

Association of inferior vena cava diameter ratio measured on computed tomography scans with the outcome of patients with septic shock

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Abstract

The collapsibility and diameter of the inferior vena cava (IVC) are known to predict the volume state in critically ill patients. However, no study has examined the prognostic value of the IVC diameter ratio measured on computed tomography (CT) in patients with septic shock. A retrospective observational study was conducted on adult septic shock patients visiting the emergency department at a university hospital in Korea. The IVC diameter ratio was calculated by dividing the maximal transverse and anteroposterior diameters. Multivariable logistic regression analysis was conducted to investigate whether the IVC diameter ratio predicted in-hospital mortality. The area under the curve (AUC) was calculated, and the sensitivity, specificity, positive predictive value, and negative predictive value with the cut-off values were computed. A total of 423 adult septic shock patients were included, and the in-hospital mortality rate was 17%. The median IVC diameter ratio in non-survivors was significantly greater than in survivors (1.56 cm vs 1.4 cm, $P = .004$). The IVC diameter ratio was found to be significantly associated with in-hospital mortality on multivariate logistic regression analysis after adjustment for confounding variables (odds ratio = 1.48, confidence interval: 1.097–1.998, $P = 0.01$). The AUC for IVC diameter ratio was 0.607. A cut-off IVC diameter ratio of ≥ 1.31 cm had 75% sensitivity and 42% specificity for predicting in-hospital mortality. The IVC diameter ratio measured on CT may be helpful in predicting the prognosis of septic shock patients. However, due to its low diagnostic performance and sensitivity, further research is warranted.

Abbreviations: AUC = area under the curve, CKD = chronic kidney disease, COPD = chronic obstructive lung disease, CRP = C-reactive protein, CT = computed tomography, ED = emergency department, ICU = intensive care unit, IVC = inferior vena cava, NPV = negative predictive value, PPV = positive predictive value, SOFA = Sequential (Sepsis-related) Organ Failure Assessment.

Keywords: inferior vena cava, outcome, septic shock

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1. Introduction

Sepsis and septic shock are serious conditions with high mortality and accounted for more than 20 billion dollars in hospital costs in the USA in 2011.^[1–3] The incidence of sepsis is increasing due to the rising number of elderly people with comorbidities and patients with immunosuppression and multi-drug resistant infections.^[4,5] Although aggressive educational campaigns regarding sepsis have improved the understanding and treatment of sepsis, mortality and morbidity rates continue to be high and remain a threat to the public health system.^[6,7] Furthermore, patients who survive sepsis often have long-term physical, social, and cognitive disabilities that require significant health care associated with increasing social costs.^[8,9]

Rapid recognition, severity triage, treatment, and appropriate resource allocation is of utmost importance in sepsis and septic shock.^[10] Treatment of sepsis is mainly composed of fluid administration, antibiotic administration, removal of infection source, and intensive monitoring. Among these, fluid therapy is fundamental to the treatment of sepsis. Inadequate fluid administration is a problem, but it is reported that excessive fluid administration may also be associated with poor prognosis in patient with sepsis.^[11] Therefore, it is important to assess the volume status of the patient before making a decision to administer fluid.

Several previous studies have reported that the collapsibility of the inferior vena cava (IVC) is a predictor of fluid responsiveness

in patients with sepsis. In particular, the collapsibility of the IVC is known to predict volume status in patients with mechanical ventilation.^[12,13] Recently published studies have claimed that even in patients with spontaneous breathing, this value can help in determining the volume status.^[14] Moreover, it has been reported that the absolute value of the IVC diameter can predict the volume status.^[15] In trauma patients, the diameter of the IVC measured on a computed tomography (CT) scan has been reported to be associated with the prognosis.^[16] Among radiological investigations, CT scan is especially utilized in sepsis to identify the focus of infection and for determination of the infection source removal. However, whether the diameter of the IVC measured on CT is related to the prognosis of patients with sepsis and septic shock remains uncertain. Therefore, this study aimed to investigate whether the diameter of the IVC is associated with prognosis of patients presenting to the emergency department (ED) with septic shock.

