Clinical application of Venous Excess Ultrasound (VExUS) versus Sequential Organ Failure Assessment (SOFA) for prediction of outcome in septic shock

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Abstract

Intravenous fluid administration is an essential component of sepsis management, but giving too much fluid might result in fluid overload, which is hazardous for the patient's outcome. The VExUS score is a 4-step protocol that evaluate the presence and severity of venous congestion in the inferior vena cava (IVC), liver, gut, and kidneys. This prospective trial was carried out on 52 ICU cases with septic shock. VExUS score and SOFA score were calculated at admission and after 48 hours. Out of 52 patients, 27 patients non-survived (51.9%). The non-survived group showed statistically significant higher median VExUS score after 48 hours (p<0.001), statistically higher median SOFA score at admission (p=0.004) and after 48 hours (p<0.001) when compared to cases who survived. Moreover, increase VExUS score have the highest predictive value for bad outcome with the overall percent predicted 90.4%. The present study suggested that an increased VExUS score may prove to be a powerful predictor of morbidity and mortality in septic patients and may serve as an indicator of fluid overload in those patients.

Keywords: Septic shock, VExUS, mortality, survivors.

1. Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection, it is a time-dependent disease and requires a prompt recognition and a standardized treatment [1]. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality[2]. The core of sepsis treatment is IV fluid delivery; however, the ideal fluid balance and dosage are yet unknown. Giving too few IV fluids can lead to tissue hypoperfusion, which exacerbates organ dysfunction. On the other hand, new research indicates that a positive fluid balance is also linked to an increased mortality risk [3].Therefore, the evaluation of volume status is crucial in the early management of critically ill patients[4]. The Sequential Organ Failure Assessment (SOFA) score was designed to examines six systems and uses one or more variables to reflect dysfunction severity [5,6].The SOFA score was validated as predictor of short-term mortality (3, 5 and 28-day mortality in ICU or hospital) [7]. Venous congestion can now be graded using a new approach called Venous Excess Ultrasound (VExUS). Examining the patient for venous congestion can be done while attempting to determine their fluid status. This can also provide us with more information about when to start fluids, cease fluids, diuresis, or choose a vasopressor in patients with septic shock, congestive heart failure, or acute renal failure[8]. VExUS score comprise assessment of inferior vena cava diameter, portal vein pulsatility index, hepatic vein Doppler and intrarenal vein Doppler. Then the results of these four parameters are interpreted together as a score for evaluation of venous congestion[9]. The aim of this study is to compare **Venous Excess Ultrasound (VExUS)** and **Sequential Organ Failure Assessment (SOFA)** as predictors of morbidity and survival of critically ill patients with septic shock.

2. Methods

2.1. Population and data collection

This prospective trial was carried out on 52 ICU cases with septic shock, who were admitted to Mansoura

University`s Specialized Medical Hospital ICU units from July 2022 to July 2023. Study protocol was submitted for approval by Institutional Research Board (IRB), Faculty of Medicine, Mansoura University. Patients with septic shock were identified by a specific team of intensivists. **Inclusion criteria** were the Patient`s age more than 18 years old and diagnosed with septic shock according to sepsis-3 definition [10]. **Exclusion criteria** were acute pulmonary edema, acute coronary syndrome, cardiogenic shock, pregnant ladies, right-sided heart disease, known pulmonary conditions (pneumectomy; pulmonary fibrosis; persistent pleural effusion), chronic kidney disease (stage 5) or indication for emergency renal replacement therapy (RRT) and portal hypertension. Demographic, laboratory, and clinical data were registered including age, sex, comorbidities, source of infection, routine laboratory investigations including: Complete Blood Count (CBC), serial arterial blood gases, blood culture, full liver & kidney function tests and circulatory system biomarkers such as the mixed venous oxygen saturation and serum lactate. ECG and echocardiography were done. Sequential Organ Failure Assessment score at admission, after 48 hours and calculation of delta SOFA. Venous Excess Ultrasound (VExUS) assessment at admission and after 48 hours. Net fluid balance will be assessed every 24 hours. Length of ICU stay and survival rate, Need for mechanical ventilation or vasopressor days and Development of other organ failure were documented.

