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Prediction of Intradialytic Hypotension by Respiratory Changes in Inferior Vena Cava Diameter and Passive Leg Raising Test in Patients with Renal Failure

Mohammed Bakry Elkholy, Lamiaa Kamel Gaber*, Khalaf Ibrahim Eldehily, Sherif Medhat Sabry

Critical Care Medicine Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

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Abstract

Background: The incidence of intradialytic hypotension (IDH) is approximately 10-12% of treatments. Recurrent interruption of blood flow to vital organs in individuals with IDH may adversely affect the cardiovascular, central neurological, renal, and gastrointestinal systems[1].
Aim of the work : To investigate the ability to predict hemodynamic intolerance to fluid removal by respiratory variations in IVC diameter and PLR test before intermittent renal replacement therapy.to **Methods:** This prospective cohort observational work was carried out on 40 individuals aged 18 years old or more, both sexes, with clinical criteria of acute kidney disease and sinus rhythm. Participants were categorized into two groups: group I:patients who didn't develop IDH, and group II: patient who developed IDH. **Results:** The IVC collapsibility and change in COP (cardiac output) were significantly greater in Group II (16 patients) contrasted to Group I (24 patients). The ROC curve of predicted probability [COP response (>12.0%) and IVC collapsibility response (>50.0%)] is associated with intradialytic hypotension 0.775 (95% CI 0.624-0.926, P =0.004). **Conclusions:** COP response (>12.0%) and IVC collapsibility response (>50.0%) had a good predictive value of IDH.

Keywords: Intradialytic Hypotension, Inferior Vena Cava Diameter, Passive Leg Raising Test, Renal Failure, Respiratory Changes

1. Introduction:

In the context of hemodialysis, the occurrence of intradialytic hypotension (IDH) is an often-seen consequence [1]. The incidence of IDH is approximately 10-12% of treatments [2], and its pathogenesis depends on many factors, such as the relationship between cardiac output, ultrafiltration rate, and arteriolar tone [1].

The recurrent interruption of adequate blood flow to vital organs in individuals with IDH may result in a range of adverse effects on the cardiovascular, central neurological, renal, and gastrointestinal systems [1].

Many technical advancements have been included in the hemodialysis equipment to mitigate the occurrence of IDH. These advancements revolve on the implementation of relative blood volume monitoring, which serves as an indirect means of evaluating plasma volume. Despite the apparent efficacy of these advancements in reducing the occurrence of severe IDH episodes, they cannot completely eliminate hypotension due to their inability to manage excessive weight increases and the resulting need for excessive ultrafiltration. Therefore, with the advancements in hemodialysis machine technology aimed at mitigating IDH, it is important to direct emphasis on minimizing intradialytic weight increases, therefore minimizing the demand for ultrafiltration [3].

The use of respiratory/ventilatory alterations in the diameters of the inferior vena cava (IVC) and cardiac index enables the evaluation of intravascular volume, hence facilitating the prediction of IDH [4].

The measurement of IVC may be conducted utilising 2D or M-mode evaluation. In normovolemic individuals who breathe spontaneously, inspiration leads to negative intrathoracic pressure, resulting in a reduction in the IVC size. Individuals in a hypovolemic condition may have an increased reaction in the IVC that causes it to collapse during the inspiratory phase [5].

Passive leg raising (PLR) test is used to investigate hemodynamic instability during fluid removal in dialysis and can help us predict IDH [6].

We aimed to investigate the ability to predict hemodynamic intolerance to fluid removal by respiratory variations in IVC diameter and PLR test before intermittent renal replacement therapy.

2. Patients and Methods:

This prospective cohort observational work was carried out on 40 individuals aged 18 years old or more, both sexes, with clinical criteria of acute kidney disease and sinus rhythm. The research protocol underwent the process of obtaining permission from the ethics committee of the Faculty of Medicine at Beni-Suef University from June 2022 to March 2023. Informed written consent was obtained from the patients.

Exclusion criteria : shocked patients (mean arterial pressure (MAP) less than 65%), right-side heart failure, severe valvular heart disease, lower limb fracture, aortic regurgitation, cardiomyopathy patients (EF less than 40%) and arrhythmias.

