ± 6.29	154.49 ± 6.84	< 0.001
Weight (kg)	58.69 ± 11.34	61.33 ± 11.26	54.90 ± 10.40	< 0.001
BMI (kg/m^2)	22.30 ± 3.82	21.82 ± 3.48	23.00 ± 4.18	0.041
Amount of adipose tissue				
TAT (cm^2)	198.95 ± 119.91	177.77 ± 114.99	229.42 ± 121.04	0.004
VAT (cm^2)	79.21 ± 55.43	78.19 ± 58.11	80.68 ± 51.68	0.769
SAT (cm^2)	119.74 ± 78.94	99.58 ± 68.59	148.74 ± 84.14	< 0.001
VAT/TAT (%)	40.37 ± 14.02	43.85 ± 14.29	35.35 ± 12.04	< 0.001
APACHE II score	28.70 ± 10.55	30.13 ± 10.67	26.63 ± 10.11	0.029
Lactate (mmol/L)	6.66 ± 4.41	6.63 ± 4.56	6.71 ± 4.21	0.913
CRP (mg/dL)	16.47 ± 11.11	15.59 ± 9.72	17.74 ± 12.82	0.206
Appropriateness of antibiotics	99 (61.5%)	61 (64.2%)	38 (57.6%)	0.696
Source of infection				0.139
Respiratory infection	79 (44.4%)	53 (50.5%)	26 (35.6%)	
Intraabdominal infection	48 (27.0%)	25 (23.8%)	23 (31.5%)	
Soft tissue infection	20 (11.2%)	10 (9.5%)	10 (13.7%)	
Primary bloodstream infection	10 (5.6%)	8 (7.6%)	2 (2.7%)	
Urinary tract infection	10 (5.6%)	3 (2.9%)	7 (9.6%)	
Intravascular catheter infection	3 (1.7%)	1 (1.0%)	2 (2.7%)	
Central nervous system infection	1 (0.6%)	0 (0.0%)	1 (1.4%)	
Other infection	7 (3.9%)	5 (4.8%)	2 (2.7%)	

Table 2. Baseline characteristics of participants.

	Total	Male (n=105)	Female (n=73)	P value
ICU stay length (day)	9.13 ± 10.69	10.18 ± 12.02	7.62 ± 8.27	0.116
Hospital stay length (day)	39.65 ± 33.73	38.85 ± 33.06	40.79 ± 34.85	0.706
Severe sepsis	169 (94.9%)	102 (97.1%)	67 (91.8%)	0.108
Number of organ failure	2.76 ± 1.38	2.90 ± 1.35	2.55 ± 1.42	0.091
ARDS (n=178)	96 (53.9%)	65 (61.9%)	31 (42.5%)	0.010
AKI (n=157)	104 (66.2%)	67 (63.8%)	37 (50.7%)	0.177
INR >1.5 (n=165)	104 (63.0%)	60 (57.1%)	44 (60.3%)	0.783
PLT <100 (n=134)	100 (74.6%)	63 (60.0%)	37 (50.7%)	0.344
T.Bil >2 (n=157)	87 (55.4%)	49 (46.7%)	38 (52.1%)	0.698
Septic shock	132 (74.2%)	81 (77.1%)	51 (69.9%)	0.275
Need for RRT	99 (55.6%)	63 (60.0%)	36 (49.3%)	0.158
Mortality				
28-day mortality*	64 (36.0%)	40 (38.1%)	24 (32.9%)	0.775
In-ICU mortality	89 (50.0%)	54 (51.4%)	35 (47.9%)	0.648
In-hospital mortality	105 (59.0%)	65 (61.9%)	40 (54.8%)	0.343

* Data for 28-day mortality were unavailable for 7 patients.

Table 3. Sepsis outcomes.

2. Association of VAT with sepsis outcomes

A paired *t* test revealed that VAT and VAT/TAT were higher in patients with in-hospital mortality than in survivors (92.00 cm^2 vs. 60.82 cm^2, $P < 0.001$; 45.88% vs. 32.79%, $P < 0.001$, respectively), and this tendency was not altered when stratified by sex (Table 4), or analyzed in terms of 28-day mortality instead of in-hospital mortality (data not shown). VAT/TAT was also higher in patients with a need for RRT or septic shock, but not VAT (data not shown). There was no association between VAT or VAT/TAT and duration of stay in MICU or hospital.