2. Material and methods

2.1. Study design and population

From January 2016 to September 2019, a retrospective observational study was conducted on consecutive patients (≥ 18 years old) with septic shock who visited the ED of a university affiliated hospital located in Seoul, Korea. Septic shock was defined as suspected infection with blood culture and requiring administration of intravenous antibiotics and vasopressors. Exclusion criteria were as follows: patients who were directly transferred to other hospitals from the ED and those who did not undergo a CT scan. Patients were also excluded if they had signed a “do not attempt resuscitation” order. Infection was judged clinically through chart review. Systemic inflammatory response syndrome was not mandatory for the judgement of

infection. In our hospital, 20 to 30 ml/kg of crystalloid solution was administered to patients with sepsis or septic shock.^[10] Vasopressor was used in case of refractory hypotension despite fluid administration. Refractory hypotension was defined as persistent hypotension despite the administration of fluids or the requirement of vasopressors to maintain systolic blood pressure ≥ 90 mm Hg or mean arterial pressure ≥ 70 mm Hg.^[10] All methods were carried out in accordance with surviving sepsis campaign. All experimental protocols were approved by Hanyang university hospital institutional review board. Hanyang university hospital institutional review board waived the requirement for informed consent (HYUH 2019-11-035-003) due to the retrospective nature of the study.

2.2. Definitions and outcome

In patients with sepsis and septic shock, the decision to perform CT was at the discretion of the treating physician. All CT scans were obtained at 5-mm intervals with or without radiocontrast. The CT scan was reviewed by an emergency medicine chief resident who was blinded to outcome of patients. The IVC diameter ratio was calculated by dividing the maximal transverse diameter by the anteroposterior diameter (Fig. 1). The IVC diameter was measured at a level located directly below the renal vein. This location was selected for the study because it has been shown to display no change in the diameter of IVC with respiration.^[17] The primary endpoint of this study was in-hospital mortality.

2.3. Statistical analysis

The study data were reported as mean \pm standard deviation or median with an interquartile range for continuous variables as appropriate. For the categorical variables, data were presented as