All participants had subjected to take a history, full clinical assessment, and investigations within 24 hours of admission (venous blood gas (VBG), complete blood count (CBC), kidney functions, and electrolytes).

All patients were subjected to a standard study protocol consisting of:

1. Hemodynamic variables (MAP, pre-dialysis blood pressure, pulse, respiratory rate).
2. IVC diameters by echocardiography before dialysis:
   IVC maximum diameter (IVC Max)
   IVC minimum diameter (IVC Min)
3. Echocardiographic measurements of cardiac output before dialysis by

- LVOT VTI 1: (Left Ventricular Outflow Tract Velocity Time Integral) before passive leg raising test.
- LVOTD :(Left Ventricular Outflow Tract Diameter)
- HR: (Heart rate)
- COP 1: cardiac output before passive leg raising test.

4. Passive leg raising test (PLR).
5. Echocardiographic measurements of cardiac output after PLR

- LVOT VTI 2: (Left Ventricular Outflow Tract Velocity Time Integral) after passive leg raising test.
- LVOTD :(Left Ventricular Outflow Tract Diameter).
- HR: (heart rate).
- COP 2: cardiac output after passive leg raising test.

6. Monitoring blood pressure after one hour from dialysis to assess IHD.
7. Dialysis machine parameter: pump (250), temperature (36.5-37.5),dialysate (bicarbonate), these parameters were fixed to all patients .

Inferior vena cava diameters by echocardiography:

Bedside echocardiography was conducted utilizing a Vivid S5 General Electric® (3.5 MHz) transducer. The probe was positioned in the subcostal region, specifically beneath the process of the xiphoid, with the probe label oriented towards the subject's head. It was then gently angled towards the right side of the patient. These measurements were conducted using a subcostal long-axis view that was positioned perpendicular to the IVC. The participant was in a supine posture, and the measurements were taken at a distance of 1.0 to 2.0 cm from the junction with the right atrium. The measurement of the diameter was conducted to evaluate the passive expiration, as well as the inspiration or a forceful inspiratory effort. The maximum and lowest diameters of the IVC were obtained. The minimal diameter of the IVC was observed throughout the phase of inspiration. The application of the IVC collapsibility index (IVCCI) is a viable approach for determining the respiratory variability % of the IVC. (Figure 1)

[(Maximum IVC diameter – Minimum IVC diameter) / Maximum IVC diameter] x 100]

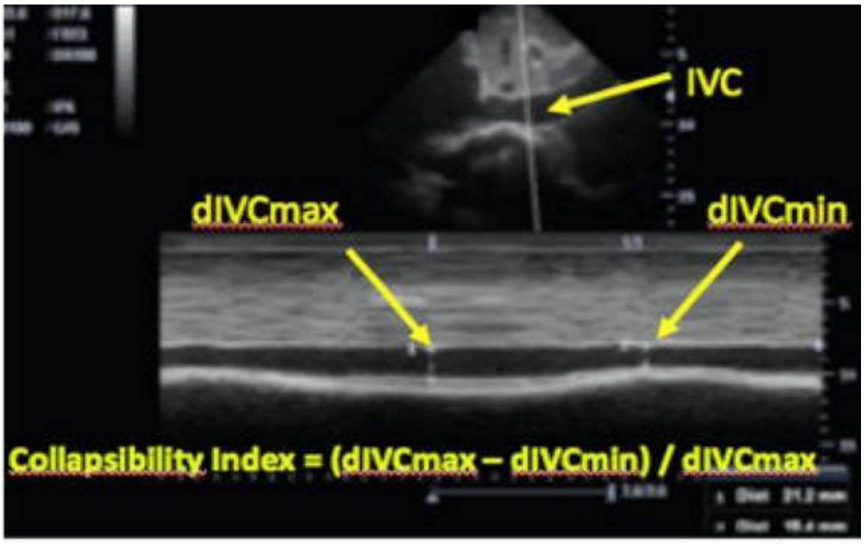


Figure 1: Measurement of inferior vena cava diameters by echocardiography

Echocardiographic measurement of cardiac output

Bedside echocardiography was being conducted utilizing a Vivid S5 General Electric® (3.5 MHz) transducer, cardiac output was calculated from the equation: -

