

## Original Article

# Correlation of Caval Index and Central Venous Pressure in Non-ventilated Critically ill Patients

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## Abstract:

**Background:** Determination of intravascular volume status can sometimes be challenging part of critically ill patient's management in ICU. Invasive haemodynamic monitoring of central venous pressure is a useful guide in directing early resuscitative efforts and assist in reducing the morbidity and mortality of ICU patients with severe sepsis/septic shock. Obtaining invasive hemodynamic monitoring can lead to complications and time consuming. Sonographic measurement of the inferior vena cava (IVC) diameter and IVC collapsibility, termed the caval index is a non-invasive method of estimating the fluid status in critically ill patients. The study was designed to see the correlation between caval index and central venous pressure (CVP) in non-ventilated critically ill patients.

**Objectives:** The aim of the study was to evaluate the correlation of caval index and central venous pressure in non-ventilated critically ill patients.

**Methods:** It was a hospital based descriptive type of cross-sectional study, carried out in the ICU at the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, Dhaka Medical College Hospital, Dhaka from the period of May 2017 to October 2018. A total number of 86 patients were enrolled in this study. Study subjects were patients (age >18 years) with critically-ill non-ventilated and whom central venous catheter inserted for CVP monitoring. Central venous pressure was measured first by CVP manometer. Then IVC diameter and caval index were measured with curvilinear probe of the Sonosite ultrasound device. The correlation of CVP and CI was calculated. Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

**Results:** In this study, according to CVP 33.7% (29) of patients were hypovolemic with mean ( $\pm$ SD) CVP  $5.3 \pm 1.2$  cm H<sub>2</sub>O, euvolemic were 38.3% (33) with mean ( $\pm$ SD) CVP  $10.6 \pm 1.7$  cm H<sub>2</sub>O and hypervolemic were 27.9% (24) with mean  $\pm$ SD CVP  $16.1 \pm 1.5$  cm H<sub>2</sub>O. Mean caval index (CI) (%) mean ( $\pm$ SD) was found  $57.1 \pm 7.23$  in hypovolemic patients,  $39.5 \pm 2.65$  in euvolemic & hypervolemic patients. So, the result shows >50 % CI is associated with CVP < 8 mm of Hg and < 50% CI is associated with CVP > 8 mm of Hg. Pearsons correlation coefficient test used to assess the strength and nature of correlation between two variables. There was a statistically significant correlation between the mean CVP and the caval index ( $p < 0.001$ ). So findings revealed that there is an inverse relationship between the caval index and CVP.

**Conclusion:** The caval index had acceptable correlation with CVP at the level of IVC entry into the right atrium. It was concluded that there is an inverse relationship of CVP with the caval index.

**Keywords:** Central venous pressure, Inferior Vena Cava, Intravascular, Hemodynamic, Sonographic.

## Introduction:

Accurate assessment of volume status, as well as whether they will respond to a fluid challenge with an increase in cardiac output, is a critical task in critically ill patient. Despite this, most decisions regarding fluid therapy are made either empirically or with limited and poor data. Given recent data highlighting the negative impact of either inadequate or overaggressive fluid therapy, understanding the tools and techniques available for accurate volume assessment is critical<sup>1</sup>. Nazemi showed that measurement of the central venous pressure (CVP) is an important way of estimating the preload volume and the intravascular fluid volume of critically ill patient who require emergency attention to their hemodynamic status<sup>2</sup>. Abdel wahab and El-Wahabl, 2017 showed that sonographic measurement of the inferior vena cava (IVC) diameter and caval index (IVC collapsibility index) is a non-invasive method of estimating the fluid status

in critically ill patient<sup>3</sup>.

Central venous catheter insertion is needed to determine the CVP which is used to detect the fluid need<sup>3</sup>. The CVP is the mean pressure in the superior vena cava, reflecting right ventricular end diastolic pressure<sup>2</sup>. Rivers et al, 2001 demonstrated that a protocol of early goal-directed therapy, which included aggressive fluid resuscitation targeted to CVP and physiological variables, reduce organ failure and improve survival in patients with severe sepsis and septic shock<sup>4</sup>. However, Vincent et al, 2006 has demonstrated in critically ill patients that excessive fluid resuscitation and markedly positive net fluid balance is associated with higher rates of complications and increased mortality<sup>5</sup>. In a European multicenter observational study of patients admitted to the intensive care unit (ICU), each 1 liter of positive fluid balance during the first 72 hrs of ICU stay was associated with 10% increase in mortality after adjustments for other risk factors<sup>5</sup>.