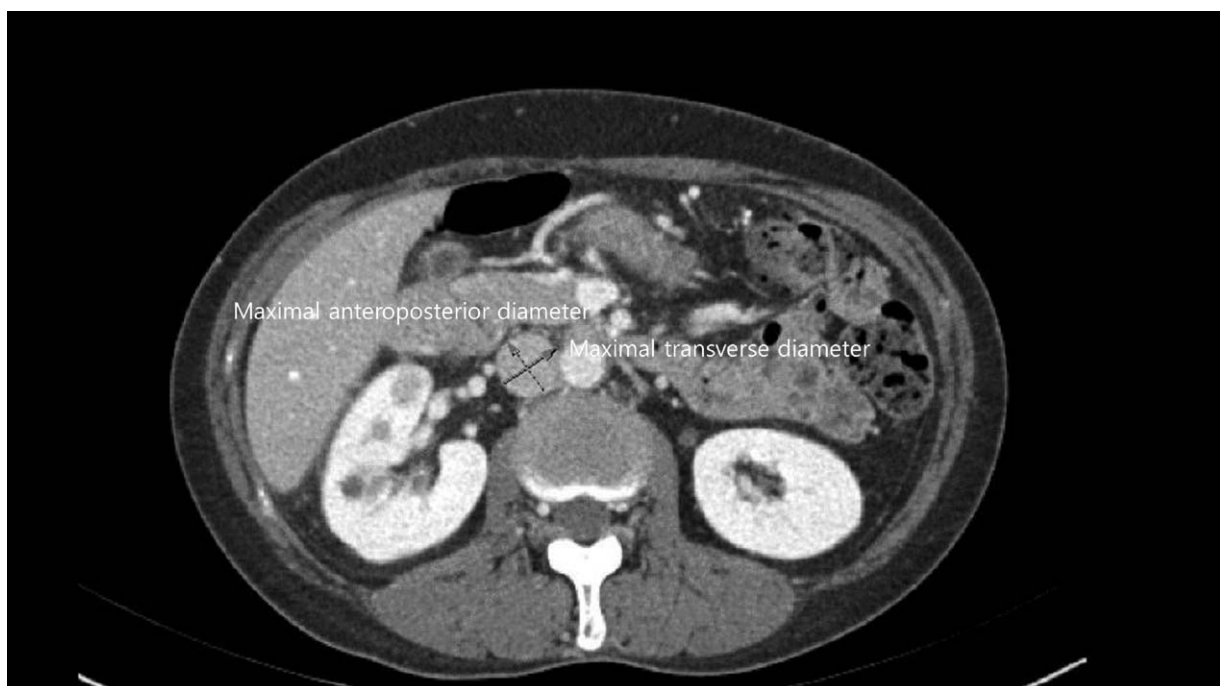


Figure 1. Measurement of the maximal transverse diameter and maximal anteroposterior diameter of the inferior vena cava. The measurements of the inferior vena cava were performed immediately below the level of the renal vein on abdominal computed tomography.

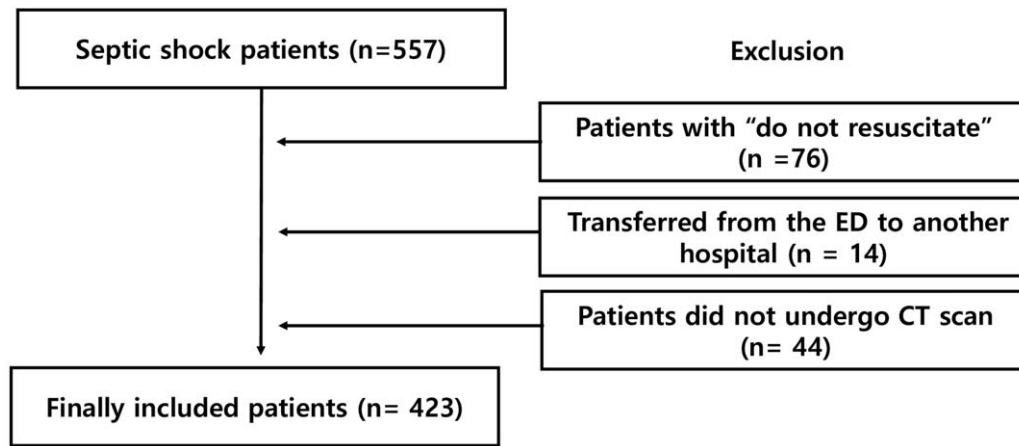


Figure 2. Flow diagram of the study population.

absolute or relative frequencies. Patients who died in-hospital after ED admission were compared to those who did not. Student *t*-test or the Mann–Whitney *U* test was used to compare continuous variables. The Chi-Squared test was used to compare categorical variables. A logistic regression model was used to assess the independent effect of IVC diameter ratio on in-hospital mortality, with multivariable adjustment for confounding variables that were significant in univariate analysis. Variables yielding *p* below 0.1 in the univariate analysis were entered into backward multivariable logistic regression analysis. The area under the receiver operating characteristic (AUC) curve was computed to examine the prognostic value of IVC diameter ratio for in-hospital mortality. Optimal threshold values were determined by maximizing the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the IVC diameter ratio were calculated and a two-sided test was performed. A *P* value $\leq .05$ was considered as significant. All statistical analyses were performed by using SPSS version 18 (IBM Inc, Chicago, IL, USA).

3. Results

3.1. Participant characteristics

During the study period, 557 adult septic shock patients were screened by chart review. Fourteen patients were directly transferred from the ED to another hospital and 44 patients did not undergo a CT scan. Additionally, the patients with “do not resuscitate” order (*n*=76) were excluded from the final analysis. Ultimately, 423 septic shock patients were included in the analysis (Fig. 2). The in-hospital mortality rate was 17% (*n* = 72). The average age of non-survivors was significantly higher than that of survivors (74.9 vs 71.6 years, *P* = .024) (Table 1). There were no significant differences in the initial vital signs between survivors and non-survivors. The frequency of heart failure and liver cirrhosis among non-survivors was significantly higher than that among survivors. In contrast, the frequency of urinary tract infections was significantly higher among survivors than among non-survivors (35.6% vs 20.8%, *P* = .019). The median levels of C-reactive protein (CRP) and lactate in non-survivors were significantly higher than that in survivors. Notably, the median value of the IVC diameter ratio in non-survivors was significantly higher than that in survivors (1.56 cm vs 1.4 cm, *P* = .004).