COP= Stroke Volume x HR = LVOT VTI × Cross Sectional Area of (LVOTD) x HR = LVOT VTI x 3.14 x (LVOT/2) *2 x HR

Measurement of LVOT VTI

During the examination using the five-chamber view, we saw the LVOT and the aortic valve, which was found to be situated close to the chest. (Figure 2A)

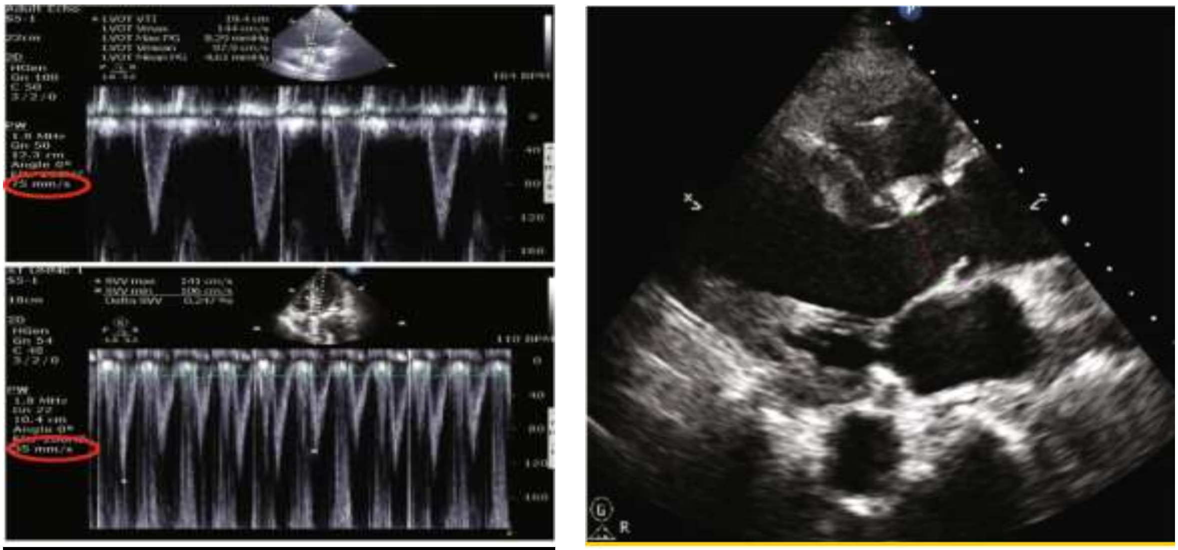
Measurement of LVOTD: -

The Parasternal Long Axis view is acquired by positioning the transducer in the 3rd or 4th intercostal space, with the label oriented toward the recipient's right shoulder. This positioning allowed for the visualization of the longest axis of the heart in the majority of individuals, however, a minor clockwise or anticlockwise rotation may be necessary to accommodate variations in the heart's orientation. To get the most favorable perspective of the maximum diameter of the left ventricle and the maximal excursion of the mitral valve, a little adjustment in both medial and lateral angulation may be necessary.

Passive leg raising test (PLR):

All patients were subjected to PLR before dialysis and calculated maximal increase in cardiac output before and after the test.

Maintain a semi-recumbent posture with the individual's tilted 45 degrees head up. The recommended procedure involves lowering the recipient's upper body to a horizontal position and thereafter raising their legs passively to an angle of 45 degrees. The maximum effect is seen within a time frame of 30 to 90 seconds. Cardiac output was calculated as CO (ml/min) = LVOT area *(LVOT VTI) *HR. The measurement of the LVOT] was conducted using parasternal long-axis imaging, with a focus on obtaining measurements as proximal to the aortic valve as feasible. The measurement of the LVOT-VTI was conducted using pulsatile Doppler LVOT flow pattern pictures acquired from an apical 5-chamber perspective. (Figure 2B)