Thus, outcomes are clearly influenced by fluid balance with either inadequate or over aggressive resuscitation associated with excess morbidity and mortality.

While giving intravenous fluids, two key clinical questions are asked: (1) what is the current state of the patient's intravascular volume? and (2) if the patient receives continued fluid resuscitation or a fluid bolus, will physiological variables such as blood pressure, tissue perfusion, and urine output improve? Fundamentally, the only reason to give a patient a fluid challenge is to increase the stroke volume (SV) by at least 10–15% and improve organ perfusion. It is therefore crucial during the resuscitation phase of critically ill patients to determine not only the volume status but also whether the patient is fluid-responsive or not. In clinical practice, physical examination, radiography, laboratory parameters, and in case of the critically ill patients in the ICU, monitoring of central venous pressure and cardiac output are combined to assess the patient's intravascular volume. As with any diagnostic tests, clinicians utilizing these volume assessment techniques need to be understand their limitations and diagnostic accuracy. Abdel wahab and El-wahab, 2017 found that ultrasonographic assessment of IVC diameter and caval index seems to be a simple and non-invasive method to assess the volume status in spontaneously breathing patients but its use in mechanically ventilated patients is not helpful<sup>3</sup>.

In theory, fluid resuscitation in the hypovolemic patient increases right ventricular end-diastolic volume, left ventricular end-diastolic volume, and depending upon the position on the Frank–Starling curve, SV and cardiac output (CO). If this holds true, measuring such parameters would be a useful tool in guiding decisions regarding fluid resuscitation. The most common of these parameters are CVP, pulmonary artery occlusion pressure (PCWP) and right ventricular end-diastolic volume<sup>1</sup>.

CVP is the most commonly used parameter for guiding fluid management in ICU. Surveys among intensivists and anesthesiologists suggest that more than 90% use CVP to guide fluid management<sup>6</sup>. In addition, guidelines have recommended the use of CVP in guiding fluid management in critically ill septic patients<sup>7</sup>.

CVP is dependent on venous return (VR) to the heart, right ventricular compliance, peripheral venous tone, and posture. CVP is particularly unreliable in pulmonary vascular disease, right ventricular disease, patients with tense ascites, isolated left ventricular failure, and valvular heart disease<sup>8,9</sup>. In patients with an intact sympathetic response to hypovolemia, CVP may actually fall in response to fluid, as compensatory venoconstriction is reduced<sup>9</sup>. Thus, it is possible to have a low CVP and not be volume responsive, as well as have a high CVP and be volume responsive. Moreover, complications such as arrhythmias, pneumothorax, haemothorax, hematoma, infection and thrombosis may occur with catheter insertion<sup>10</sup>.

Sonographic evaluation of the IVC diameter and its usefulness in evaluating the volume status are studied and documented<sup>2,3</sup>. Ultrasound imaging has several advantages; it is simple, noninvasive and can be used for repeated assessment. Ultrasound units are present in most intensive care units to routinely perform the focused assessment sonography in critically ill patients<sup>11</sup>. The IVC is a thin-walled and compliant vessel. By changing its diameter, it adjusts to the body's volume status. Inspiration generates negative pressure which results in increase venous return, subsequently collapsing the IVC. Expiration decreases venous return and the IVC diameter returns to its original value. IVC collapse will be proportionately higher than in cases with increased intravascular volume. The IVC collapsibility is determined by the calculation of the caval index (%)<sup>12</sup>. Therefore, aim of this study was to detect the correlation between IVC caval index with CVP in spontaneously breathing patients to provide a guiding method in evaluation of the intravascular volume status in critically ill patients.

## Methodology

This cross-sectional study was carried out in the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, Dhaka Medical College Hospital (DMCH), Dhaka during May, 2017 to October, 2018. Study subjects were critically-ill, non-ventilated patients, age >18 years, in whom central venous catheters were inserted for CVP monitoring according to their clinical indications in the intensive care unit (ICU) of DMCH. Purposive sampling was done. Patients were excluded if they had excessive bowel gas, huge ascites, severe tricuspid regurgitation, or midline incision following immediate laparotomy, or if they were obese, or pregnant. Patients were also excluded if the required ultrasound examination could not be done e.g. when the supine position is medically contraindicated or not tolerated, including patients with severe orthopnea or severely elevated intracranial pressure. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, & observation. Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

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Operational definitions:

**A) Parameter assessment with volume status:**

- Hypovolemia CVP < 8 cm of H<sub>2</sub>O
- Euvolemia CVP 8-12 cm of H<sub>2</sub>O
- Hypervolemia CVP > 12 cm of H<sub>2</sub>O.

