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Article

Lung Ultrasound versus Transpulmonary Thermo-dilution in Assessing Extravascular Lung Water in Septic Shock after Initial Resuscitation: A Prospective observational Study

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Abstract. *Background:* The prognostic value of extravascular lung water index (EVLWI) which is determined by transpulmonary thermodilution has been widely investigated. The aim of this study is to investigate the hypothesis that lung ultrasound provides a valuable prognostic tool compared to transpulmonary thermodilution in assessing extravascular lung water and determining outcomes in patients with septic shock. *Materials & Methods***:** This is a prospective observational study where fifty adult patients of both genders with septic shock received initial fluid resuscitation and underwent continuous hemodynamic monitoring using pulse index continuous cardiac output (PiCCO) and simplified lung ultrasound protocol, analyzing the prognostic value of lung ultrasound score (LUS) compared to EVLWI in 48 hours after initial resuscitation. *Results:* With ICU mortality as the end point, 50 patients were divided into a survivor group (30 patients) and a non-survivor group (20 patients). LUS showed significant linear correlation with EVLWI (Spearman's r=0.848, P=<0.001* at T48). LUS and EVLWI were significantly higher in non-survivors than in survivors (P =<0.001*at T48). The areas under the receiver operating characteristic curves of LUS and EVLWI measured by PiCCO were 0.843 and 0.921 at T48, respectively. The cut-off of LUS and EVLWI for prognosis prediction were 12 and 12.7, respectively. Pairwise comparison of both ROC curves showed no significant difference between LUS and EVLWI as predictors of mortality at T48, p =0.125. *Conclusion:* Lung ultrasound is a useful, simple, non-invasive tool for predicting the prognosis of septic shock patients compared to EVLWI measured by PiCCO.

Keywords: Lung ultrasound, Extravascular lung water**,** Transpulmonary Thermodilution, Septic shock.

Introduction

Sepsis is a life threatening medical condition.(1) According to the Third International Consensus Definitions for Sepsis and Septic Shock, sepsis is a potentially fatal condition where organ failure occurs due to an imbalanced response of the body to an infection. Among the sepsis cases, there is a subgroup called septic shock, which involves abnormalities in circulation, cellular function, and metabolism that significantly increase the risk of death. The diagnosis of septic shock can be made based on specific clinical criteria, including the requirement of a vasopressor to maintain the mean arterial pressure (MAP) above 65 mmHg and a serum lactate level higher than 2 mmol/L (18 mg/dL) despite appropriate fluid resuscitation.(2)

According to the current guidelines of the Surviving Sepsis Campaign (SSC), patients diagnosed with sepsis and septic shock are recommended to receive an initial fluid bolus of 30 mL/kg of intravenous crystalloids within one hour.(3) Multiple studies have demonstrated a notable correlation between fluid balance and mortality in sepsis cases. These studies have also revealed that the initial fluid boluses administered do not necessarily lead to a proportionate increase in cardiac output.(4-8) Moreover, the development of interstitial edema caused by increased capillary permeability in sepsis plays a crucial role in initiating tissue ischemia and subsequent organ failure.(9)

Extravascular lung water (EVLW) refers to the quantity of water present in the space outside the blood vessels within the lungs. This measurement reflects the extent of pulmonary edema, which can increase due to elevated hydrostatic pressure or increased permeability of the pulmonary capillaries.(10) Transpulmonary thermodilution is a technique employed to measure extravascular lung water (EVLW) as a means of estimating both the degree of capillary permeability and volume overload in the lungs.(11, 12) It was found that higher EVLW was independently associated with mortality in septic shock patients.(13)

Lung ultrasound is a valuable method for evaluating the condition of the lungs in critically ill patients, including those with septic shock. One of the advantages of lung ultrasound is its ease of use and the ability to repeat the examination as needed.(14) Ultrasound is a readily accessible and non-invasive tool utilized by intensivists at the bedside. When performing lung ultrasound, the presence of B-lines is indicative of pulmonary edema. B-lines are visualized as comet-tail artifacts that originate from the pleural line and move synchronously with lung sliding. These lines are characterized by their long, well-defined, and hyperechoic appearance. If more than two B-lines are observed between the ribs, it is referred to as "lung rockets" and serves as a diagnostic marker for interstitial lung syndrome.

