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The predictive value of vascular leak index as a measure of fluid accumulation and mortality in septic patients

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Abstract:

Background: Sepsis is a leading cause of morbidity and mortality throughout the world. Intravenous (IV) fluid infusion is recommended by expert guidelines to increase venous return, cardiac stroke volume, cardiac output, and tissue perfusion. **Objectives:** to evaluate the prognostic value of vascular leak index (VLI) to identify the risk of in-hospital death and fluid accumulation in critically ill septic patients. **Methods:** In a prospective study, we enrolled 50 patients with sepsis in the critical care department, 30 cases survived (60%) and 20 cases died (40%). All patients were subjected to: History, clinical examination, acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score, Bed side chest x-ray, base line 12-leads ECG full laboratory work for sepsis, Lactate level, and VLI was measured. **Results:** There was statistically significant difference between both groups regarding increased lactate in non-survivors (9.5±17.3 mmol/L) when compared with survivors (1.54 ± 0.31 mmol/L).Thirty percent of survivors needed vasopressors and 23.3% needed mechanical ventilation while 70% of non-survivors needed vasopressors and 95% needed mechanical ventilation. The median length of ICU stay was much longer for non-survivors than survivors (28 vs 8 days respectively). There was a significant positive correlation between VLI and mortality as it correlated significantly with APACHEII score, initial SOFA score, SOFA score after 48 hours and Lactate level. VLI significantly increased in patients needed vasopressors, MV and those with prolonged ICU stay. **Conclusion:** VLI had a significant correlation with ICU sepsis related mortality with high sensitivity (93.3%) and specificity (70%).

Keywords:

Sepsis, Vascular leak index, fluid accumulation, mortality in septic patients.

1. Introduction:

Sepsis is a major cause of death worldwide. [1] Recent guidelines considered IV fluid is very crucial in treatment of sepsis and septic shock to augment tissue perfusion. ([2-7]

Despite the effective role of IV fluids in increasing cardiac output (COP), only around half of patients with septic shock respond to IV fluid (increased COP by≥ 15%), even in these patients in whom COP increased , fluid administration is ineffective or sometimes be harmful.[8]

The net result of excessive IV fluids and the inflammatory cascade of sepsis lead to increased vascular permeability (vascular leak syndrome). [8]

Multiple studies investigated the effect of a positive fluid balance on mortality .Fluid balance is the difference between total fluid intake and total fluid output and a positive fluid balance refers to a retain of more than 10% of the fluids infused to the patient , with impaired organ function and a higher risk of death. [9–11]

The degree of vascular leak can be expressed by measuring the level of hematocrit which is a too large protein to leak out of the vasculature. If the infused fluids remain inside the circulation, hematocrit level will be declined, if fluid leaks increased, the level of hematocrit will be slowly declining or even may be increased. [12, 13]

Aim of the study:

To evaluate the prognostic value of novel vascular leak index to identify the risk of in-hospital death and fluid accumulation in critically ill septic patients.

2. Patient and methods:

2.1. Study patients and design:

This prospective study was conducted on 50 patients in the critical care Department in Beni-Suef University Hospitals, the period of the study ranging from March to October 2023.

Inclusion criteria: Adult patients (age above 18 years), both gender, admitted with sepsis to the critical care department in Beni-Suef university hospital.

Exclusion criteria: age under 18 years, bleeding and or receiving blood products, renal replacement therapy, patients who had other causes of excess

fluid output (eg:burn), Hematological malignancies (leukemia, myelodysplastic syndrome), anemia (HB less than 8gm/dl), pregnancy, hypoalbuminemia and patients receiving renal replacement therapy.

2.2. Methodology:

All patients included in this study were subjected to the following:

***I. Clinical evaluation*:** history taking and full clinical examination.

II. Scoring System: APACHE II score was assessed on admission, SOFA score and Glasgow coma score were assessed on daily basis.

III. Investigations: Bed side chest x-ray & base line 12-leads ECG, Laboratory investigations including: complete blood count, liver function test including: Alanine transaminase, Aspartate transaminase, total & direct bilirubin, total protein, serum albumin, serum ammonia level, Coagulation profile: (PC, PT and INR), kidney functions: (urea and creatinine), Electrolytes as Na & k, Arterial blood gases, Random blood sugar, serum lactate withdrawn on admission and Cultures & sensitivity were done on admission and whenever needed.