2.2. Definitions

Septic shock (11): sepsis with persisting hypotension requiring vasopressors to maintain mean arterial blood pressure (MAP) 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

2.3. Statistical analysis

The collected data were coded, processed, and analyzed using the Statistical Package for Social Science (SPSS) version 25 for Windows on personal computers. Qualitative data were described as percentages and numbers, while quantitative data were described as means [± standard deviation (SD)] for parametric variables or medians (interquartile range; IQR), for nonparametric variables, as suitable. To assess the normality of distribution of variables, Shapiro-Wilk test were used. For comparing between two groups, t-test was used for normally distributed variables, while Mann Whitney test was used for non-normally distributed variables. Chi-square test was used for comparing between qualitative variables. Receiver operating characteristic (ROC) curve was performed to allocate a cut-off point of balance on the first day and the cut-off point was chosen relying on the best possible specificity without sacrificing the sensitivity of choice. The level of significance was considered at 5% (P ≤ 0.05).

3. Results and Discussion
3.1. Baseline characteristics

A total of 52 patients were included in the analysis. Epidemiologic results were as follows: males comprise 55.8% of the studied group; the mean age was 68.27±11.14 years. The source of sepsis among the studied cases is distributed as follows: 55.8% pneumonia, 48.1% urinary

tract infection, 25% diabetic foot and soft tissue infection, and 3 cases of ascending cholangitis. 71.2% of the studied patients have comorbidities of hypertension, and 51.9% diabetic, and 76.9% are others including cardiomyopathy, hypothyroidism, COPD, IHD, CKD, RA, alzheimer disease. 27 out of 52 patients were died.

3.2. Comparison between survivors and non survivors

There were no significant differences between survivors and non-survivors as regard gender, other sociodemographic characteristics, comorbidities and source of septic shock. However, survivors showed statistically significant higher GCS (P=0.001), lower CVP (P<0.001) and near statistically lower age (P=0.062), also they showed statistically significant lower serum lactate (p= 0.001) in comparison to the non-survivors (Table 1). Moreover, survivors showed statistically significant lower median SOFA at admission (p=0.004), statistically significant lower median SOFA after 48 hours (p<0.001) and lower median delta SOFA (p<0.001) when compared with non survivors. On the other hand, the present study revealed a statistically significant higher median VExUS score after 48 hours and statistically near significant higher VExUS at admission (P=0.06) among non-survivor cases in comparison to survived cases (Table 2). The study of predictors of bad outcome revealed that a decrease GCS and increase CVP but increase VExUS score showed the highest predictive value (highest beta and odds ratio) with the overall percent predicted 90.4%. Every increase one point in VExUS score increase risk of bad outcome by 4.7 more times. This prospective trial was conducted on a total of 52 consecutive adult patients with septic shock admitted to ICU of medical critical care unit. The present study revealed a nearly significant higher age among non-survived patients than survived patients. Also, *Wardi et al, 2021* [12].showed that increasing age is associated with bad outcome in septic shock. The study showed no statistically significant difference as regard sex between non-survived and survived. *Luethi et al, 2020* [13].and *Sunden-Cullberg et al, 2020* [14].also reported that there was no difference in mortality from sepsis or trauma between male and female genders (Table 3). However, *Pietropaoli et al, 2010* [15]. found that females with severe sepsis/septic shock had a higher risk of dying in the hospital than did males. The current study showed also no difference between survived group and non-survived group as regard diabetes mellitus and hypertension. In the same line with the current study, *Lin et al, 2021* [16].and *Singla et al, 2014* [17].proposed that the presence of type II diabetes mellitus is not associated with bad clinical outcomes in septic shock patients with ARDS. In the present study, the source of sepsis is not statistically different between the survived and non-survived group. On the other hand, *Shen et al, 2018* [18].found significant differences between the survivors and non survivors when the cause of septic shock was respiratory and urinary cause, but the abdominal cause was not statistically significant between the 2 groups. In the present trial, the study also showed lower Glasgow Coma Score among the non-survived group than the survived patients. This is consistent with *Liu et al, 2021* [19].which showed that higher GCS is documented among survivor than non-survivor (Table 4).