This ultrasound-based approach provides clinicians with valuable information about the presence and severity of pulmonary edema in critically ill patients.(15)

Pulse contour analysis with transpulmonary thermodilution used to determine EVLW index requires both a specialized arterial catheter and a central venous line. In the setting of limited resources, Ultrasound of the lung is a non-invasive and cost-effective technique can be used to assess a patient's fluid status compared to pulse contour cardiac output (PiCCO).

The aim of this study is to investigate the hypothesis that lung ultrasound provides a valuable prognostic tool compared to transpulmonary thermodilution in assessing extravascular lung water and determining outcomes in patients with septic shock.

Patients and Methods

This study was conducted at the main university hospital in Alexandria, involving fifty patients of both genders who were admitted to the Emergency Department and Critical Care Units. The sample size for this study was determined using the PASS Version 20 Program,(16) taking into consideration a 95% confidence level and a 3% precision using a z-test.(17) Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was obtained (IRP NO: 00012098). An informed consent was taken from the patients' next of kin before their enrollment in the study.

Patients' selection criteria included septic shock patients above 18 years old undergoing continuous hemodynamic monitoring after initial resuscitation. Exclusion criteria included Pregnancy, Burn patients, Patients with significant intracardiac shunts, aortic aneurysms, pneumonectomy, massive pulmonary embolism, Intraaortic balloon pumps, undergoing extracorporeal circulation, cardiogenic and non-cardiogenic pulmonary edema.

All data about patient's demographics, principal diagnosis and all clinical, laboratory and radiological parameters were collected at time of enrollment. Initial severity of illness was determined using Acute Physiology and Chronic Health Evaluation II (APACHE II) and SOFA scores.(18, 19) Patients were subjected on admission to all possible microbiological culturing prior to antibiotic therapy.

All patients were included in the study after receiving the followings in the ED: Early initial fluid resuscitation with 30 ml/kg crystalloids for hypotension or lactate ≥ 4 mmol/L, Early broad spectrum antibiotic therapy directed to the source of infection within one hour after presentation, Early vasopressors within one hour if patient is

hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥ 65 mm Hg and Mechanical ventilation with protective lung strategy if indicated.

Patients included in the study received continuous hemodynamic monitoring after initial resuscitation including: MAP, cardiac index (CI), stroke volume index (SVI), global end-diastolic volume index (GEDVI), pulmonary vascular permeability index (PVPI) and extravascular lung water index (EVLWI) using Pulse contour analysis with transpulmonary thermodilution after establishment of a femoral arterial catheter and a jugular or subclavian central venous line.

Hemodynamic parameters were measured using *Benevision N series 17* monitors. A bolus of 15 ml 0-4°C normal iced saline was injected in the CVC, while the resultant drop in temperature was analyzed by the arterial catheter. The mean of three consecutive boluses were used to obtain an average value of measurements.

All patients underwent Simplified lung ultrasound protocol,(20) this protocol was performed using standard ultrasound equipment (3.5-MHz curved array probe). This method entails that the patients were scanned while in supine position, and four intercostal spaces (ICSs) were examined: the ICS between the 3rd and 4th ribs and the ICS between the 6th and 7th ribs to the left and right of the sternum between the parasternal and midclavicular line. The number of single and confluent B lines were recorded, and a score ranging from 0 to 32 was calculated to summarize the B lines of the four ICSs. (Table 1)

Table (1): Ultrasound scoring system

Ultrasound finding	Score
No B line/ICS	0
One B line/ICS	1
Two B lines/ICS	2
Three B lines/ICS	3
Four B lines/ICS	4
Five B lines/ICS	5
Confluent B lines >50% ICS	6
Confluent B lines >75% ICS	7
Confluent B lines 100% ICS	8

ICS: Intercostal space (20).