A B

Figure 2: Measurement of (A) LVOT VTI and (B) LVOTD

Statistical analysis

The statistical tool utilized in the analysis is SPSS version 15. The information was summarized utilizing descriptive statistics, namely the mean and standard deviation for continuous variables, and frequencies and percentages for categorical variables when deemed suitable. The mean values and standard deviations were contrasted by utilizing a t-test for two parameters or an ANOVA test for more than two variables. Percentages are compared using the chi-square (χ^2) test. The Pearson correlation coefficient was used to examine the relationship between the two variables. Linear regression has been utilized to calculate the coefficient and linear equation that include one or more independent variables, to predict the value of the dependent variable most accurately. ROC curve analysis was done to predict the cutoff points of the test variables that best predict the binary state of other variables. A P value < 0.05 was considered statistically significant.

3. Results:

No significant difference between the two groups regarding sociodemographic data, SBP, DBP predialysis, and MAP. The SBP, DBP intradialysis, and MAP for Group I was significantly higher than the mean of Group II. **(Table 1)**

Table 1: Sociodemographic data, predialysis, intradialytic blood pressure, and MAP between the two studied groups

Variables		Group I (n=24)	Group II (n=16)	p-value
Age		52.42 ±17.5	56.25 ±18.4	0.511
Sex	**Male**	9 (37.5%)	9 (56.3%)	0.243
	Female	15 (62.5%)	7 (43.8%)	
DM		3 (12.5%)	5 (31.3%)	0.229
HTN		7 (29.2%)	4 (25.0%)	0.772
Predialysis blood pressure				
SBP predialysis		122.08 ±12.9	116.88 ±10.8	0.189
DBP predialysis		78.33 ±8.7	76.25 ±8.1	0.449
MAP		92.92 ±8.4	89.79 ±8.3	0.255
Intradialytic blood pressure				
SBP intradialytic		120.00 ±23.0	81.87 ±3.6	**<0.001***
DBP intradialytic		76.25 ±12.1	55.94 ±3.3	**<0.001***
MAP		90.83 ±14.9	64.58 ±1.8	**<0.001***

Data are presented as mean ± SD, and number of (%), *: significant p-value. DM: diabetes mellitus. HTN: hypertension. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure.

There were no significant differences in the blood gas parameters (pH, PCO_2, and HCO_3), CBC parameters (Hb, TLC, and platelets), (lactate, Na, and K) between the two groups. However, a significant difference existed in creatinine levels among the two groups (p=0.002) with Group II having higher levels. **(Table 2)**

Table 2: Investigation between the two studied groups

Variables	Group I (n=24)	Group II (n=16)	p-value
Blood gases			
PH	7.32 ±0.07	7.27 ±0.10	0.165
PCO_2 (mmHg)	34.45 ±8.32	33.19 ±7.41	0.859
HCO_3 (mmol/L)	25.92 ±39.66	17.58 ±3.39	0.967
CBC			
Hb (g/dL)	8.99 ±1.33	8.74 ±1.24	0.633
TLC x 10^3	11.58 ±5.79	11.81 ±4.81	0.672
Platelets x 10^3	176.38 ±81.55	219.75 ±123.02	0.292
Minerals			
Lactate (mmol/L)	1.54 ±0.87	1.14 ±0.61	0.183
Na (meq/L)	134.04 ±6.98	135.06 ±9.65	0.792
K (meq/L)	4.23 ±0.81	4.38 ±0.82	0.652
KFT			
Urea (mg/dL)	131.37 ±53.71	127.69 ±66.27	0.539
Creatinine (mg/dL)	6.82 ±2.18	8.41 ±2.20	**0.002***

Data are presented as mean ± SD, *: significant p-value. CBC: complete blood count. Hb: hemoglobin. TLC: total leucocytic count. KFT: kidney function tests.

no significant difference were observed among the two groups for IVC max, IVC min, LVOT, VTI1 (P=0.652), VTI2 heart rate (HR), and COP1. A significant difference existed in COP_2 among the two groups. However, the IVC collapsibility (%) and change in COP (%) were revealed to be significantly greater in Group II contrasted to Group I. **(Table 3)**