Table 1: Comparison of socio-demographic characteristics & Comorbidities between cases who survived (n=25) and cases who don`t survive (n=27).

	survival		test of significance
	Survived N=25	**Not survived N=27**	
Age / years mean±SD	65.28±9.96	71.04±11.64	t=1.91 p=0.062
Sex **Male** **Female**	15(60.0) 10(40.0)	14(51.9) 13(48.1)	χ2=0.349 p=0.554
Diabetes	11(44.0)	16(59.3)	χ 2=1.21 p=0.271
Hypertension	17(68.0)	20(74.1)	χ 2=0.233 p=0.629
Others	21(84.0)	19(70.4)	χ 2=1.36 p=0.329

Table 2: Comparison of source of infection, and vital signs, examination results between cases who survived (n=25) and cases who don`t survive (n=27).

	survival		test of significance
	survived N=25(%)	**Not survived N=27(%)**	
Pneumonia	11(44.0)	18(66.7)	χ 2=2.70 p=0.100
UTI	12(48.0)	13(48.1)	χ 2=0.0 p=1.0
DM foot as source of infection **No** **Perianal abscess** **Infected wound** **Diabetic foot** **Cellulitis** **Bed sores**	18(72.0) 1(4.0) 1(4.0) 2(8.0) 1(4.0) 2(8.0)	21(77.8) 0 1(3.7) 1(3.7) 0 4(14.8)	χ 2MC=3.16 p=0.676
other sources **Ascending cholangitis**	2(8.0)	1(3.7)	FET=0.441 P=0.603
GCS	14.60±1.04	11.41±4.34	t=3.58 p=0.001*
CVP	11.72±5.81	20.22±8.01	t=4.35 p<0.001*
Mixed venous O2 saturation	72.36±7.21	73.41±6.49	t=0.551 p=0.584
Serum lactate	4.15±1.32	5.50±1.48	t=3.47 p=0.001*
Ejection fraction	57.16±13.42	51.31±10.91	t=1.73 p=0.09
Fractional shortening	29.45±8.03	25.29±5.45	t=2.20 p=0.032*

Table 3: Comparison of SOFA score at admission, after 48 hour and delta SOFA between cases who survived (n=25) and cases who don`t survive (n=27).

	survival		test of significance (Mann Whitney U test)
	Survived N=25	**Not survived N=27**	
SOFA score at admission	8(4-12)	10(3-17)	z=2.84 p=0.004*
SOFA score after 48 h	4(0-7)	14(5-20)	z=5.99 p<0.001*
Delta SOFA score	3(0-7)	-4(-9 , 3)	z=5.94 p<0.001*
Wilcoxon signed rank test	z=0.905 p=0.366	z=4.08 p<0.001*	

Table 4: Comparison of VExUS score at admission and after 48 hour between cases who survived (n=25) and cases who don`t survive (n=27).

	survival		test of significance (Chi-Square test)
	Survived N=25	**Not survived N=27**	
VExUS score at admission Grade 0 Grade 1 Grade 2 Grade 3	21(84) 2(8) 1(4) 1(4)	13(48.1) 6(22.2) 4(14.8) 4(14.8)	χ2=7.42 p=0.06
VExUS score after 48 hours Grade 0 Grade 1 Grade 2 Grade 3	15(60) 10(40) 0 0	0 5(18.5) 12(44.4) 10(37.0)	χ2=38.65 p<0.001*
Wilcoxon signed rank test	z=0.905 p=0.366	z=4.08 p<0.001*	

Table 5: Predictors of bad outcome among studied cases

|	β	p value	odds ratio (95%CI)
GCS	-1.23	0.008*	0.293 (0.118-0.727)
CVP	0.239	0.01*	1.27 (1.06-1.53)
Serum lactate	0.662	0.064	1.94 (0.961-3.91)
Fractional shortening	0.025	0.728	1.03 (0.891-1.18)
SOFA score at admission	-0.498	0.335	0.608 (0.221-1.67)
SOFA score after 48 h	1.37	0.074	3.94 (0.875-17.78)
VExUS score after 48 hours	2.3	0.001*	4.7 (1.23-9.8)
Overall % predicted =90.4%			

Table 6: Validity of SOFA and VExUS at admission and SOFA and VExUS after 48 hours in differentiating cases with primary or secondary endpoints