The monitoring times were recorded at T0, 24 h and 24-48 h after initial resuscitation. T0 was the first reading of hemodynamic parameters after

establishment of the monitor of pulse contour cardiac output (PiCCO). The daily maximum value of EVLWI, its corresponding lung US score, and other hemodynamic parameters were recorded. Data collection included fluid balances, days of mechanical ventilation, and the length of ICU stay and 28-day prognosis.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. **(**Armonk, NY: IBM Corp**)**. Categorical data were represented as numbers and percentages. **Chi-square test** was applied to investigate the association between the categorical variables. Alternatively, **Fisher's Exact correction** test was applied when more than 20% of the cells have expected count less than 5. For continuous data, they were tested for normality by the **Shapiro-Wilk test**. For normally distributed quantitative variables data was expressed as mean and standard deviation and **Student t-test** was used to compare between two groups. On the other hand, for not normally distributed quantitative variables data was expressed as median and Inter quartile range and **Mann Whitney test** was used to compare between two groups. **Spearman coefficient** was used to correlate between not normally distributed quantitative variables. A **Receiver operating characteristic curve (ROC)** was used to determine the diagnostic performance of the markers, area more than 50% gives acceptable performance and area about 100% is the best performance for the test. Significance of the obtained results was judged at the 5% level.

Results

This study included 50 patients with septic shock, out of which 20 died within 28 days. Three non-survivors passed away before the 48-hour monitoring period could be completed. Table 2 summarizes the demographic and baseline clinical characteristics of the patients. The results showed that survivors had significantly lower APACHE II scores, SOFA scores, and CRP levels compared to non-survivors. However, there were no significant differences in age, sex, sources of infection, serum lactate levels, or frequency of underlying diseases between the two groups. Moreover, important hemodynamic variables such as MAP, CI, SVI, GEDVI, EVLWI, PVPI, and LUS were similar between the survivors and non-survivors at T0 (i.e., the first measurements taken after initial resuscitation). (Table 2)

Table (2): Comparison between the two studied groups according to demographic data and baseline clinical characteristics

	Total (n = 50)	Mortality 28 days		Test of Sig.	p
		Survived (n = 30)	Died (n = 20)		
Gender					
Male	28 (56%)	16 (53.3%)	12 (60%)	χ^2= 0.216	0.642
Female	22 (44%)	14 (46.7%)	8 (40%)		
Age (years)	60.7 ± 16.9	60.2 ± 16.6	61.4 ± 17.7	t=0.244	0.808
Co-morbidity					
Chronic cardiovascular disease	21 (42%)	13 (43.3%)	8 (40%)	χ^2=0.055	0.815
Chronic renal failure	14 (28%)	8 (26.7%)	6 (30%)	χ^2=0.066	0.797
DM	12 (24%)	6 (20%)	6 (30%)	χ^2=0.658	^{FE}p=0.506
Liver cirrhosis	9 (18%)	3 (10%)	6 (30%)	χ^2=3.252	^{FE}p=0.130
COPD	6 (12%)	2 (6.7%)	4 (20%)	χ^2=2.020	^{FE}p=0.202
Source of infection					
Pneumonia	16 (32%)	10 (33.3%)	6 (30%)	χ^2=0.061	0.804
UTI	10 (20%)	6 (20%)	4 (20%)	χ^2=0.000	^{FE}p=1.000
Intra-abdominal sepsis	9 (18%)	4 (13.3%)	5 (25%)	χ^2=1.107	^{FE}p=0.454
Catheter related infection	6 (12%)	4 (13.3%)	2 (10%)	χ^2=0.126	^{FE}p=1.000
Skin, soft tissue infection	4 (8%)	3 (10%)	1 (5%)	χ^2=0.408	^{FE}p=0.641
Others	5 (10%)	3 (10%)	2 (10%)	χ^2=0.000	^{FE}p=1.000
APACHE II	26 (21 – 27)	23 (15 – 26)	26.5 (23 – 27)	U=186.0	0.023*
SOFA	10.3 ± 2.3	9.6 ± 2	11.3 ± 2.3	t=2.727*	0.009*
CRP	191 (125 – 298)	185 (120 – 308)	214 (185 – 265)	U=196.0*	0.039*
Serum lactate level	4.9 (3 – 5.9)	4.7 (2.7 – 5.5)	5 (3.6 – 8.1)	U=206.0	0.062
Hemodynamic parameters T0					
MAP	82 (73 – 84)	82 (73 – 90)	78.5 (73 – 84)	U=290.0	0.842
CI	3.3 (2.7 – 3.7)	3.3 (2.65 – 3.8)	3.2 (2.7 – 3.5)	U=281.0	0.706
SVI	30 (26 – 35)	30.5 (23 – 36)	30 (27 – 33.5)	U=288.0	0.812
GEDVI	720 (657 – 754)	697 (640 – 754)	729.5(666 – 786)	U=248.0	0.303
EVLWI	10.9 (9.7 – 12.5)	10.7 (9.7 – 11.8)	11.2 (9.5 – 13)	U=255.50	0.378
PVPI	2.1 (1.5 – 2.8)	2.1 (1.2 – 2.8)	2.2 (1.5 – 2.8)	U=274.0	0.605
LUS	8 (7 – 12)	8 (7 – 12)	8.5 (7 – 12)	U=284.0	0.749