2.3. Vascular leak index measurement:

Vascular leak index can be measured through the following equation:(13)

$$VLI = \left(\frac{Hct_{final} - Hct_{initial}}{\text{net fluid balance}}\right) * (\text{body surface area}) * 1000$$

Where; initial hematocrit refers to hematocrit level at study baseline (0 h)

Final hematocrit refers to the average of hematocrit values at 18, 36 and 84 hs

Net fluid balance = output-input. (From the first hour of admission to 84h)

We started the fluid infusion according to surviving sepsis campaign (SSC) guidelines which suggested treating septic patients with at least 30mg/kg IV crystalloids within the 1st three hours then fluid therapy was tailored according to patient tolerance and response. (14)

The net fluid balance was calculated as total fluid input (From the first hour of admission to 84h) minus the total fluid output.

2.4. Study outcomes:

Primary outcome: the prognostic value of VLI to identify the risk of hospital death and fluid accumulation.

Secondary outcomes: length of ICU stay, need for mechanical ventilation, need of vasopressors.

2.5. *Ethical considerations:*

This study was approved by ethical committee, faculty of medicine Beni-Suef University (Approval No: FMBSUREC/05032023/Abd Elaziz). Informed written consent was signed by all patients to be included in the study.

2.6. Statistical analysis:

The collected data was organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 21 (SPSS Inc, Chicago, USA). For qualitative data, frequency and percent distributions was calculated. For quantitative data, mean, standard deviation, minimum and maximum was calculated. For comparison between two groups, the independent samples test was used. For all tests, p-value less than 0.05 were considered significant.

3. Results:

As shown in table (1), out of fifty patients, 24 (48%) were males and 26 (52%) were females. And out of the same number (50), survivors were 30 patients (60%), 14 were males and 16 were females, non survivors were 20 (40%), 10 males and 10 females. The mean age was 52.9±18.4 years for the whole group, where the mean age of survived and non-survived groups was 50.83±19.38 vs 56±16.87 years respectively, with no significant difference between both groups regarding age or sex **(p-value 0.336 and 0.817** respectively). There was a number of comorbidities and risk factors prevalent among study patients, where (44%) of patients had diabetes mellitus, (40%) had hypertension, and (22%) had ischemic heart diseases, while there was no significant difference between survivors and non-survivors regarding comorbidities. Vital signs were assessed, there was a statistically significant difference between both groups regarding respiratory rate was 21.5±5.4 breath/min in survivors and 26.25±7.2 breath/min in non survivors **(p-value 0.011),** regarding heart rate was 88.7±14.8 bpm among survivors and 103.75±16.8 bpm among non-survivors **(p-value 0.002)**,but there was no statistically significant difference regarding mean arterial pressure(75.13±19.4 mmHg in survivors) and (74.95±22.9mmHg in non survivors)with **p-value=0976**,regarding temperature was 37.8±0.6**°C** among survivors and 37.6±0.6 **°C** among non-survivors **(p-value=0.291).**There was a statistically significant difference between both groups regarding increased lactate level in non-survivors (9.5±17.3 mmol/L)

when compared with survivors (1.54 ± 0.31 mmol/L) with **p-value 0.014**. GCS was evaluated for the whole group with a median of 15 and ranging from 4 to 15. Where the survived group scored a median of 15 and ranging from 9 to 15 that was higher than the non-survived group who scored a median of 13.5, and ranging from 4 to 15, with a statistically significant difference between both groups **(p=0.011)**. BSA was measured for the whole group with a mean of (1.74±0.17 m^2), where the survived group had a mean of (1.7±0.17 m^2) that was lower than the non-survived group who scored a mean of (1.8±0.16 m^2), with a statistically significant difference between both groups **(p=0.035)**. Sepsis was mainly encountered due to chest and urinary tract infection (both resemble 48% of sources), followed by skin and abdomen infections; 30% and 12% respectively. However, there was a statistically significant difference between both survivor and non-survivor groups regarding UTI and skin infections as a source of sepsis (p=0.008 and 0.002 respectively), while no significant difference regarding chest or abdominal infections.