	AUC (95%CI)	p value	cut off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
VExUS at admission	0.682 (0.536-0.829)	0.024*	1.0	30.0	92.0	80.0	54.8	59.6
VExUS after 48 hours	0.963 (0.920-1.01)	0.001*	2	81.5	100.0	100.0	83.3	90.4
SOFA at admission	0.728 (0.589-0.867)	0.005*	8.5	66.7	72.0	72.0	66.7	69.2
SOFA after 48 h	0.983 (0.954-1.0)	0.001*	5.5	96.3	80.0	83.9	95.2	88.5
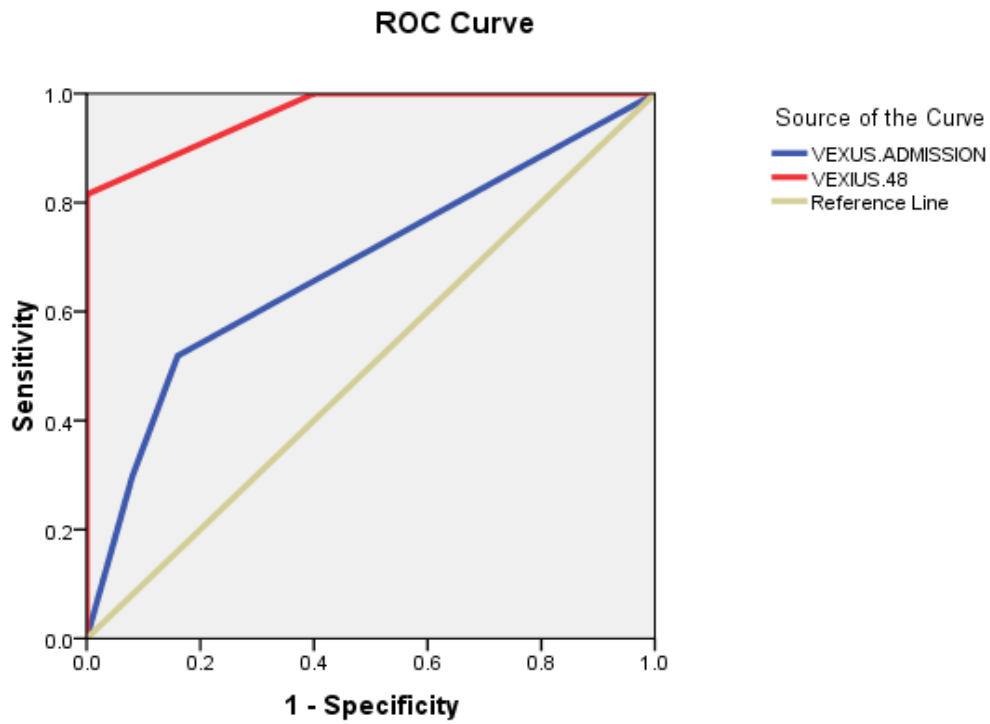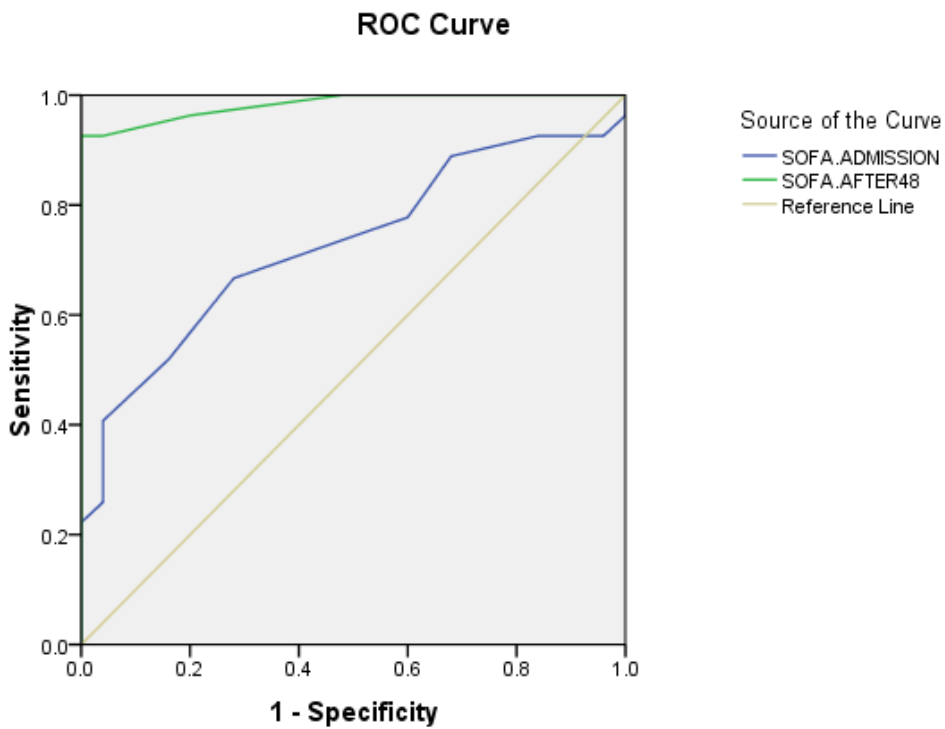
Figure 1: ROC Curve