Table 3: Assessment of intravascular volume, cardiac parameters, COP response (%) and IVC collapsibility response (%) between the two studied groups

Variables		Group I (n=24)	Group II (n=16)	p-value
Intravascular volume				
IVC max (cm)		1.75 ±0.57	1.76 ±0.41	0.838
IVC min (cm)		0.94 ±0.52	0.73 ±0.35	0.267
IVC collapsibility (%)		47.01 ±19.06	60.06 ±10.12	**0.013***
LVOT D (cm)		2.07 ±0.19	2.18 ±0.20	0.183
VTI 1 (cm)		19.91 ±3.17	19.64 ±3.06	0.652
VTI2 (cm)		21.22 ±3.37	21.60 ±1.98	0.967
Cardiac parameters				
HR		88.00 ±10.43	90.00 ±12.25	0.692
COP1 L/m		6.33 ±1.56	5.9 ±1.7	0.504
COP_2 L/m		6.19 ±1.61	7.4 ±1.84	0.025*
Change in COP (%)		7.25 ±23.45	20.86 ±20.83	**0.005***
COP response (%) and IVC collapsibility response				
COP response (%)	<12%	17 (70.8%)	4 (25.0%)	**0.004***
	>12%	7 (29.2%)	12 (75.0%)	
IVC collapsibility response (%)	<50%	15 (62.5%)	3 (18.8%)	**0.010***
	>50%	9 (37.5%)	13 (81.3%)	

Data are presented as mean ± SD, and number of (%), IVC: Inferior vena cava. LVOT D: Left Ventricular Outflow Tract Diameter. VTI: velocity time integral. HR: heart rate. COP1: cardiac output. *: significant p value.

The ROC curve of predicted probability (COP response (>12.0%) and IVC collapsibility response (>50.0%)) with associated with intradialytic hypotension 0.775 (95% CI 0.624-0.926). The standard error was 0.077, and the asymptotic significance was 0.004, indicating that the model's performance is statistically significant. **(Figure 1)**

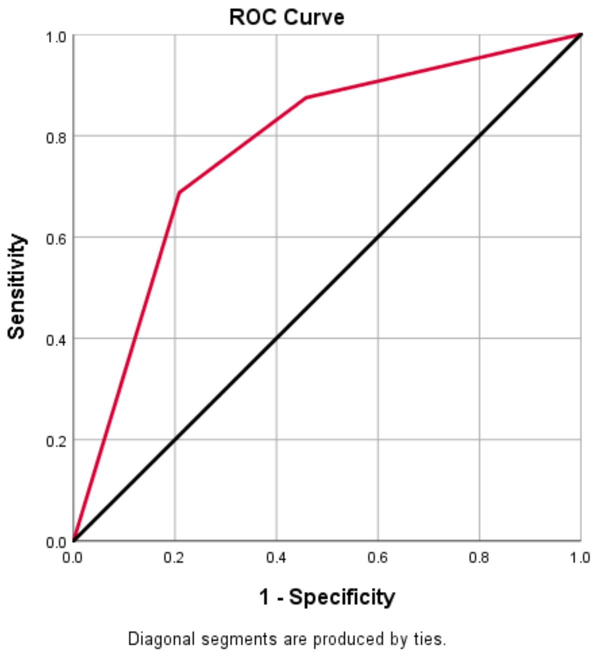


Figure 3: ROC curve of Predicted probability (COP response (>12.0%) and IVC collapsibility response (>50.0%)) associated with intradialytic hypotension

4. Discussion:

The use of ultra-sonographic measures of the IVC is considered to be a straightforward, practical, and efficacious approach for assessing the volume status during the first stages after a surgical procedure. Nevertheless, there exist certain limitations associated with IVC ultrasonography that may be classified as variables influencing the diameter and collapsibility of the IVC, as well as its clinical interpretations [7, 8] and those which restrict the achievement of ideal visualizations [9]. The aforementioned issue may be mitigated by a methodical comprehension of the possible biases' trajectory, as well as the interpretation of outcomes within the therapeutic framework of an individual patient [10].