3.2. Multivariable logistic regression analysis and diagnostic performance of IVC diameter ratio

In order to examine the effect of the IVC diameter ratio on in-hospital mortality in patients with septic shock, multivariable logistic regression analysis was performed utilizing variables with a *P* value less than .1 in the univariate analysis as covariates. The

Table 1
Comparison of the characteristics of survivors and non-survivors.

Variables	Survivors (n=351)	Non-survivors (n=72)	<i>P</i> value
Age, years	71.6 ± 14.3	74.9 ± 10.3	.024
Men	144 (43%)	43 (48.9%)	.337
Initial vital signs			
Systolic blood pressure, mm Hg	105.4 ± 26.8	102.1 ± 29.3	.34
Diastolic blood pressure, mm Hg	59.3 ± 18.9	58.1 ± 18.4	.622
Heart rate, per minute	103.6 ± 23.1	107.6 ± 28.3	.266
Respiratory rate, per minute	20.2 ± 7.1	21 ± 10.4	.539
Comorbidities			
Hypertension	163 (46.4%)	37 (51.4%)	.517
Diabetes mellitus	110 (31.3%)	21 (29.2%)	.781
COPD	49 (14%)	13 (18.1%)	.464
Heart failure	50 (14.2%)	18 (25%)	.033
Liver cirrhosis	11 (3.1%)	10 (14.1%)	.001
CKD with renal replacement	6 (1.7%)	5 (6.9%)	.025
Origin of infection			
Respiratory	125 (35.6%)	34 (47.2%)	.082
Urinary	125 (35.6%)	15 (20.8%)	.019
Gastrointestinal	40 (11.4%)	7 (9.7%)	.838
Others	40 (11.4%)	8 (11.1%)	1.000
Laboratory findings			
WBC, 1000/mm ³	12.8 (7.7–17.7)	11.4 (6.0–16.9)	.199
CRP, mg/dl	14.9 (8.5–23.9)	19.2 (9.2–29.3)	.048
procalcitonin, ng/ml	5.7 (0.8–27.9)	8.8 (1.4–33.9)	.382
Creatinine, mg/dl	1.16 (0.81–1.72)	1.69 (1.06–2.65)	<.001
Total bilirubin, mg/dl	0.82 (0.56–1.35)	1.07 (0.7–1.85)	.004
Lactate, mmol/L	2.0 (1.3–3.5)	4.1 (2.2–7)	<.001
SOFA score	7 (5–9)	11 (8.3–13)	<.001
IVC diameter ratio	1.4 (1.19–1.85)	1.56 (1.31–2.52)	.004
Time to CT scan, min	133 (101–184)	128 (85–175)	.291
Volume to CT scan, ml	1000 (400–1155)	960 (370–1200)	.659

COPD = chronic obstructive lung disease, CKD = chronic kidney disease, CRP = c-reactive protein, IVC = inferior vena cava, CT = computed tomography, SOFA = Sequential (Sepsis-related) Organ Failure Assessment.

Table 2
Multivariable logistic regression analysis to predict in-hospital mortality.

	Odds ratio [confidence interval]	P value
Age	1.03 [1.003–1.057]	.028
IVC diameter ratio	1.48 [1.097–1.998]	.01
SOFA	1.375 [1.232–1.533]	<.001
Lactate	1.102 [1.000–1.215]	.049
CRP	1.023 [1.000–1.046]	.051

IVC diameter ratio was adjusted for age, sex, heart failure, liver cirrhosis, CKD with renal replacement, respiratory, urinary, SOFA, lactate, CRP
 CKD = chronic kidney disease, CRP = c-reactive protein, IVC = inferior vena cava, SOFA = Sequential (Sepsis-related) Organ Failure Assessment

odds ratio (OR) for IVC diameter ratio was 1.48 [confidence interval: 1.097–1.998] and was statistically significant ($P=.01$) (Table 2). The age, lactate level, and Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score were independently associated with in-hospital mortality (OR: 1.03, 0.102, and 1.375, respectively).