	Nonsurvivors	Survivors	P value
Total (n)	105	73	
BMI (kg/m^2)	22.40 ± 3.50	22.17 ± 4.25	0.699
VAT (cm^2)	92.00 ± 59.62	60.82 ± 42.87	< 0.001
VAT/TAT ratio (%)	45.88 ± 13.06	32.79 ± 11.60	< 0.001
Male (n)	65	40	
BMI (kg/m^2)	21.76 ± 3.16	21.91 ± 4.00	0.831
VAT (cm^2)	91.32 ± 60.91	56.85 ± 46.51	0.003
VAT/TAT ratio (%)	49.86 ± 12.10	34.10 ± 12.10	< 0.001
Female (n)	40	33	
BMI (kg/m^2)	23.43 ± 3.82	22.49 ± 4.58	0.339
VAT (cm^2)	93.09 ± 58.19	65.63 ± 38.16	0.023
VAT/TAT (%)	39.54 ± 12.14	30.26 ± 9.87	0.001

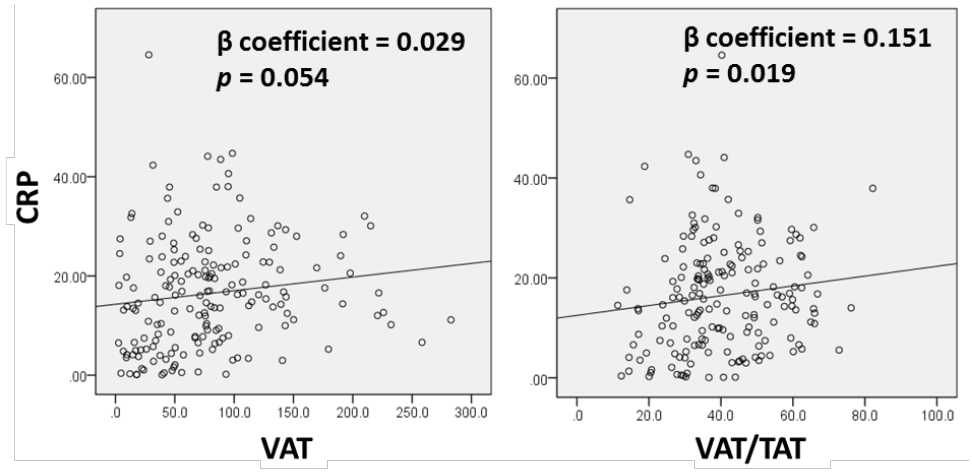
Table 4. Comparison of VAT and VAT/TAT in survival versus mortality group, according to sex.

When they were analyzed according to organ dysfunction variables, patients with renal dysfunction (urine output <0.5 mL/kg/h for more than 2 h or serum creatinine >2.0 mg/dL) showed higher VAT than those without renal dysfunction. Coagulopathy was correlated with both VAT and VAT/TAT, but ALI, thrombocytopenia, and hyperbilirubinemia caused by sepsis did not show significant association with VAT or VAT/TAT (Table 5).

	With organ dysfunction	Without organ dysfunction	P value
AKI (n)	104	53	
VAT (cm^2)	87.48 ± 59.89	67.38 ± 48.79	0.036
VAT/TAT (%)	42.05 ± 14.41	37.74 ± 14.00	0.076
ARDS (n)	96	82	
VAT (cm^2)	75.19 ± 54.74	83.92 ± 56.19	0.296
VAT/TAT (%)	40.60 ± 14.59	40.09 ± 13.40	0.809
Coagulopathy (n)	104	61	
VAT (cm^2)	86.75 ± 55.30	67.65 ± 50.76	0.029
VAT/TAT (%)	43.98 ± 14.84	35.26 ± 10.72	< 0.001
Thrombocytopenia (n)	100	34	
VAT (cm^2)	75.78 ± 57.78	79.84 ± 50.72	0.716
VAT/TAT (%)	40.82 ± 14.32	37.88 ± 14.59	0.304
Hyperbilirubinemia (n)	87	70	
VAT (cm^2)	85.93 ± 59.57	74.33 ± 53.43	0.206
VAT/TAT (%)	42.68 ± 14.16	38.45 ± 13.91	0.063

Table 5. VAT and VAT/TAT according to organ dysfunction variables.