Table (1): Basic demographic and clinical characteristics of the study patients (n=50)

	Total (n=50)	Survivors (n=30)	Non-survivors (n=20)	p-value
Sex				
Male	24 (48%)	14 (46.7%)	10 (50%)	0.817 [a]
Female	26 (52%)	16 (53.3%)	10 (50%)	
Age (mean ±SD)	52.9±18.4	50.83±19.38	56±16.87	0.336 [b]
Comorbidities				
DM	22 (44%)	11 (36.7%)	11 (55%)	0.201 [a]
HTN	20 (40%)	10 (33.3%)	10 (50%)	0.239 [a]
IHD	11 (22%)	5 (16.7%)	6 (30%)	0.311 [c]
Examination				
GCS	15,4-15	15,9-15	13.5,4-15	0.011
BSA (m^2)	1.74±0.17	1.7±0.17	1.8±0.16	0.035
MAP (mmHg)	75.06±20.6	75.13±19.4	74.95±22.9	0.976
RR(B/min)	23.4±6.5	21.5±5.4	26.25±7.2	0.011
Heart Rate (bpm)	94.7±17.2	88.7±14.8	103.75±16.8	0.002
Temperature (**°C)**	37.7±0.6	37.8±0.6	37.6±0.6	0.291
Lactate level(mmol/L)	4.7±11.5	1.54±0.31	9.5±17.3	0.014
Chest infection	24 (48%)	15 (50%)	9 (45%)	0.729 [a]
Intra-abdominal infection	6 (12%)	4 (13.3%)	2 (10%)	1.00 [b]
UTI	24 (48%)	19 (63.3%)	5 (25%)	0.008 [a]
Skin infection	15 (30%)	4 (13.3%)	11 (55%)	0.002 [a]

a: Chi-square test. b: Independent samples T-test. c: Fisher's exact test.

As shown in table (2),Fluid balance was calculated for the whole group with a mean of 4832±2811.3 ml, the survived group had a lower mean than that of the non survivors (3413.7±1231.35 vs 6959.5±3182.38 ml respectively), with a statistically significant difference between both groups**(p<0.001)**.There was a statistical significant difference

between survivors and non survivors regarding the need of vasopressors (30% vs 70% respectively)with **p-value 0.005**, as well as, There was a statistical significant difference between survivors and non survivors regarding the need of mechanical ventilation(23.3% vs 95% respectively) with **p-value<0.001**. The median length of ICU stay was much longer for non-survivors (28 days) than survivors (8 days) with **p-value<0.001.**

Table (2): Net fluid balance and complications in studied groups

	Total (n=50)	Survivors (n=30)	Non-survivors (n=20)	p-value
Fluid balance ml (mean ±SD)	4832 ±2811.3	3413.7 ±1231.35	6959.5 ±3182.38	<0.001 b
Need vasopressors	23 (46%)	9 (30%)	14 (70%)	0.005 a
Need Mechanical Ventilation	26 (52%)	7 (23.3%)	19 (95%)	<0.001 a
ICU stay (Median, range)	13.0, 4.0-65.0	8.0, 4.0-42.0	28.0, 7.0-65.0	<0.001 b

a: Chi-square test. b: Mann Whitney test.

As shown in table (3), There was a statistical significant difference between VLI, APACHEII score, initial SOFA score, SOFA score after 48 hour, ICU stay and lactate level; **(r = 0.56,0.431,0.538,0.405 and 0.33** respectively) with **p-value < 0.001, 0.002, < 0.001, 0.007 and 0.016** respectively.

Table (3): Correlation between Vascular leak index, APACHEII score, lactate, initial SOFA score and SOFA after 48 hours.

VLI	R	p-value
APACHEII score	0.6	<0.001
Initial SOFA score	0.431	0.002
SOFA score after 48 hours	0.538	<0.001
ICU stay	0.405	0.007
Lactate	0.33	0.016