The AUC of the IVC diameter ratio for predicting in-hospital mortality was 0.607. The cut-off value of the IVC diameter ratio for predicting in-hospital mortality based on the maximum sum of sensitivity and specificity was 1.31 cm. Over all diagnostic accuracy of the cut-off value for IVC diameter ratio (≥ 1.31) was 58%. The sensitivity, specificity, positive predictive value, and negative predictive value of the cut-off value were 75%, 42%, 20%, and 89%, respectively (Table 3).

3.3. Comparison between the patients with higher and lower IVC diameter ratio

The mean age of the patients with higher IVC diameter ratio was significantly higher than that of patients with lower IVC diameter ratio (73.3 vs 70.4 years, $P=.038$) (Table 4). There were no significant differences in the initial vital signs between the 2 groups. The number of patients with hypertension was significantly higher in the higher IVC diameter ratio group than in the lower IVC diameter ratio group (52.5% vs 39%, $P=.007$). The median creatinine and lactate levels in the higher IVC diameter ratio group were significantly greater than that in the lower IVC diameter ratio group (1.4 mg/dl vs 1.1 mg/dl and 2.4 mmol/L vs 1.9 mmol/L, respectively). The median SOFA score of patients in the higher IVC diameter ratio group was significantly greater than that of patients in the lower IVC diameter ratio group (8 vs 7, $P=.005$). There were no significant differences in the time to CT scan and the volume of fluid administered prior to CT scan between the 2 groups. The higher IVC diameter ratio group demonstrated a significantly higher in-hospital mortality rate than the lower IVC diameter ratio group (20.8% vs 11%, $P=.011$). There was no significant frequency difference in ventilator and vasopressor use during CT scans between the 2 groups.

Table 3
Sensitivity, specificity, positive predictive value, and negative predictive value of IVC diameter ratio for in-hospital mortality.

	Accuracy	Sensitivity	Specificity	PPV	NPV
IVC diameter ratio ≥ 1.31 cm	58%	75%	42%	20%	89%

IVC = inferior vena cava, PPV = positive predictive value, NPV = negative predictive value.

3.4. Subgroup analyses

The OR for IVC diameter ratio was 2.146 [confidence interval: 1.362–3.383] and was statistically significant ($P=.001$) (Table 5) for predicting in-hospital mortality in patients not requiring mechanical ventilation during CT scan. The IVC diameter ratio was also found to be significant for predicting in-hospital mortality in patients not requiring vasopressors during CT scan (OR: 1.696, CI: 1.155–2.49, $P<.001$). The AUC of the IVC ratio for predicting in-hospital mortality in patients without mechanical ventilation during CT scan was 0.63 and in patients not requiring vasopressors during CT scan was 0.598. Importantly, the IVC diameter ratio was significantly associated with in-hospital mortality in patients satisfying the Sepsis 3 definition (OR: 1.475, CI: 1.093–1.991, $P=.011$). The AUC of the IVC ratio for predicting in-hospital mortality in patients satisfying the Sepsis 3 definition was 0.604.

4. Discussion

In this study, we found that the IVC diameter ratio measured on CT scans was helpful in predicting the outcome of septic shock patients. The median IVC diameter ratio in non-survivors was greater than that in survivors. Elevated IVC diameter ratio might indicate inappropriate volume replacement therapy and need for additional fluid administration. In the subgroup analyses, the IVC diameter ratio continued to be associated with in-hospital mortality in patients not requiring mechanical ventilation and vasopressor treatment as well as those satisfying the Sepsis 3 definition. However, additional well-designed studies are required given the low diagnostic performance and sensitivity of the IVC diameter ratio.

To the best of our knowledge, this is the first study to address the prognostic value of IVC diameter ratio measured on CT scan in patients with septic shock. Previous studies have investigated the association between IVC collapsibility or diameter and outcome of patients with sepsis or septic shock using ultrasonography instead of CT scan. Among the septic shock patients in our study, only 7% of the patients who did not undergo CT were excluded from this study. This suggests that the IVC diameter ratio measured on CT scan can have prognostic value for the outcome of all septic shock patients and not just in a specific group that underwent CT. In addition, we performed various subgroup analyses in patients who did not receive mechanical ventilation and vasopressor treatment to exclude the effect of these factors on the IVC diameter ratio. Notably, the IVC diameter ratio was still associated with the outcome of septic shock patients after adjustment for these factors.