**B) Caval index (%) measured as following:**

IVC expiratory diameter - IVC inspiratory diameter/ IVC expiratory diameter×100

Interpretation:

Caval index (CI) > 50 % -Fluid sensitive  
Caval index (CI) < 50% - Not fluid sensitive

**Results**

**Table-I: Age distribution of the study patients (N=86)**

| Age (years)  | Male (n=51) |       | Female (n=35) |       | Total (%) | P value             |
|--------------|-------------|-------|---------------|-------|-----------|---------------------|
|              | No.         | %     | No.           | %     |           |                     |
| 18 -30       | 2           | 3.9   | 7             | 20.0  | 9(10.4)   | 0.413 <sup>ns</sup> |
| 31-43        | 8           | 15.6  | 12            | 34.2  | 20(23.2)  | 0.072 <sup>ns</sup> |
| 44 -56       | 19          | 37.2  | 10            | 28.5  | 29(33.7)  | 0.148 <sup>ns</sup> |
| 57-69        | 16          | 31.3  | 6             | 17.1  | 22(25.5)  | 0.627 <sup>ns</sup> |
| ≥70          | 6           | 11.7  | 0             | 0     | 6(6.9)    | 0.764 <sup>ns</sup> |
| <i>Total</i> | 51          | 100.0 | 35            | 100.0 | 86        |                     |
| Mean±SD      | 52.6±10.7   |       | 46.4±11.6     |       |           | 0.072 <sup>ns</sup> |

Data were presented as frequency, percentage and mean±SD

Unpaired t-test was used to compare between two groups

N = Number of study population

Ns = Not significant

SD = Standard deviation

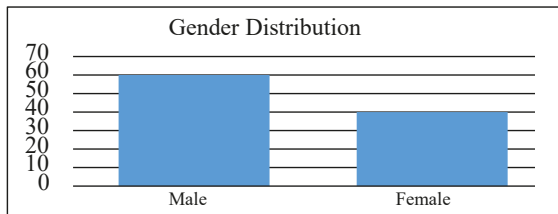


Table- I shows age distribution of patients. This study was conducted on patients with age ranging from 18 to 78 years. It was observed that majority 29 patients (33.7%) belonged to age 44-56 years, followed by 22 patients (25.5%) belonged to age 57-69 years. Both male and female subject were included with a mean (SD) age of 52.6±10.7 years in male subject and 46.4±11.6 years in female group. There was no significant difference between two groups.

**Fig 1: Gender distribution of study subjects**

Figure 1 shows gender distribution in study subjects. Male : female ratio was 1.4:1. Sex difference between two groups was not statistically significant.

**Table-II: Distribution of the patients according to indication for ICU admission (N=86)**

| Diagnosis                | Male (n=51) |      | Female (n=35) |      | Total (%) |
|--------------------------|-------------|------|---------------|------|-----------|
|                          | No.         | %    | No.           | %    |           |
| Sepsis                   | 12          | 23.5 | 7             | 20.0 | 19 (22.0) |
| Head injury              | 11          | 21.5 | 5             | 14.2 | 16 (18.6) |
| Heart failure            | 10          | 19.6 | 5             | 14.2 | 15(17.4)  |
| Resp. failure            | 9           | 17.6 | 4             | 11.4 | 13(15.1)  |
| Pre-Eclampsia/ Eclampsia | 0           | 0    | 8             | 22.8 | 8(9.3)    |
| PPH                      | 0           | 0    | 4             | 11.4 | 4(4.6)    |
| Meningo-encephalitis     | 5           | 9.8  | 2             | 5.7  | 7(8.1)    |
| Stroke                   | 4           | 7.8  | 0             | 0    | 4(4.6)    |

Data were expressed as frequency and percentage

Chi-square test was used to see the association between groups

Table-II shows the distribution of the patients according to indication for ICU admission. Common indication was sepsis, head injury, heart failure and resp. failure with H/O COPD, 22.0%, 18.6%, 17.4% and 15.1% respectively. In case of females, Pre-Eclampsia/ Eclampsia (9.3%) and post-partum hemorrhage (PPH) (4.6%), were important causes of ICU admission.