R: Correlation coefficient

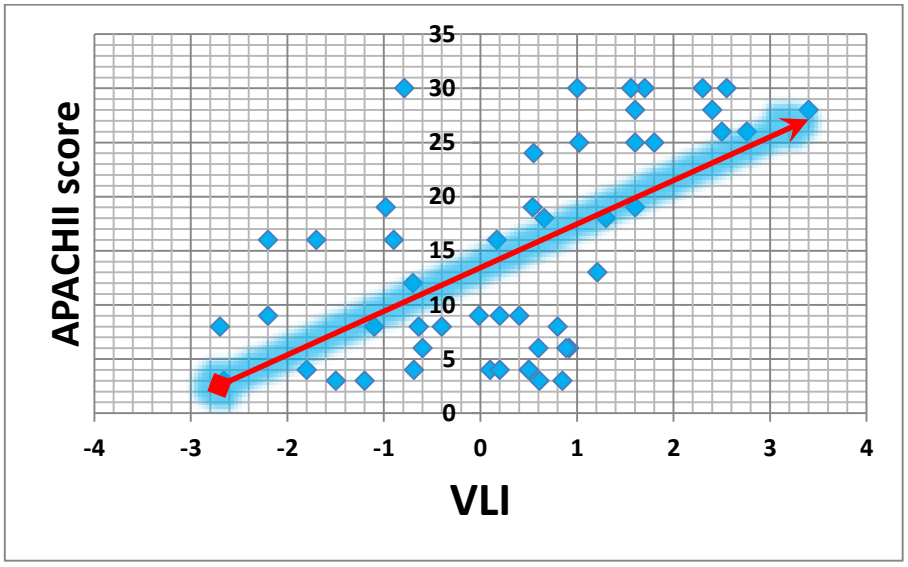

Figure (1): Positive correlation between VLI and APACHEII score.

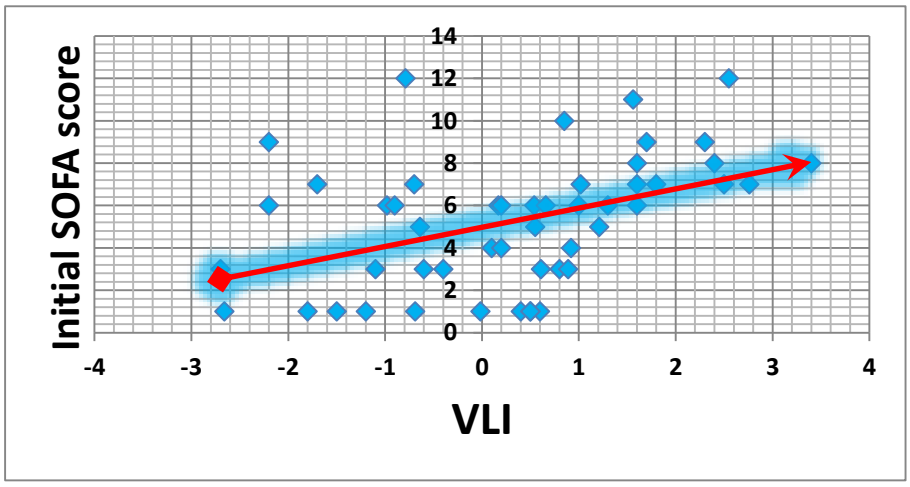

Figure (2): Positive correlation between VLI and initial SOFA score.

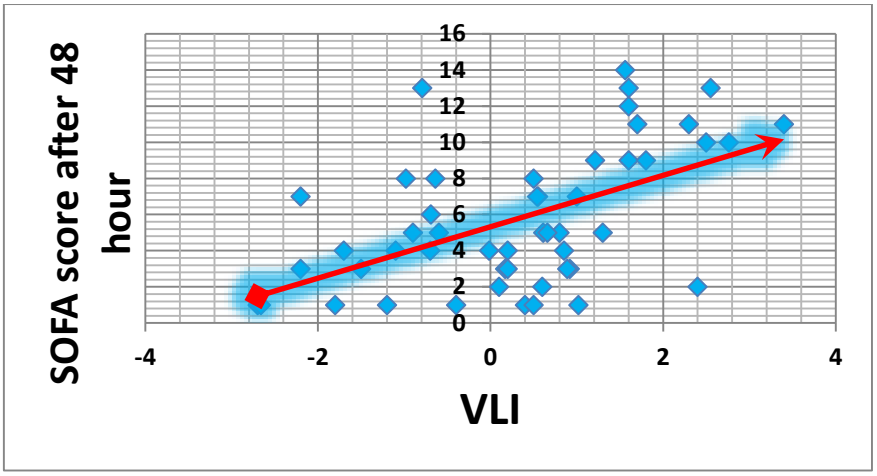

Figure (3): Positive correlation between VLI and SOFA score after 48 hour.