Volume replacement is an immediate priority and plays a fundamental role in the treatment of sepsis and septic shock. Volume replacement increases cardiac output, and consequently, oxygen transport to tissues. However, numerous studies have reported the harmful effects of inappropriate fluid administration. Therefore, predicting fluid responsiveness is very important.^[11,18,19] Respiratory variation in IVC diameter has been shown to predict volume responsiveness in mechanically ventilated patients in multiple studies. Moreover, it has been reported that variation in IVC diameter is associated with volume responsiveness in spontaneously breathing patients. In addition to the variation in IVC diameter, the absolute diameter of the IVC has also been known to predict volume responsiveness in critically ill patients. IVC diameter has been demonstrated to

Table 4
Comparison of the characteristics of patients with high IVC diameter ratio and low IVC diameter ratio.

Variables	low IVC diameter ratio (n = 166, <1.31 cm)	high IVC diameter ratio (n = 257, ≥ 1.31 cm)	P value
Age, years	70.4 ± 13.9	73.3 ± 13.6	.038
Men	70 (42.7%)	117 (45.2%)	.617
Initial vital signs			
Systolic blood pressure, mm Hg	104.9 ± 26.3	104.8 ± 27.8	.971
Diastolic blood pressure, mm Hg	59.1 ± 16.7	59.1 ± 20.1	.988
Heart rate, per minute	103.9 ± 22.3	104.5 ± 25.1	.794
Respiratory rate, per minute	20.1 ± 7.4	20.5 ± 8	.628
Comorbidities			
Hypertension	64 (39%)	136 (52.5%)	.007
Diabetes mellitus	44 (26.8%)	87 (33.6%)	1.161
COPD	26 (15.9%)	36 (13.9%)	.672
Heart failure	31 (18.9%)	37 (14.3%)	.223
Liver cirrhosis	7 (4.3%)	14 (5.4%)	.653
CKD with renal replacement	5 (3%)	6 (2.3%)	.756
Origin of infection			
Respiratory	60 (36.3%)	99 (38.2%)	.758
Urinary	52 (31.7%)	88 (34%)	.672
Gastrointestinal	18 (11%)	29 (11.2%)	1.000
Others	23 (14%)	25 (9.7%)	.208
Laboratory findings			
WBC, 1000/mm ³	13.3 (7–18.4)	12.3 (7.5–17.5)	.546
CRP, mg/dl	15.6 (9.5–23.9)	15.4 (7.5–25.6)	.847
Procalcitonin, ng/ml	5.9 (0.8–19.8)	5.7 (1.1–33.9)	.269
Creatinine, mg/dl	1.1 (0.8–1.6)	1.4 (0.8–2.3)	<.001
Total bilirubin, mg/dl	0.8 (0.6–1.5)	0.8 (0.6–1.4)	.907
Lactate, mmol/L	1.9 (1.2–3.6)	2.4 (1.3–4.6)	.015
SOFA score	7 (5–9)	8 (6–10)	.005
Time to CT scan, min	140 (104–186)	132 (97–181)	.387
Volume to CT scan, mL	1000 (500–1225)	980 (307–1157)	.431
Ventilator during CT scan	50 (30.1%)	72 (28%)	.661
Vasopressor during CT scan	47 (33.1%)	77 (34.8%)	.736
Hospital mortality	18 (11%)	54 (20.8%)	.011

COPD = chronic obstructive lung disease, CKD = chronic kidney disease, CRP = c-reactive protein, IVC = inferior vena cava, CT = computed tomography, SOFA = Sequential (Sepsis-related) Organ Failure Assessment.

Table 5
Multivariable logistic regression analysis to predict in-hospital mortality in subgroups.