CRP level at the time of diagnosis of sepsis was correlated with VAT/TAT after adjusting age, sex, and APACHE II score (Figure 2), but its strength in diagnosis was diminished after excluding patients with LC (data not shown).



* Adjusted by age, sex, and APACHE II score.

Figure 2. Association of CRP level and VAT or VAT/TAT at the time of diagnosis of sepsis by Pearson's partial correlation analysis.

After we stratified VAT and VAT/TAT into four quartiles, our analysis showed that in-hospital sepsis mortality increased according to elevated quartile by linear association analysis ($P = 0.004$ and $P < 0.001$, respectively), which shows a dose-dependent relationship between VAT and mortality (Figure 3).

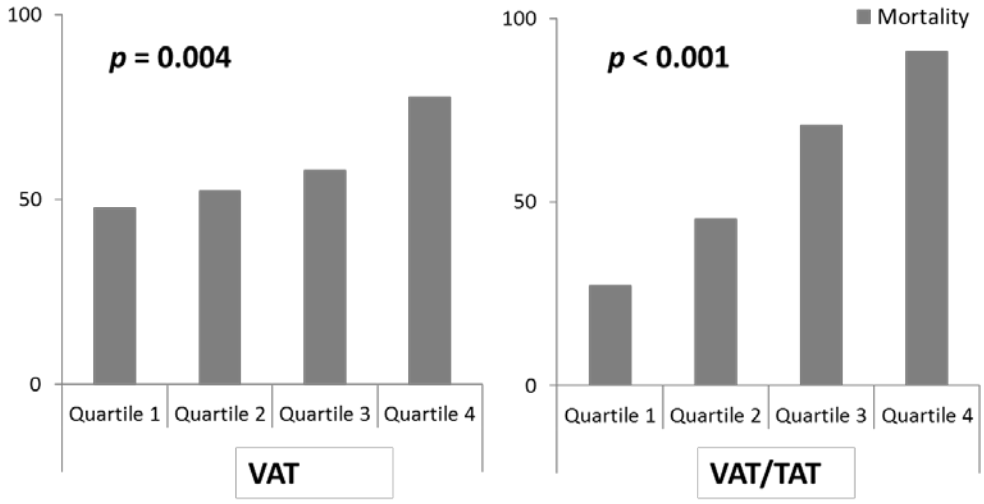


Figure 3. Linear association analysis stratified into quartiles of VAT or VAT/TAT.

3. Model for VAT and VAT/TAT as predictors of sepsis mortality

After multiple logistic regression adjusting age, sex, APACHE II score, comorbidities, and BMI, source of infection, and appropriateness of antibiotics, increasing quartiles of VAT/TAT was independently associated with increased in-hospital sepsis mortality, showing an apparent dose-dependent relationship (adjusted odds ratio 8.518 in the third to first quartiles, 35.820 in the fourth to first quartiles, both $P < 0.001$). The other variables consistently associated with mortality were APACHE II score, presence of liver cirrhosis, or hematologic malignancy (Table 6, 7). The same association was found with 28-day, in-ICU, and in-hospital mortality (data not shown).

Independent variables	Odds ratio (95% confidence interval)	P value
Age	0.996 (0.977-1.016)	0.715
Sex	0.746 (0.407-1.368)	0.343
Comorbidities		
Diabetes mellitus	0.843 (0.435-1.633)	0.613
Liver cirrhosis	2.946 (1.199-7.242)	0.019
Solid tumor	1.206 (0.643-2.262)	0.558
Hematologic malignancy	3.556 (1.586-7.970)	0.002
Immunocompromised	1.612 (0.836-3.110)	0.154
BMI	1.016 (0.939-1.099)	0.697
APACHE II score	1.076 (1.039-1.114)	< 0.001
Appropriateness of antibiotics	0.983 (0.874-1.106)	0.778
Source of infection	0.876 (0.738-1.040)	0.131
VAT		
Quartile 1	1	
Quartile 2	1.200 (0.520-2.769)	0.670
Quartile 3	1.499 (0.649-3.460)	0.343
Quartile 4	3.833 (1.530-9.606)	0.004
VAT/TAT		
Quartile 1	1	
Quartile 2	2.222 (0.912-5.412)	0.079
Quartile 3	6.564 (2.603-16.555)	< 0.001
Quartile 4	27.333 (8.050-92.804)	< 0.001

Table 6. Odds ratio for in-hospital mortality by univariable logistic regression analysis.