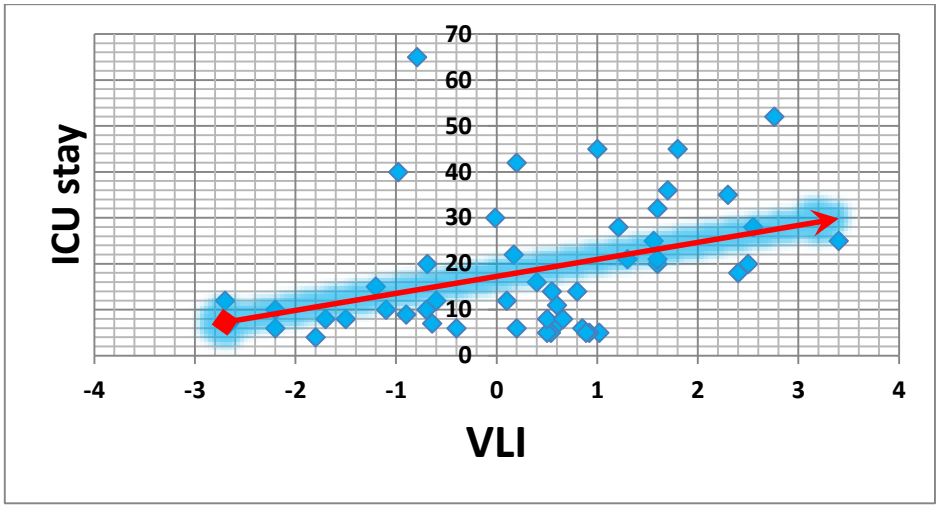

Figure (4): Positive correlation between VLI and ICU stay.

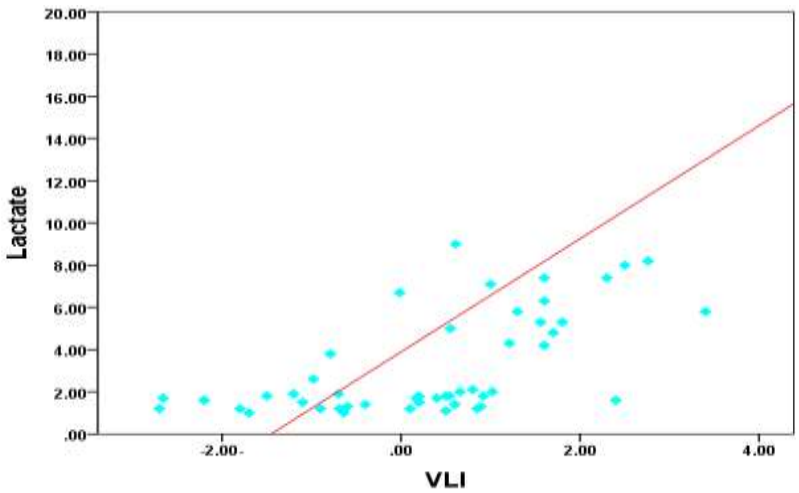

Figure (5): Positive correlation between VLI and lactate

As shown in table (4), there was a statistically significant increased VLI in patients needed MV (0.94 ± 1.23) when compared with patients didn't need MV (- 0.36 ± 1.39) with **p-value = 0.011**.And also there was a statistically significant increased VLI in patients needed vasopressors (0.88 ± 1.07) when compared with patients didn't need vasopressors (- 0.15 ± 1.5) with **p-value = 0.011**.

Table (4): Correlation between VLI with the need for mechanical ventilation and vasopressors

	Need for MV		T	p-value
	No (n = 24)	Yes (n = 26)		
VLI (Mean, ±SD)	- 0.36 ± 1.39	0.94 ± 1.23	3.5	0.011
	Need for vasopressors		T	p-value
	No (n = 27)	Yes (n = 23)		
	- 0.15 ± 1.5	0.88 ± 1.07	2.66	0.011

T: independent sample T test.

As shown in figure (6), ROC curve analysis was done for VLI to predict mortality among study patients, with 93.3% sensitivity and 70% specificity, the area under the curve was 0.83, with a cut-off point of 0.96; where VLI more than this point can strongly predict mortality.