Figure 2: ROC Curve

The present study showed also higher CVP among the non-survived group than the survived patients. Also, *Vellinga et al, 2013* [20].found that elevated CVP is associated with impairment of microcirculation and affecting outcome in sepsis. The current study demonstrated no difference as regard blood pressure, pulse, respiratory rate and mixed venous O2 saturation between the survived and non-survived patients. Also, *Jain and Vikyath, 2023* [21].found no significant change in survivor and non-survivor as regard mixed venous oxygen saturation. A statistically significant lower Serum lactate was in survivor than the non-survivor patients is detected in the present study. This consistent with *NI and Qin, 2023* [22].and *Sadigov and Alizamin, 2023* [23].who found that is higher serum lactate among cases who developed AKI in septic shock than in cases who did not develop AKI. The study found a statistically significant higher median SOFA score at admission, after 48 hours and delta SOFA were detected among non-survived group when compared with the survived group. Also, *Acheampong and Vincent, 2015* [24]. study reported significant lower SOFA score in survivors than non-survivors in septic shock. The current study demonstrated a statistically near significant higher VExUS score at admission and a statistically significant higher median VExUS score after 48 hours among the non-survived group when compared with the survived group (Table 5). This is consistent with *Rolston et al, 2021* [25]. which showed higher VExUS scores were significantly associated with higher odds of mortality. Also, Increasing VExUS scores at the time of ED presentation in patients with sepsis were associated with an increased odds of 24-hour mortality as demonstrated by *Forrester et al, 2023* [26]. While *Andrei et al, 2023* [27].did not report any association between admission VExUS and AKI and lack of association between VExUS and the risk of 28-day mortality. Also, *Magin et al, 2023* [28].reported no statistically significant association between VExUS grading and all-cause complications or AKI. Study of predictors of bad outcome among the studied cases, the present study found a decrease in GCS, an increase in CVP, and an increase in the VExUS score, but the highest predictive value was detected for the VExUS score. Whereas *Sasko et al, 2015* [29].reported that CVP was of no prognostic value regarding the 28-day survival in septic shock. The validity of SOFA score in differentiating cases with new organ failure, need mechanical ventilation and died cases is good & excellent in the present study. Also *Lin et al, 2021*[16]. reported that SOFA is a straightforward prognostic tool to use for critically ill elderly patients. A SOFA score ≥ 6 is significantly associated with in-hospital and long-time mortality (Table 6).

3.3. Limitations

- This study establishes a link between VExUS and outcome of septic shock, but further investigation and validation of the technique is required. Larger studies including a wider range of patient pathologies should be conducted to better evaluate relationships between invasively measured cardiac pressures and VExUS.
- Additional confounding comorbidities such as cirrhosis, valvular disease, diastolic dysfunction, and other potential hemodynamic confounders of VExUS imaging will need to be carefully evaluated.
- Moreover, fluid balance better to be evaluated for better assessment of fluid status to be complementary to VExUS score
- Overall, the application of the VExUS score provided crucial guidance for decision-making and allowed clinicians to tailor the therapeutic approach to address venous congestion and achieve optimal fluid balance. Monitoring the VExUS score in real time facilitated adjustments to the treatment strategy, leading to improvements in clinical parameters and patient outcomes.

4. Conclusions

- The current study suggested that an increased VExUS score may prove to be a powerful predictor of morbidity and mortality in septic patients and may serve as an indicator of fluid overload in those patients.
- This observation supports the suggestion that fluid administration needs to be carefully titrated after hemodynamic stabilization. Therefore, there is a need for a multimodal approach that combines different parameters to assess the fluid status in patients with septic shock

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