Independent variables	Odds ratio (95% confidence interval): Model for VAT	P value	Odds ratio (95% confidence interval): Model for VAT/TAT	P value
Age	0.981 (0.953-1.009)	0.183	0.981 (0.951-1.011)	0.218
Sex	0.872 (0.416-1.827)	0.716	1.825 (0.769-4.330)	0.172
Comorbidities				
Diabetes mellitus	1.324 (0.559-3.138)	0.523	1.551 (0.617-3.898)	0.351
Liver cirrhosis	7.819 (2.582-23.680)	< 0.001	9.663 (2.940-31.753)	0.001
Solid tumor	2.055 (0.922-4.583)	0.078	2.292 (0.943-5.570)	0.051
Hematologic malignancy	5.938 (2.199-16.034)	< 0.001	5.960 (2.015-17.633)	0.014
Immunocompromised	0.744 (0.266-2.080)	0.573	0.686 (0.222-2.116)	0.512
BMI	0.844 (0.745-0.955)	0.007	1.005 (0.895-1.127)	0.939
APACHE II score	1.067 (1.028-1.108)	0.001	1.058 (1.016-1.103)	0.007
Appropriateness of antibiotics	0.986 (0.850-1.144)	0.855	0.988 (0.841-1.160)	0.878
Source of infection	0.947 (0.791-1.133)	0.553	0.914 (0.753-1.108)	0.360
VAT				
Quartile 1	1			
Quartile 2	1.417 (0.505-3.977)	0.508		
Quartile 3	1.949 (0.686-5.542)	0.211		
Quartile 4	9.229 (2.402-35.461)	0.001		
VAT/TAT				
Quartile 1			1	
Quartile 2			2.593 (0.935-7.189)	0.067
Quartile 3			8.518 (2.782-26.084)	< 0.001
Quartile 4			35.820 (8.946-143.417)	< 0.001

Table 7. Independent predictors of in-hospital mortality by multiple logistic regression analysis.

4. Comparison of ROC curves and Kaplan-Meier survival analysis

The comparison of ROC curves using AUC showed that VAT/TAT and APACHE II score were comparable predictors of sepsis mortality (AUC 0.796 vs. 0.700, P = 0.056), and VAT/TAT was superior to VAT (AUC 0.796 vs. 0.664, P = 0.005; Figure 4).

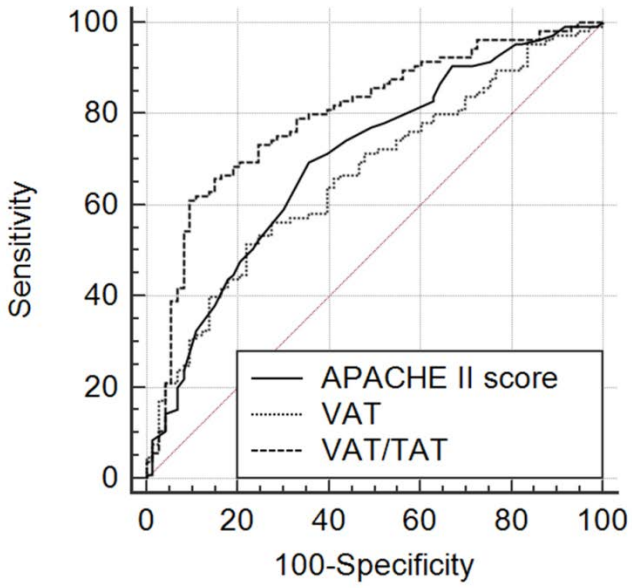


Figure 4. Comparison of receiver-operating characteristic (ROC) curves.

The best cut-off value of VAT/TAT predicting sepsis mortality was 42.1%, so we divided the participants into two groups: high VAT/TAT (>42.1%) and low VAT/TAT (<42.1%). Kaplan–Meier survival analysis showed that 90-day mortality was reduced remarkably among patients with high VAT/TAT group compared with low VAT/TAT group (P < 0.001; Figure 5).