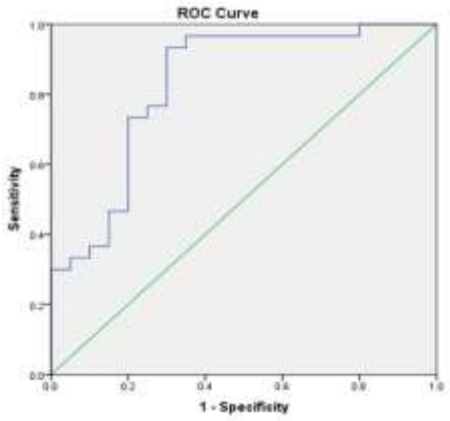

Figure (6): ROC curve for area under the curve of VLI.

4. Discussion:

Sepsis is defined as a life-threatening syndrome caused by a dysregulated host response to infection. (15)

Despite the effective role of IV fluids in increasing cardiac output (COP), only around half of patients with septic shock respond to IV fluid (increased COP by≥ 15%), even in these patients in whom COP increased , fluid administration is ineffective or sometimes be harmful.(8)

The net result of excessive IV fluids and the inflammatory cascade of sepsis lead to increased vascular permeability (vascular leak syndrome). (8)

The degree of extravascular leakage can be expressed by measuring the level of hematocrit which is a too large protein to leak out of the circulatory system. If the infused fluids remain inside the circulation, hematocrit level will be declined, if fluid leaks increased, the level of hematocrit will be slowly declining or even may be increased. (12, 13)

Our aim of the study was to evaluate the prognostic value of novel vascular leak index to identify the risk of in-hospital death and fluid accumulation in critically ill septic patients. We enrolled 50 patients with sepsis in the critical care department, out of the fifty patients 30(60%) were survivors and 20 (40%) were non survivors.

In our study we found a statistically significant ***higher lactate level*** among non-survivors group (9.5±17.3 mmol/L) than survivors (1.54 ± 0.31 mmol/L) with p-value=0.014, we also found a statistically significant positive correlation (r = 0.33) between VLI and lactate level, these findings supported the association between VLI and mortality.

In agreement with ***Mohamed et al. in 2017***, who reported higher serum lactate level(4.42 ± 2.24 mmol/L)in the non survivors group as compared with the survivors group (2.28 ± 1.54 mmol/L) with p-value=0.006. (16)

In the same line ***Chebl et al.in 2020***, studied 16,447 patients admitted to ICU. *Patients were stratified into 3 groups*: those with a serum lactate of <2 mmol/L (normal level), 2 to 4 mmol/L (intermediate level), and >4 mmol/L (high level). They found that, hospital mortality was the highest in high lactate level group, followed by the intermediate and then the normal level group (47.4%, 26.5% and 19.6% respectively with *P*. value < .0001).(17)

Moreover, ***Shapiro et al. in 2005***, observed 1278 patients admitted to ICU for an infection related causes. According to their study, mortality rates increased as lactate increased. (18)

In our study, **higher heart rate** were significantly associated with mortality, this finding was in agreement with **Mohamed et al.in 2017**, who reported that higher heart rate in septic patients at the time of admission could predict mortality, though these observations were of borderline statistical significance. (16)

Also **Rudiger et al. in 2018**, reported that there was strong correlation between higher heart rate and mortality in septic patients and increased heart rate from baseline by ≥50 bpm could predict mortality with positive predictive value 78% and negative predictive value 93%. (19)

Altered mental state, evaluated by **Glasgow Coma Scale (GCS**), is an important category for assessment of sepsis measured in both SOFA as well as qSOFA score, in the current study we found lower GCS in non survivors group, this was in agreement with **Alalawi et al. in 2017**,who found that lower GCS scores were associated with high mortality rates. (20)

On the contrary, **Polito et al. in 2015,** studied 437 patients and found that there was no strong statistical correlation between GCS and mortality (P-value 0.36). (21)

Regarding different studies by **Lesur et al.in 2018 and Dalimonte et al.in 2020**, found that there was a linear correlation between the need to vasopressors and mortality and it might be due to severity of the disease or side effects of vasopressors like arrhythmia and splanchnic hypoperfusion. (22, 23)

In our study, the need of vasopressors had occurred more among non-survivors than survivors(70% of non survivors vs 30% of survivors with p-value 0.005), Furthermore, ICU stay was much longer for non-survivors than survivors (28 vs 8 days respectively with p-value <0.001).