**Table-III: Central venous pressure (CVP) among the study subject (N=86)**

| CVP (cmH <sub>2</sub> O) | n  | %     | Mean ± SD |
|--------------------------|----|-------|-----------|
| <8 cmH <sub>2</sub> O    | 29 | 33.7  | 5.3±1.2   |
| 8-12 cmH <sub>2</sub> O  | 33 | 38.3  | 10.6±1.7  |
| >12 cmH <sub>2</sub> O   | 24 | 27.9  | 16.1±1.5  |
| Total                    | 86 | 100.0 | 11.2±1.2  |

Data were expressed as frequency and percentage

Table-III shows the CVP of the study subject. CVP <8 cmH<sub>2</sub>O was detected in 29 (33.7%) of patients with mean±SD 5.3±1.2 cmH<sub>2</sub>O. CVP 8-12 cmH<sub>2</sub>O was identified in 33 (38.3%) of patients with mean±SD 10.6±1.7 cmH<sub>2</sub>O. CVP >12 cmH<sub>2</sub>O was detected in 24 (27.9%) of patients with mean±SD 16.1±1.5 cmH<sub>2</sub>O. Table-IV Shows >50% caval index (CI) was in 29 (33.7%) of patients with mean±SD 57.1±7.23. CI < 50% was present in 57 (66.2%) of patients with mean±SD 39.5±2.65. Table-V shows the correlation of caval index with CVP. Mean caval index (%) was found 57.1±7.23 in hypovolemic patients and 39.5±2.65 in euvolemic & hypervolemic patients

**Table-IV: Caval index (CI) among the study subjects (N=86)**

| Caval index | n  | %    | Mean ± SD |
|-------------|----|------|-----------|
| >50%        | 29 | 33.7 | 57.1±7.23 |
| <50%        | 57 | 66.2 | 39.5±2.65 |

Data were expressed as frequency and percentage

**Table-V: Correlation of caval index with CVP (N=86)**

| Variables           | CVP (cm of H <sub>2</sub> O)      |   | p value            |
|---------------------|-----------------------------------|---|--------------------|
|                     | Hypovolemic<br>(n1=29)<br>Mean±SD | Euvolemic &<br>Hypervolemic<br>(n2=57)<br>Mean±SD |                    |
| IVC caval index (%) | 57.1±7.23                         | 39.5±2.65   | 0.001 <sup>s</sup> |

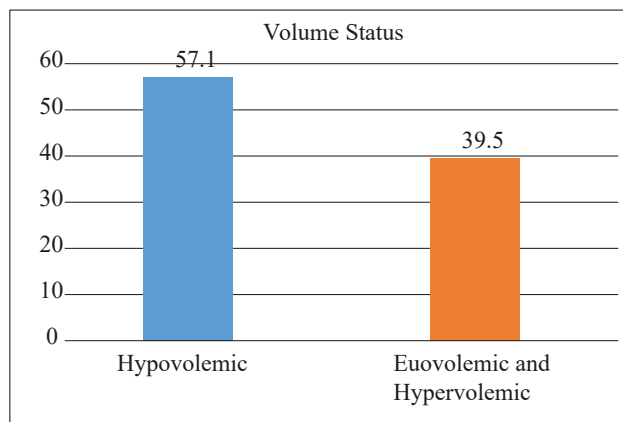
Continuous variables are expressed as mean and standard deviation

n=Number of study population

s= Significant

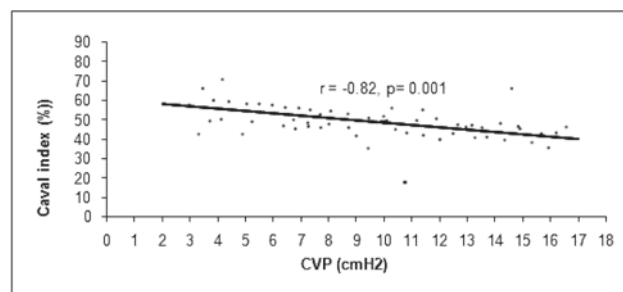
P value extracted from student's t test

SD=Standard deviation



**Figure-2: IVC mean caval index (%) of the study patients (N=86)**

Figure-2 shows the IVC mean caval index (%) of the study patients. In this study, in hypovolemic patients mean caval index was found 57.1 (SD±7.23), in euvolemic and hypervolemic patients mean caval index was 39.5 (SD±2.65).