Patients without mechanical ventilation during CT scan		
	Odds ratio [confidence interval]	P value
Age	1.051 [1.000–1.104]	.048
IVC diameter ratio	2.146 [1.362–3.383]	.001
SOFA	1.634 [1.319–2.025]	<.001
Patients not requiring vasopressors during CT scan		
	Odds ratio [confidence interval]	P value
IVC diameter ratio	1.696 [1.155–2.49]	.007
SOFA	1.535 [1.32–1.785]	<.001
Patients satisfying the Sepsis 3 definition		
	Odds ratio [confidence interval]	P value
Age	1.03 [1.004–1.058]	.025
IVC diameter ratio	1.475 [1.093–1.991]	.011
SOFA	1.373 [1.231–1.531]	<.001

IVC diameter ratio was adjusted for age, sex, heart failure, liver cirrhosis, CKD with renal replacement, respiratory, urinary, SOFA, lactate, CRP.

CKD = chronic kidney disease, CRP = c-reactive protein, IVC = inferior vena cava, SOFA = Sequential (Sepsis-related) Organ Failure Assessment.

predict intravascular volume in haemodialysis as well as in ventilated septic patients.^[12,13,20,21] Previous studies on trauma patients have revealed that the IVC diameter predicts hypovolemia, ongoing blood loss, and hemodynamic compromise.^[22–24] Johnson et al. reported that IVC ratio had a significant correlation with other known markers of shock and is also an independent predictor of mortality in severely injured trauma patients. In their study, the IVC diameter measurement location was infrarenal similar to that in our study; however, a “flat” IVC was defined as an IVC diameter ratio of ≥1.9. This was based on a previous study that investigated the predictive value of IVC diameter in trauma patients. In our study, the median value of IVC diameter was 1.43 cm in the entire cohort, and it was lower than that in the previous trauma-related study. The main pathophysiology in sepsis is vasodilatation leading to hypovolemia, unlike in haemorrhagic shock where there is direct blood loss leading to vasoconstriction as a compensatory mechanism.^[25,26] This difference might explain the different cut-off values for IVC diameter ratio. In addition, our data revealed that positive pressure ventilation and vasopressor administration can affect the IVC diameter. Nevertheless, subgroup analyses showed that IVC diameter ratio had a significant prognostic value for the outcome of septic shock.

There are numerous markers that reflect tissue perfusion status but no single marker has shown superiority over others. Vital signs such as blood pressure or heart rate cannot be reliable markers of tissue perfusion; central venous pressure and central venous oxygen saturation fail to reflect the volume status or an association with the outcome of sepsis.^[27,28] In clinical practice, multiple variables or data to evaluate tissue perfusion status should be considered. In patients with sepsis and septic shock, measurement of the IVC using ultrasound is useful for evaluating volume status. However, ultrasound has a drawback in that there is variability depending on the operator skill, and accurate measurement is difficult when the patient is obese or there is air in the bowel. CT scan is used to identify the source of infection and determine whether source control should be performed in sepsis and septic shock. CT can help overcome the shortcomings of ultrasonography and the IVC diameter ratio can be used to evaluate the volume status and guide fluid administration in such patients.

Our study has several limitations. Firstly, this was a single centre retrospective study, and therefore, it is difficult to generalize our results to other institutions. Secondly, IVC diameter measurement was performed by a single investigator, and we did not compare the measured value with that measured by another investigator. Therefore, the possibility of bias in IVC diameter measurement cannot be ruled out. It would be beneficial to compare the difference between the values of IVC diameter measured by independent investigators using intraclass correlation coefficients in a future study. Third, although the amount of fluid administered prior to CT scan and time to CT scan were not different between the lower IVC diameter ratio group and higher IVC diameter ratio group, we cannot exclude the effect of other variables on the IVC diameter ratio and outcome of septic shock. However, our findings from various subgroup analyses were consistent with the principal findings of the study. Lastly, we conducted multivariable analysis by including variables that can influence the diameter of the inferior vena cava and the prognosis of septic shock patients. However, we did not include the specific disease, such as valvular heart disease, right heart failure, cor pulmonale and very old patients.

5. Conclusions

The IVC diameter ratio as measured on CT scan was found to be significantly associated with the outcome of patients with septic shock. Various subgroup analyses yielded similar results. The IVC diameter ratio can be a marker of tissue hypoperfusion and appropriate fluid administration might be needed in such cases. However, further well-designed studies are required given the low diagnostic performance and sensitivity of IVC diameter ratio.

Author contributions

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