The overestimation of relative intravascular volume might manifest in situations that restrict the flow to the right heart, such as valve anomalies, heart failure, pulmonary hypertension, or limited respiratory excursions. The presence of severe tricuspid regurgitation has been observed to result in a reduction in IVC CI and a potential rise in IVC max. Rheumatic valvular heart disease is associated with an elevation in the maximum velocity of blood flow in the IVC. Under these conditions, if the IVC exhibits a high degree of collapsibility or complete collapse, there is probably relative intravascular hypovolemia, and it might be necessary to consider volume resuscitation.

Intra-abdominal hypertension can lead to an underestimation of intravascular volume. Consequently, the presence of a dilated IVC in such cases might be indicative of intravascular hypervolemia.

The understanding of vena cava physiology may face challenges when certain situations limit the normal range of physiological changes in the IVC. These disorders include venous thrombosis, external compression caused by masses, or the presence of large extracorporeal membrane oxygenation catheters. Individuals who have undergone liver transplantation have notable modifications in their central venous architecture, necessitating consideration of various surgical techniques. This phenomenon has not been thoroughly examined systematically. The analysis of the physiological attributes of the IVC ought to be conducted within the framework of the individual's clinical situation and supplementary information [11].

Regarding IVC CI in the current work; the IVC collapsibility (%) was revealed to be substantially greater in the IDH group (60.06 ± 10.12%) compared to the control group (47.01 ± 19.06); the IVC collapsibility greater than 50%, was significantly higher in Group II (81.3%) compared to only 37.5% in Group I. In agreement with da Hora Passos et al. [12] study objective was to assess the predictive capability of various pre-dialysis ultrasonography cardiac profiles with IDH. A study was conducted on a cohort of 248 critically sick individuals diagnosed with acute renal damage who underwent intermittent hemodialysis. The study revealed that a significant proportion of individuals with IDH had IVC collapsibility, as determined by a VCDi value of 11.5 mm m^2 or less. Specifically, 60 individuals (75.9%) with IDH demonstrated this characteristic, whereas only 14 patients (8.3%) without IDH displayed the same collapsibility ($p < 0.001$). The development of IVC collapsibility was found to be linked with the predictive multiple logistic regression model of IDH. Our findings were supported by Kaptein et al. [13] who found that Patients who are critically ill and have a reduced IVC CI below 20, indicating relative intravascular volume overload, are more likely to tolerate ultrafiltration (UF). On the other hand, individuals who have an elevated IVC CI above 50, indicating low relative intravascular volumes, are less inclined to tolerate UF. Similar to our findings Purushothaman et al. [14] aimed to assess the effectiveness of pre-induction measurement of IVC-CI in predicting the occurrence of substantial hypotension following the administration of propofol during anaesthesia induction. The study included two groups of individuals: a non-hypotensive group consisting of 35 individuals, and a hypotensive group consisting of 15 individuals. The calculated correlation between substantial hypotension and IVC-CI of 0.43 has been determined to be statistically significant.

In our study; we further used the PLR test for cardiac output changes assessment and we found the change in COP (%) was significantly higher in the IHD group (20.86 ±20.83) compared to the control group (7.25 ±23.45). the COP response greater than 12%, was significantly higher in the IDH Group, with 75% of patients having a COP response compared to only 29.2% in the control group.

In harmony with Kaptein et al. [4] in patient encounters, it was seen that there was a higher occurrence of a cardiac output rise greater than 10% in cases of a lesser degree of IDH, whereas a lower occurrence was noted in cases of more severe IDH. The use of intravenous drug therapy, specifically IDH, has been observed to potentially cause myocardial stunning and hence contribute to a reduction in cardiac output in certain instances. The observed correlation between the frequency of CO fluctuations and the severity of IDH implies that the occurrence of more severe IDH episodes may have contributed to a reduction in CO during patient contact. This reduction in CO could potentially be associated with myocardial stunning, a phenomenon that has been previously documented [15].