Data were expressed as mean and SD

Pearsons correlation coefficient was used to see the association between two variables

n = Number of the study population

% = Percentage of the study population

r = Correlation-coefficient

SD = Standard deviation

**Figure-3: Scatter plot display for correlation between CVP and IVC-CI values (N=86)**

Scatter plot display for correlation between CVP and IVC-CI values in figure 3. Results show that there is an inverse relationship between the caval index and the CVP. IVC caval index was statistically higher in the Hypovolemic group. Gradually plot is downhill inclination with increasing CVP and statistically lowers in the hypervolemic group (r = -0.823, p<0.001). So, statistically significant correlation found in the mean CVP and the IVC caval index.

**Discussion**

The main objective of the study was to assess correlation between caval index and central venous pressure in estimating the volume status of non-ventilated critically ill patients. Eighty six patients with critically-ill, non-ventilated and



whom central venous catheter inserted for CVP monitoring according to their clinical indications in the ICU of DMCH were selected for the study.

This study was conducted on patients with age ranging from 18 to 78 years. It was observed that majority 29 patients (33.7%) belonged to age 44-56 years, mean (SD) age was  $52.6 \pm 10.7$  years in male and  $46.4 \pm 11.6$  years in female group. Gender distribution shows, male: female ratio 1.4:1. There was no significant difference between two groups. Demographic profile between groups were statistically non-significant ( $p > 0.05$ ). All these findings consistent with result of another study. Abdel wahab and El-Wahab, conducted a study where 120 patients were enrolled among them 57 (47.5%) patients were males<sup>3</sup>. In another study, Nazemi found that among 70 patients, 28.6% female and 71.4% male<sup>2</sup>. The mean (SD) age was  $30.78 \pm 8.01$ . Ilyas et al, 2017 conducted a study where 32% were females and 68% were males with a mean age of  $50.4 \pm 19.3$  years<sup>13</sup>.

In this study common indications of ICU admissions were sepsis, head injury, heart failure and resp. failure with H/O COPD, 22.0%, 18.6%, 17.4% and 15.1% respectively. In case of female, PPE/ Eclampsia (9.3%) and PPH (4.6%), were important causes of ICU admission. Abdelwahab and El-Wahab, showed the distribution of patients according to diagnosis and that was, pneumonia 75 (62.5%), chronic obstructive pulmonary disease 22 (18.3%), pulmonary embolism 3 (2.5%), heart failure 7 (5.8%), etc<sup>3</sup>.

In this study, 29 (33.7%) patients were hypovolemic with mean $\pm$ SD CVP  $5.3 \pm 1.2$  cm of H<sub>2</sub>O. Euvolemic were 33(38.3%) of patients with mean $\pm$ SD CVP  $10.6 \pm 1.7$  cm of H<sub>2</sub>O and hypervolemic were 24 (27.9%) of patients with mean $\pm$ SD CVP  $16.1 \pm 1.5$  cm of H<sub>2</sub>O. In a study mean central venous pressure was  $10.38 \pm 4.14$  cmH<sub>2</sub>O. The CVP was found less than 8 cm of H<sub>2</sub>O in 26% patients, while 48% had CVP between 8–12 cm of H<sub>2</sub>O and 26% patients had CVP greater than 12 cm of H<sub>2</sub>O<sup>13</sup>.

The IVC caval index is the difference between the maximum and minimum IVC diameters divided by the maximum IVC diameter, expressed as a percentage (%)  $[(IVCd_{max} - IVCd_{min}) / IVCd_{max} \times 100\%]$ . In this study, mean caval index (%) was found  $57.1 \pm 7.23$  in hypovolemic patients, and  $39.5 \pm 2.65$  in euvolemic and hypervolemic patients. There was statistically significant correlation in the mean CVP and the IVC caval index ( $p < 0.001$ ). So overall findings revealed that an inverse relationship between the IVC caval index with CVP or intravascular volume status. A study conducted by Peter et al, 2009 among 83 ICU-admitted patients where the CVP and the CI were measured<sup>14</sup>. The patients were divided into 3 groups based on the CI (>60%, 20% to 60%, <20%). The results showed that the increased CI was associated with a significant decrease in the CVP ( $p=0.23$ ).