Qualitative data were described using number and percent, while normally distributed quantitative data was expressed in Mean ± SD and for not normally distributed quantitative data was expressed in Median (IQR)

χ^2: **Chi square test** FE**: Fisher Exact** **t: Student t-test** **U: Mann Whitney test**

p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

Table (3): Comparison between the two studied groups according to process of care variables

	Total (n = 50)	Mortality-28 days		U	p
		Survived (n = 30)	Died (n = 20)		
T24					
MAP	87 (72 – 92)	89 (71 – 96)	85.5 (72 – 92)	288.0	0.812
CI	3.4 (2.9 – 3.8)	3.4 (2.9 – 3.8)	3.3 (2.9 – 3.8)	277.0	0.751
SVI	31 (28 – 37)	32 (28 – 39)	31 (28 – 35)	250.0	0.321
GEDVI	755 (649 – 788)	737 (649 – 794)	761.5(703 – 788)	223.0	0.127
EVLWI	11.9(10.6 – 14.7)	11 (10.4 – 11.9)	14.1(12.9 – 16.2)	107.50*	<0.001*
PVPI	2.6 (1.6 – 2.9)	2.1 (1.5 – 2.9)	2.9 (2.1 – 3.1)	178.00*	0.015*
LUS	11 (7 – 14)	9 (7 – 12)	13.5 (10 – 16)	156.00*	0.004*
Fluid balance	1750(1500–3250)	1500(1250–3250)	2625(1750–3500)	194.0*	0.034*
T24 – 48#					
MAP	88 (75.5 – 93.5)	88 (75 – 96)	86 (76 – 90)	236.0	0.673
CI	3.4 (3.8 – 4)	3.5 (2.8 – 3.8)	3.4 (2.7 – 4)	234.0	0.641
SVI	34 (30.5 – 39)	35 (31 – 39)	33 (30 – 35)	182.0	0.105
GEDVI	753 (701 – 862.5)	753 (700 – 844)	794 (709 – 865)	222.0	0.465
EVLWI	12.2 (11.3 – 15.4)	11.4 (10.7 – 12.2)	15.5 (14.9 – 17.9)	40.500*	<0.001*
PVPI	2.7 (2 – 3.1)	2.5 (1.6 – 3)	3 (2.7 – 3.4)	102.00*	0.001*
LUS	12 (8 – 14)	9 (6 – 12)	14 (13 – 15)	80.00*	<0.001*
Fluid balance	1500(1250–2000)	1250(1000–1750)	1750(1500–2750)	110.0*	0.001*
MV days	4 (1 – 6)	4 (0 – 6)	4.5 (2 – 8)	239.0	0.224
ICU stay days	6 (4 – 10)	9 (4 – 16)	5 (3 – 8)	182.0*	0.019*

For not normally distributed quantitative data was expressed in Median (IQR); **U: Mann Whitney test;** #: 3 patients died before 48 hours; p: p value for comparing between the studied groups; *: Statistically significant at $p \leq 0.05$

In terms of the care provided to both survivors and non-survivors, several process-of-care variables were compared. The results showed that the EVLWImax values at T24 and T24-48 were significantly higher in non-survivors compared to survivors. Similarly, the PVPI values at T24 and T24-48 were also significantly higher in non-survivors than in survivors. Moreover, the non-survivors had a significantly higher daily fluid balance at T24 and T24-48, and their LUS values were significantly higher as well. On the other hand, survivors had a longer length of ICU stay compared to non-survivors. There were no significant differences between the two groups in terms of other hemodynamic parameters such as MAP, CI, SVI, and