In parallel with our findings; Monnet et al. [6] determine if hemodynamic resistance to fluid loss throughout intermittent renal replacement treatment (RRT) in people with critical illnesses may be anticipated using a PLR test performed before RRT; they included 39 individuals receiving intermittent RRT. They revealed that among individuals with IDH, CI increased after the PLR test 15 % above baseline.

In the current study, The ROC curve of Predicted probability (COP response (>12.0%) and IVC collapsibility response (>50.0%)) was associated with intradialytic hypotension 0.775 (95% CI 0.624-0.926). The standard error was 0.077, and the asymptotic significance was 0.004, indicating that the model's performance is statistically significant.

Regarding our knowledge, there were no previous studies that assessed both parameters together in hemodynamic intolerance to fluid removal.

However, some studies discussed each parameter “sensitivity and specificity” and cutoff value separately; In a comprehensive analysis of four publications, each containing over 50 extractable information points, a total of 298 individuals who weren't involved in sniffing were examined. The analysis aimed to determine the ideal sensitivity (80%) and specificity (79%) for predicting a mean RAP below 5 mmHg. The findings revealed that an IVC CI cutoff of ≥47.3% (about 50%) yielded the most accuracy in predicting the desired outcome. This roughly corresponds to the 50% [11] threshold value for IVC CI in Rudski and colleagues' echocardiography recommendations [16, 17] and used in our study.

IVC CI can be used as a predictor of volume responsiveness. In mechanically ventilated individuals, the IVC CI has shown a pooled sensitivity of 75% and specificity of 82%. Similarly, in spontaneously breathing individuals, the IVC CI has shown a pooled sensitivity of 71% and specificity of 81% [18, 19].

On the other side; Ismail et al. [20] a cross-sectional analytical investigation was undertaken on a cohort of 102 individuals who came with shock symptoms at the emergency center. The researchers observed that an IVC-CI cut-off point of 40 exhibited a sensitivity of 93.3% and specificity of 70.7%. Additionally, the AUC was determined to be 0.908, indicating a high level of accuracy. The 95% CI ranged from 0.84 to 0.975, suggesting a favourable level of precision. These findings suggest that an IVC-CI measurement of 40% or greater may serve as an indicator of fluid responsiveness among individuals experiencing shock.

The study conducted by Purushothaman et al. [14] aimed to examine the association between substantial hypotension and IVC-CI through the utilization of ROC curve analysis. The researchers determined that the integral of the curve yielded an area of 0.959 when evaluated at a threshold of 0.43, corresponding to a collapsibility of 43%. The correlation between substantial hypotension and IVC-CI was evaluated and was determined to be statistically significant ($P < 0.001$).

Regarding Monnet et al. [6] The rise in CI generated by PLR was found to be a significant predictor of IDH. The area under the ROC curve was calculated to be 0.89 (95% confidence interval: 0.75-0.97) ($p < 0.05$ from 0.50). The optimal diagnostic threshold was determined to be 9%. The sensitivity of the test was determined to be 77% with a 95% confidence range ranging from 46% to 95%. The specificity of the test was found to be 96% (80% to 100%). The positive predictive value was calculated to be 91% (57% to 100%). Lastly, the negative predictive value was determined to be 89% (72% to 98%).

The established reliability of the PLR test in determining preload response has been well-documented through the publishing of multiple research [21]. The test exhibits favourable sensitivity and specificity rates of 85% and 91% respectively, as well as commendable positive and negative predictive values and likelihood ratios [22]. The utilisation of the test has experienced an increase in popularity, and it is highly recommended for implementation in the hemodynamic therapy of septic shock as advised by the Surviving Sepsis Campaign [23].

Limitations: • Because we conducted this study in a single location, we were unable to generalize our findings.

•The study was done on non-ventilated group of patients and did not include other group of ventilated patients.

•Small sample size.

•Single center.

5. Conclusions:

The IVC collapsibility (%) and the change in COP (%) assessed by PLR were significantly higher in cases developed IDH. Furthermore, the COP response >12% was found in 75% of IDH patients. Similarly, the IVC collapsibility >50 response was in (81.3%) of IDH patients (significantly higher than non-IDH group). They could predict interdialytic hypotension with a good predictive value.

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Conflict of Interest: Nil

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