Nazemi et al, showed that there is a positive relationship between the inspiratory phase IVC diameter and the CVP and also between the expiratory phase IVC diameter and the CVP so that increase in the CVP causes increase in inspiratory and expiratory IVC diameters<sup>2</sup>. Magder, Sheldon and Fahad,

demonstrated that the CVP threshold where the fluid replacement therapy increases the cardiac output is less than 10 mm of Hg (=13.59 cm of H<sub>2</sub>O, 1 mm of Hg=1.359 cm of H<sub>2</sub>O)<sup>15</sup>. Many studies have been conducted in this area and they all confirmed that portable sonography of the IVC is a fast and non-invasive method for detecting the low CVP. Minutiello reported that, the CI  $\geq 20\%$  indicates a normal CVP<sup>16</sup>. Change in the IVC diameter during respiration is an accurate predictor of the good response to fluid replacement therapy in sepsis. Nazemi conducted a study where the IVC diameter which was estimated by transesophageal echocardiography was compared with the CVP and the results were similar to this study<sup>2</sup>. It seems that the portable IVC sonography of the emergency patients is non-invasive and a fast way to estimate the CVP and hemodynamic condition of the patient.

On evaluation of correlation between CVP and IVC-CI values, results showed that there is an inverse relationship between the caval index and the CVP. IVC caval index was statistically higher in the hypovolemic group. Gradually plot is downhill inclination with increasing CVP and statistically lowers in the hypervolemic group ( $r = -0.823$ ,  $p < 0.001$ ). So, statistically significant correlation found in the mean CVP and the IVC caval index. Ilyas et al, 2017 found statistically significant relation among the mean CVP, the IVC collapsibility index, the maximum and minimum IVC diameter as determined by one-way analysis of variance (ANOVA) ( $p < 0.001$ ). There was a strong negative correlation between CVP and IVC collapsibility index (%), which was statistically significant ( $r = -0.827$ ,  $n = 100$ ,  $p < 0.0005$ ). A strong positive correlation between CVP and maximum IVC diameter ( $r = 0.371$ ,  $n = 100$ ,  $p < 0.0005$ ) and minimum IVC diameter ( $r = 0.572$ ,  $n = 100$ ,  $p < 0.0005$ ) was also found.

Ilyas et al, 2017 found that IVC collapsibility index is statistically higher in the hypovolemic group and statistically lower in the hypervolemic group ( $p < 0.001$ )<sup>13</sup>. They also found a significant difference in IVC (maximum diameter) between the hypovolemic and hypervolemic group ( $p = 0.004$ ), as well as between the hypervolemic and euvolemic group ( $p = 0.025$ ). The IVC (minimum diameter) was statistically higher in the hypervolemic group ( $p < 0.001$ ) and statistically lower in the hypovolemic group. Nazemi showed that, there is a positive relationship between the inspiratory phase IVC diameter and the CVP and also between the expiratory phase IVC diameter and the CVP so that increase in the CVP causes increase in inspiratory and expiratory IVC diameters<sup>2</sup>. Also, the caval index >50% has a sensitivity of 94% and the specificity of 97% in the prediction of the low CVP (<8 mmHg). Abdel wahab and El-Wahab found significant relationship between CVP and sonographic IVC measurements (IVC diameter and caval index) in spontaneously breathing patients<sup>3</sup>. However, this correlation was weak in mechanically ventilated patients whatever the mode (volume or pressure) and peak inspiratory pressure level.

In accordance the results suggest that IVC diameter may be used for assessment of the intravascular volume status of

spontaneously breathing patients but it does not give accurate measure in mechanically ventilated patients. Abdelwahab and El-Wahab and Lorsomradee found strong correlation between IVC diameter and CVP (when CVP were  $\leq 11$  mmHg) in cardiac surgical patients<sup>3,17</sup>. Wiryana found that there is a strong negative correlation between CVP and collapsibility index of IVC<sup>18</sup>. This finding indicates that the collapsibility index of the IVC may substitute CVP in determining the status of the intravascular volume. Abdel wahab and ElWahab concluded that, ultrasonographic assessment of IVC diameter and caval index seems to be a simple and non-invasive method to assess the volume status in critically ill patients<sup>3</sup>.

Therefore, caval index has acceptable correlation with CVP at the level of IVC entry into the right atrium. There is an inverse relationship of CVP with the caval index. So, it is concluded that bedside measurements of caval index could be a useful noninvasive tool in assessment of volume status in non-ventilated critically ill patients.

### Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

### Conclusion

Ultrasonographic measurement of caval index is a simple and non-invasive method to assess the volume status. Central venous pressure (CVP) value is strongly correlated with caval index (IVC-CI). Ultrasonographic measurement of caval index is considered safer than CVP. Advantages of using this technique includes safe, non-invasive, portable, faster than CVP in assessing volume status. In this present study we found that CVP strongly correlated with IVC-CI ( $r = -0.823$ ;  $p < 0.001$ ), this indicates that there is an inverse relationship between the caval index and CVP. This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

### Acknowledgements

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