GEDVI. Additionally, the duration of mechanical ventilation days was similar for both groups. (Table 3)

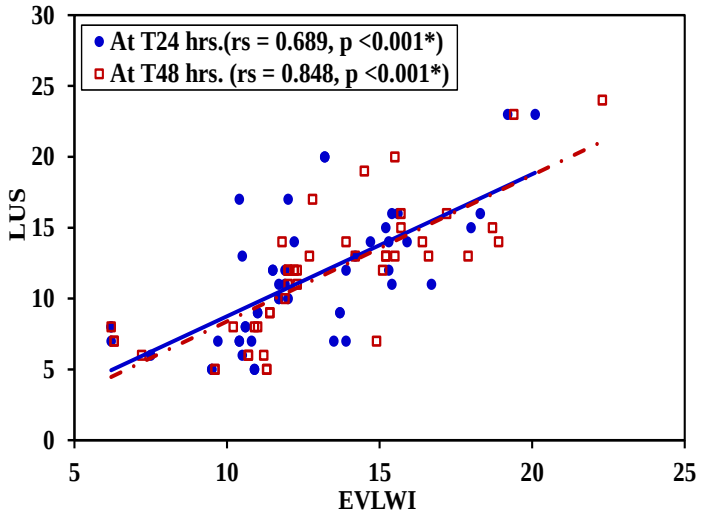

Figure (1): Correlation between EVLWI and LUS in total sample

Correlation between EVLWI and LUS was done at T24 and T48. LUS showed significant linear correlation with EVLWI (Spearman's r_s=0.689, p<0.001* at T24, r_s=0.848, p<0.001* at T48). (Fig. 1)

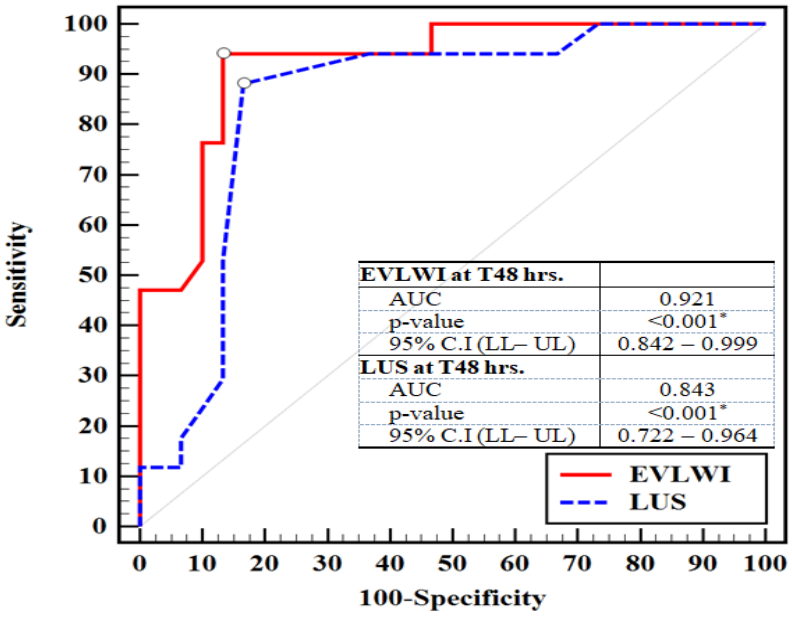

Figure (2): ROC curve to predict mortality (n = 17 vs. 30) at T48 hrs.