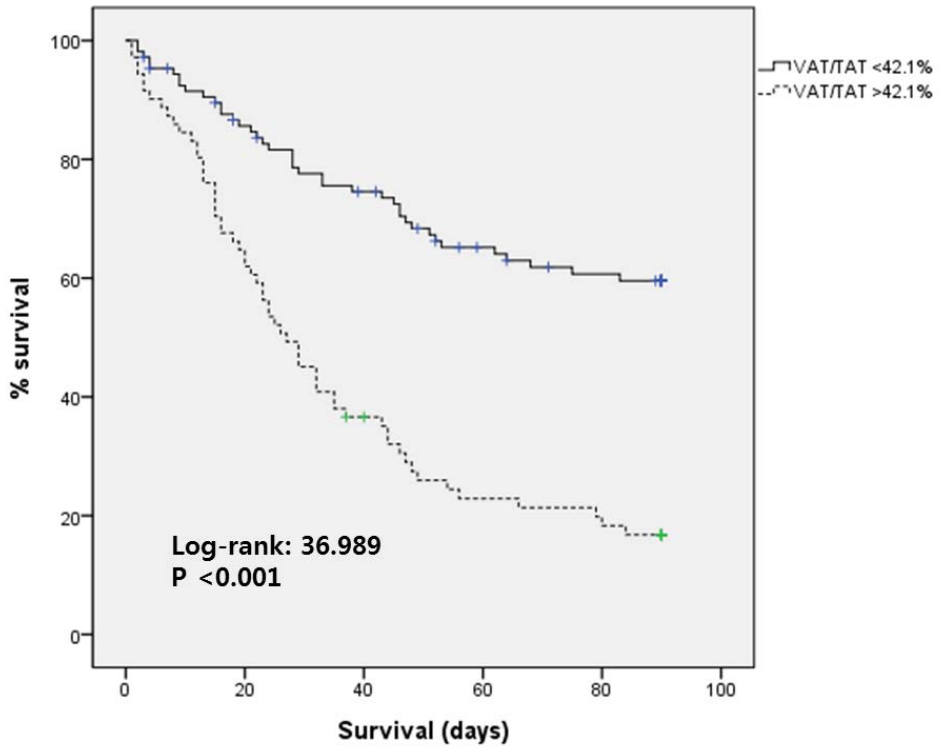


Figure 5. Impact of high VAT/TAT on mortality.

DISCUSSION

To our knowledge, this is the first study of the relationship of sepsis outcomes and quantitatively measured VAT and VAT/TAT. In this study, we found that sepsis mortality was dose-dependently associated with the amount of VAT and VAT/TAT directly measured by A-CT after adjustment for predisposing and downstream factors of sepsis including comorbidities, sepsis severity, source of infection, and appropriateness of antimicrobial agents. This result suggests that excessive visceral adiposity could contribute to a worse sepsis outcome.

The association between VAT and proinflammatory process is now well recognized. Circulating proinflammatory cytokines such as IL-6 were increased with the accumulation of VAT (14, 15, 17), and a large prospective cohort study measuring the volume of VAT reported that VAT was associated with systemic inflammation presenting as high IL-6, CRP, and monocyte chemoattractant protein-1 (16).

This proinflammatory milieu seems to cause adverse outcomes in systemic inflammatory illnesses such as sepsis. Adipokine levels in septic patients are as high as morbidly obese patients compared with control patients (31), and high cytokine levels are related with increased sepsis mortality (6, 17). The mechanism of this relationship is proposed as microcirculatory failure and local hypoxia in the condition of severe sepsis contribute to adipocyte destroy, which releases proinflammatory cytokines causing tissue injury.

With the growing interest in visceral obesity, the association between visceral obesity and metabolic complications and cardiovascular risk has been studied widely in large cohort studies (32, 33). However, clinical studies concerning the relationship between visceral obesity-induced systemic inflammation and critical illness are scarce, although the theoretical background of laboratory data supports the idea of a proinflammatory process of VAT. SAD as a surrogate of VAT is a predictor of worse outcome of critical illness (21) and sepsis (22). However, the major pitfall of SAD is decreasing specificity for VAT, which might contain a confounding effect of muscle or fluid mass and gas space, and may therefore not be sufficiently precise to predict VAT (34).