Our study was also in agreement with **Roberts et al.in 2020**, who mentioned increasing vasopressor dosing intensity during the first 24 hours after septic shock was associated with increased mortality. This association varied with the amount of early fluid administration and the timing of vasopressor titration. (24)

In the current study, we found that in non-survivors group fluid balance was higher than survived group (6959.5±3182.38 vs 3413.7±1231.35 ml respectively) that indicated its association with mortality, this finding

was in agreement with a study done by **Teboul et al. in 2015 and Sakr et al. in 2017**. (25, 26)

In concordance with **Huang et al. in 2019**, who observed that there was a significantly higher fluid balance in non-survivors than in survivors among patients with septic shock from the intensive care unit of a tertiary care hospital, they also observed a significantly higher fluid balance in patients with multiple organ dysfunction (MODS) than in those without at 24 hours and 72 hours after the onset of septic shock. (27)

Results from sepsis resuscitations performed using fluid sparing techniques have shown promise in recent research. Shock control, fluid balance, and risk of cardiogenic pulmonary edema were all reduced with a fluid restrictive approach, according to the CENSER trial, which compared the early use of norepinephrine to fluid-based sepsis resuscitation **(Permpikul et al. 2019)**. (28)

In a prospective research conducted by **Douglas et al. in 2020,** patients were randomly assigned to undergo sepsis resuscitation guided by invasive measurements of fluid responsiveness. The FRESH randomized controlled trial found that limiting intravenous fluids to patients who displayed signs of fluid responsiveness resulted in improved fluid balance, decreased likelihood of requiring renal replacement therapy. and reduced risk of mechanical ventilation. This trial compared the conventional approach of fluid resuscitation with the use of a noninvasive fluid responsiveness monitor to guide intravenous fluid administration. (29)

In our study we found a significant positive correlation between VLI and mortality as it correlated significantly with APACHEII score, initial SOFA score and SOFA score after 48 hours (p-value< 0.001, 0.002 and < 0.001 respectively). Furthermore, VLI also significantly increased in patients who needed vasopressors, needed MV and had longer ICU stay.

Consistent with the findings of **Chandra et al. In 2022,** who observed in their study that there was a significant relationship between changes in the smoothed VLI and changes in in-hospital mortality (p <0.001). (13)

The ROC curve analysis in our study was done for VLI to predict mortality among study patients, VLI had high sensitivity (93.3%) and specificity (70%), with a cut-off point of 0.96.

The VLI does not need specialized equipment, making it attractive to care

settings with low resources **(Chandra et al. 2022)**. (13)

Our research indicates that clinicians can potentially identify patients with significant vascular leakage within the initial 36 to 84 hours of intensive care unit admission. This knowledge can help to determine which patients are unlikely to benefit from, or may even experience adverse effects from additional IV fluid administration. Understanding a patient's VLI can help to determine the appropriate course of treatment. If a patient has a high VLI, it may be necessary to limit the administration of intravenous fluids. This is because excessive leakage of fluid and a positive fluid balance can lead to impaired organ function and an increased risk of mortality, this also stated by **Huang et al. in 2019**. (27)

Strength: Regarding our knowledge, this study was the first study assessed the ability of new VLI index to identify the risk of in-hospital death and fluid accumulation in critically ill septic patients in Beni Suef university hospital.

Limitations:-

1- Because we conducted this study in a single location, we were unable to generalize our findings.

2- Fluid balance in the first 36 hours can have a substantial impact on fluid balance and death within 36-84 hours, depending on how fluids are administered. Describing the link between VLI and 36-84 h fluid balance becomes challenging due to this reason.

3- Vascular leak index may be not able to differentiate between the vascular leak versus venodilatation or venoconstriction that may affect the venous blood volume and hence hematocrit level. (30)

5. Conclusion:-

Novel vascular leak index had a significant correlation with ICU sepsis related mortality with high sensitivity (93.3%) and specificity (70%), at a cut-off point of 0.96. Furthermore, VLI had significant correlation with the need of vasopressors, mechanical ventilation and the length of ICU stay.

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