Receiver operating characteristic (ROC) curve was constructed to evaluate the ability of LUS compared to EVLWI to predict mortality in septic shock patients after

initial resuscitation at T48. Regarding EVLWI, the AUC was 0.921, the cut-off value of >12.7 showed sensitivity 94.12 and specificity 86.67 with positive predictive value 80.0 and negative predictive value 96. Regarding LUS, The AUC was 0.843, the cut-off value of >12 showed sensitivity 88.24 and specificity 83.33 with positive predictive value 75.0 and negative predictive value 92.6. Pairwise comparison of both ROC curves showed no significant difference between LUS and EVLWI as predictors of mortality at T48 ($p = 0.125$). (Fig. 2)

Discussion

This prospective study aimed to evaluate the prognostic value of lung ultrasound compared to transpulmonary thermodilution in assessing extravascular lung water (EVLW) in septic shock patients after initial resuscitation. Since measuring EVLW using transpulmonary thermodilution requires specialized invasive monitoring, we sought to investigate the potential of lung ultrasound as a non-invasive and cost-effective alternative, particularly in resource-limited settings. Previous studies have demonstrated a significant correlation between B-lines detected by lung ultrasound and extravascular lung water levels.(21)

In line with existing research, Wang et al. conducted a study on the prognostic value of EVLWI in septic shock after initial resuscitation. Their findings showed a significant correlation between the maximum EVLWI value and daily fluid balance at 24 and 24-48hours post-resuscitation.(13) Enghard et al. also investigated the use of a simplified lung ultrasound protocol to assess extravascular lung water in ventilated intensive care patients, revealing a significant correlation between ultrasound score and EVLWI.(20)

Our study findings were consistent with previous research, demonstrating a significant correlation between lung ultrasound and EVLWI at 24 and 24-48 hours after initial resuscitation. Notably, the maximum EVLWI at 48 hours was significantly higher in non-survivors compared to survivors. We identified a cutoff value of >12.7 for EVLWI at 24-48 hours as a predictor of 28-day mortality, with high sensitivity and specificity. Wang et al. reported a prognostic cutoff value of 12.5 mL/kg for EVLWI in the 48 hours following initial resuscitation.(13)

Our study also revealed that lung ultrasound was a reliable predictor of 28-day mortality in septic shock patients. A cutoff value of >12 at 24-48 hours demonstrated good sensitivity and specificity for prognosis prediction. Notably, we found no significant difference between lung ultrasound and EVLWI as predictors of mortality. These findings align with Zhao et al.'s study on patients with acute respiratory distress syndrome, which showed significant positive linear correlations between lung ultrasound scores and EVLWI. They also identified a significant

difference in lung ultrasound scores between non-survivor and survivor groups, with both lung ultrasound and EVLWI measured by PICCO demonstrating good prognostic value.(22)

In summary, our study adds to the growing body of evidence supporting the prognostic value of lung ultrasound in assessing EVLW and predicting mortality in septic shock patients. Lung ultrasound, with its non-invasive nature and cost-effectiveness, shows promise as a valuable tool for fluid status evaluation in resource-limited settings when compared to invasive methods such as transpulmonary thermodilution with pulse contour cardiac output.

Limitations of the study

This study has a few limitations that should be acknowledged. Firstly, we only utilized a single lung ultrasound approach and did not compare different protocols such as the 8 or 28-zone protocols. Therefore, we were unable to determine the superiority of one protocol over another in assessing extravascular lung water (EVLW). Secondly, although we considered transpulmonary thermodilution as the standard method for measuring EVLW, there is currently no consensus on the exact cutoff value for defining a pathologically elevated EVLW level. This lack of agreement in the field may introduce some variability in the interpretation of EVLW measurements. Lastly, it is important to note that lung infections can potentially impact lung ultrasound findings, EVLW measurements, and pulmonary vascular permeability index (PVPI). The presence of lung infection may introduce confounding factors that can influence the accuracy and interpretation of these measurements. Addressing these limitations in future studies could provide further insights into the optimal lung ultrasound protocols, standardization of EVLW cutoff values, and the impact of lung infections on the assessment of lung status in septic shock patients.

Conclusion

Significant positive correlation was found between LUS and EVLWI measured by PiCCO. This study showed that lung ultrasound was a good predictor of 28-days mortality in septic shock patients compared to extravascular lung water measured by transpulmonary thermodilution.

Competing Interests

The authors declare that there is no conflict of interest.

Ethics

After ethical approval for this clinical trial from the local committee of ethics in the Faculty of Medicine of Alexandria University and the Department of Critical Care Medicine. Informed consents for participating and publishing were taken from the next of kin of patients after approval by Critical Care Department committee.

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Availability of Data and Materials

Please contact author for any data requests.

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