The most accurate method to evaluate VAT is a quantitative measurement with widely used imaging technology. A standard method of VAT measurement has not been established; therefore, studies that measured VAT using A-CT differ. With the difficulty of measuring the volume of VAT, the area of VAT on the slice cut of specific level in A-CT has long been used as a surrogate marker highly correlated to the volume of VAT (34, 35). We used a slice at the level of the umbilicus as our indicator of VAT volume (28, 36). Like the level of L3-4 or L4-5, the umbilical level is highly correlated to the total visceral fat volume (36). We also considered the pixels appearing with a HU of from –150 to –50 as representing commonly used fat tissue (29). Although others have used an interval of from –190 to –30 (37), these different methods were based on acceptable data supporting their

appropriateness as surrogates and varying the upper and lower limits does not seem to lead to different results in assessing the total visceral fat volume (36). In a study of healthy people, the mean values of the VAT/TAT ratio were 0.42 in men and 0.25 in women, respectively, which is similar to that found in our study with a higher ratio in men and higher SAT than in women. There was no difference in sepsis mortality between the sexes, and after adjusting for confounding factors including sex, the effect of VAT or VAT/TAT remained significant, which suggested that the relationship was independent of the composition of fat distribution in the sexes.

The major mechanism by which VAT contributes to the pathogenesis of sepsis is suggested to be the enhanced systemic inflammatory reactions from the release of proinflammatory cytokines by destroyed adipocytes. Endothelial dysfunction in sepsis triggers coagulation pathways leading to fibrin deposition and microthrombi formation causing microvascular plugging (38). Local microcirculatory failure by decreased functional capillaries causes tissue hypoxia, which eventually contributes to multiple organ failure in patients with sepsis (39). Visceral adipocytes with increased density in abdominally obese patients are vulnerable to sepsis-induced microcirculatory change and likely to influence the ‘cytokine storm’ in the early phase of sepsis with their specificity for producing proinflammatory cytokines (15). In our study, VAT/TAT was positively associated with the level of CRP at the time of diagnosis of sepsis, which was consistent with previous reports of elevated CRP in patients with visceral obesity (16). Moreover, in the analysis of the components of organ failure in sepsis, patients presenting renal dysfunction had more VAT than those not presenting with renal dysfunction, which was consistent with a recent study reporting the association between CT-defined abdominal obesity and AKI in critically ill trauma patients, suggesting the mechanism as potentiation of inflammatory response mediated by IL-6 by adipose tissue (40).

Our study findings demonstrated that visceral adiposity is an independent risk factor for mortality in patients with sepsis. We found there was a dose-dependent relationship between the amount of VAT or VAT/TAT and mortality in sepsis, which suggests a strong association between them. The predictability of a ROC curve of VAT/TAT in terms of mortality was comparable to the APACHE II score, which has been widely proven to be an excellent predictor of sepsis (41-43). Therefore, we suggest that precisely measured visceral obesity might be an important risk factor for worse sepsis outcome, and is worth considering as a comorbidity to assess the prognosis of patients with sepsis.

This study has several limitations. First, this study followed a retrospective design based on medical records, which led to a problem with the availability of some data. We carefully investigated and adjusted the confounding factors contributing to the sepsis outcomes. Nevertheless, some downstream factors such as compliance to the protocol-based sepsis management were not available, particularly in the cases with an undetermined onset of sepsis. Second, the data we used is from a single center, which may affect the generalizability of our findings. Third, we enrolled patients with sepsis who

had A-CT at the time of sepsis, which possibly produced a selection bias of patients requiring A-CT because of their intra-abdominal sources of infection. This resulted in a difference in mortality from the entire sepsis cohort (44). To validate these patients as representing the sepsis cohort, we compared the baseline characteristics of the patients with and without A-CT, which showed no significant difference between the groups, except that the source of infection was less due to respiratory and more intra-abdominal and soft tissue infection with A-CT. This may affect the necessity of A-CT and therefore lead to a different mortality between the groups. Although the mortality in our group (59.0%) was higher compared with previous reports from Europe or USA (45), it was an appropriate outcome considering the sepsis severity of our group expressed by a mean APACHE II score of 28.7 (assuming 63.9% mortality) (46).

In conclusion, our study determined that VAT and VAT/TAT quantitatively measured by A-CT were dose-dependently associated with sepsis mortality. Visceral obesity should be considered, not only a cause of various metabolic disorders, but also as a critical contributing factor to a worse outcome for individuals with sepsis. In future, there should be further study with a larger prospective design to confirm the association.

REFERENCES

1. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546-1554.
2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.
3. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244–1250.
4. Lagu T, Rothberg MB, Shieh M-S, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2012;40:754-761.
5. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003;348:138-150.
6. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA. Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. *Crit Care Med* 2000;28:2591-2594.
7. van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frölich M. Anti-inflammatory cytokine profile and mortality in febrile patients. *Lancet* 1998;351:950-953.
8. Abraham E, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor α in patients with sepsis syndrome: a randomized, controlled, double-blind, multicenter clinical trial. *JAMA* 1995;273:934-941.
9. Opal SM, Fisher CJ, Dhainaut J-FA, Vincent J-L, Brase R, Lowry SF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, doubleblind, placebo-controlled, multicenter trial. *Crit Care Med* 1997;25:1115-1124.
10. Bone RC, Fisher Jr CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987;317:653-658.
11. Katsenos CS, Antonopoulou AN, Apostolidou EN, Ioakeimidou A, Kalpakou GT, Papanikolaou MN, et al. Early administration of hydrocortisone replacement after the advent of septic shock: impact on survival and immune response. *Crit Care Med* 2014;42:1651-1657.
12. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772-783.
13. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology* 2003;144:2195-2200.
14. Fried SK, Bunkin DA, Greenberg AS. Omental and Subcutaneous Adipose Tissues of Obese Subjects Release Interleukin-6: Depot Difference and Regulation by Glucocorticoid 1. *J Clin Endocrinol Metab* 1998;83:847-

850.
15. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 2004;145:2273-2282.
16. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress the Framingham heart study. *Circulation* 2007;116:1234-1241.
17. van den Borst B, Gosker HR, Koster A, Yu B, Kritchevsky SB, Liu Y, et al. The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. *Am J Clin Nutr* 2012;96:516-526.
18. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: A meta-analysis. *Crit Care Med* 2008;36:151-158.
19. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. *Crit Care Med* 2013;41:1878-1883.
20. Sempere L, Martinez J, de Madaria E, Lozano B, Sanchez-Paya J, Jover R, et al. Obesity and fat distribution imply a greater systemic inflammatory response and a worse prognosis in acute pancreatitis. *Pancreatology* 2008;8:257-264.
21. Paolini J-BM, Mancini J, Genestal M, Gonzalez H, McKay RE, Samii K, et al. Predictive value of abdominal obesity vs. body mass index for determining risk of intensive care unit mortality. *Crit Care Med* 2010;38:1308-1314.
22. Chalkias A, Nitsotolis T, Papalexandrou A, Mikros S, Iacovidou N, Xanthos T. Sagittal abdominal diameter may effectively predict future complications and increased mortality in intensive care unit patients with severe sepsis. *J Crit Care* 2013;28:964-969.
23. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Med* 2003;29:530-538.
24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
25. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589-1596.
26. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045-1053.
27. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based

performance improvement program. *Crit Care Med* 2014;42:1749-1755.
28. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998;351:871-875.
29. Doyle SL, Bennett AM, Donohoe CL, Mongan AM, Howard JM, Lithander FE, et al. Establishing computed tomography–defined visceral fat area thresholds for use in obesity-related cancer research. *Nutr Res* 2013;33:171-179.
30. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, et al. Abdominal visceral and subcutaneous adipose tissue compartments association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007;116:39-48.
31. Hillenbrand A, Knippschild U, Weiss M, Schrezenmeier H, Henne-Bruns D, Huber-Lang M, et al. Sepsis induced changes of adipokines and cytokines-septic patients compared to morbidly obese patients. *BMC Surg* 2010;10:26.
32. Empana J, Ducimetiere P, Charles M, Jouven X. Sagittal Abdominal Diameter and Risk of Sudden Death in Asymptomatic Middle-Aged Men The Paris Prospective Study I. *Circulation* 2004;110:2781-2785.
33. Neeland IJ, Ayers CR, Rohatgi AK, Turer AT, Berry JD, Das SR, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity* 2013;21:E439-E447.
34. Schoen R, Thaete F, Sankey S, Weissfeld J, Kuller L. Sagittal diameter in comparison with single slice CT as a predictor of total visceral adipose tissue volume. *Int J Obes Relat Metab Disord* 1998;22:338-342.
35. Kvist H, Chowdhury B, Grangård U, Tylen U, Sjöström L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. *Am J Clin Nutr* 1988;48:1351-1361.
36. Van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. *Int J Obes Relat Metab Disord* 1993;17:187-196.
37. Yoshizumi T, Nakamura T, Yamane M, Waliul Islam AHM, Menju M, Yamasaki K, et al. Abdominal Fat: Standardized Technique for Measurement at CT 1. *Radiology* 1999;211:283-286.
38. De Backer D, Donadello K, Taccone FS, Ospina-Tascon G, Salgado D, Vincent JL. Microcirculatory alterations: potential mechanisms and implications for therapy. *Ann Intensive Care* 2011;1:27.
39. Trzeciak S, Rivers EP. Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. *Crit Care* 2005;9 Suppl 4:S20-26.
40. Shashaty MG, Kalkan E, Bellamy SL, Reilly JP, Holena DN, Cummins K, et al. Computed tomography-defined abdominal adiposity is associated with acute kidney injury in critically ill trauma patients. *Crit Care Med* 2014;42:1619-1628.
41. Mylotte JM, Tayara A. Staphylococcus aureus bacteremia: predictors of 30-day mortality in a large cohort. *Clin Infect Dis* 2000;31:1170-1174.

42. Kang C-I, Kim S-H, Kim H-B, Park S-W, Choe Y-J, Oh M-d, et al. Pseudomonas aeruginosa bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003;37:745-751.
43. Chen S-J, Chao T-F, Chiang M-C, Kuo S-C, Chen L-Y, Yin T, et al. Prediction of patient outcome from Acinetobacter baumannii bacteremia with Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. *Intern Med* 2011;50(8):871-877.
44. Leligdowicz A, Dodek PM, Norena M, Wong H, Kumar A, Kumar A. Association between source of infection and hospital mortality in patients who have septic shock. *Am J Respir Crit Care Med* 2014;189:1204-1213.
45. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis* 2012;12:919-924.
46. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-829.

국문 초록

서론: 지방조직은 단지 에너지 저장고가 아니라 여러 전염증성 사이토카인을 분비하는 내분비적 장기로 인식되고 있다. 특히 전신적 염증성 질환에서의 내장지방조직 (visceral adipose tissue, VAT)의 역할이 제기되고 있는데, 현재까지 VAT 과 패혈증의 관계에 관한 연구는 거의 없으며, 특히 VAT 의 정량적 측정 방법은 사용된 바가 없다.

방법: 본 연구는 후향적 코호트 연구로서, 연구 기간 내에 패혈증으로 인해 내과계 중환자실에 입실한 환자들 중 패혈증 진단 1 달 이내에 복부 컴퓨터 단층촬영을 시행하였던 환자들을 대상으로 하였다. 의무기록을 통해 나이, 성별, 체중을 포함한 인체 측정 기록, 동반 질환들, APACHE II score, 감염원, 항생제의 적절성 등을 수집하였다. 복부 컴퓨터 단층촬영의 배꼽 혹은 L4-5 높이의 횡단면에서 지방 밀도를 나타내는 화소를 모두 합하여 모든 지방조직 (total adipose tissue, TAT) 그리고 VAT 의 단면적을 계산하였다.

결과: 패혈증으로 인해 내과계 중환자실에 입실한 310 명의 환자들 중 복부 컴퓨터 단층촬영을 시행하였던 178 명이 최종 포함되었다. 나이의 중앙값은 65 세였으며, 59%가 남성이었다. 병원 내 사망률은 59%였다. 여성은 남성에 비해 많은 TAT 및 피하지방조직을 가지고 있었으며, 그로 인해 VAT/TAT 비율은 남성보다 낮았다. 병원 내에서 사망한 환자들은 생존한 환자들에 비해 평균 VAT, VAT/TAT 값이 높았다 (각각 92.00 cm2 vs. 60.82 cm2 and 45.88% vs. 32.79%, p<0.001 and <0.001). 나이, 성별, APACHE II score, 동반 질환, 감염원, 항생제의 적절성 등을 보정하여 시행한 로지스틱 회귀분석 결과 VAT 와 VAT/TAT 는 패혈증의 사망률을 예측하는 독립적인 인자들이었으며, VAT 혹은 VAT/TAT 가 상승할수록 사망률이 증가하는 뚜렷한 용량-의존적 관계가 관찰되었다.

결론: 복부 컴퓨터 단층촬영을 통해 정량적으로 측정한 VAT 와 VAT/TAT 는 패혈증의 사망률과 용량-의존적인 양의 상관관계를 보였다. 그러므로 복부 비만은 패혈증의 나쁜 예후 인자로 간주되어야 한다.

주요어 : 내장지방조직; 패혈증; 복부 컴퓨터 단층촬영

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