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Meta-Analysis of Ventilated versus Spontaneously Breathing Patients in Predicting Fluid Responsiveness by Inferior Vena Cava Variation

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Abstract

Purpose: Respiratory variation in inferior vena cava (ΔIVC) has been extensively studied in predicting fluid responsiveness, but the results are conflicting. We performed a systemic review and meta-analysis of studies aiming at investigating the diagnostic accuracy of ΔIVC in predicting fluid responsiveness. **Methods:** MEDLINE, EMBASE, Cochrane Database and Web of Science were screened for relevant original and review articles from inception to July 2016. The meta-analysis determined the pooled sensitivity, specificity, diagnostic odds ratio (DOR) and area under the ROC curve (AUROC). In addition, subgroup analyses were performed in mechanically ventilated patients and spontaneously breathing patients. **Results:** A total of 20 studies involving 635 patients were included. Cutoff values of ΔIVC varied from 12% to 42%, the pooled sensitivity and specificity was 0.68 (0.62 - 0.75) and 0.80 (0.75 - 0.85), respectively. The DOR was 14.2 (6.0 - 33.6) and the AUROC was 0.86 (0.78 - 0.93). Subgroup analysis showed better diagnostic performance in patients on mechanical ventilation than in spontaneously breathing patients with higher sensitivity (0.75 vs. 0.56), specificity (0.82 vs. 0.78), DOR (22.9 vs. 7.9) and AUROC (0.90 vs. 0.80). The best threshold of ΔIVC in patients on mechanical ventilation was IVC distensibility index (ΔdIVC ≥ 17% ± 4%), compared to IVC collapsibility index (ΔcIVC ≥ 33% ± 12%) in spontaneously breathing patients. **Conclusion:** ΔIVC is not an accurate predictor of fluid responsiveness in patients with acute circulatory failure. In patients on mechanical ventilation, the predicting ability of ΔIVC was moderate with acceptable sensitivity and specificity; in spontaneously breathing patients, the specificity remains acceptable but its sensitivity is poor.

Keywords

Fluid, Responsiveness, Inferior Vena Cava Variation

1. Introduction

Hypovolemia is a very frequent clinical situation in the intensive care unit (ICU) and is primarily treated with volume expansion (VE). The only goal of VE is to improve the cardiac output (CO) of the patients especially those with acute circulatory failure [1]. However, multiple studies have demonstrated that only approximately 50% of hemodynamically unstable patients respond to VE in the ICU [2]. It is therefore essential to have reliable tools to predict the efficacy of VE and ultimately distinguish patients who may benefit from VE from those who are unlikely to respond. Recently, many studies have focused on the prediction of fluid responsiveness. Static hemodynamic indices have been of little value in predicting fluid responsiveness [3] [4]. In contrast, dynamic indices, based on analysis of preload dependence, have been validated as factors that can help predict fluid responsiveness [3] [5] [6] [7]. However, because of invasiveness and high cost, the application of these indices is of limited use in emergency rooms and general wards.

Bedside point-of-care ultrasonography has gained considerable attention because of noninvasiveness, rapid diagnosis and low cost [8]. The diameter of the inferior vena cava (IVC) is easily recorded by transthoracic echocardiography (TTE) in a subcostal view. Because of the heart-lung interactions, the maximum IVC diameter (IVCmax) and minimum IVC diameter (IVCmin) can be measured during thecycle of breath. Then, a term named respiratory variation in IVC diameter (ΔIVC) can be calculated. In recent years, intensivist had increasing interesting on ΔIVC for predicting fluid responsiveness.

Following the first study demonstrating the accuracy of the ΔIVC, it has been extensively investigated for its usefulness. In 2014, a meta-analysis pooling eight studies published at that time confirmed that ΔIVC is of great value in predicting fluid responsiveness [9]. However, since this meta-analysis, conflicting findings on its accuracy have been reported in a number of publications.

In order to clarify these mixed results and assess the ability of ΔIVC to predict fluid responsiveness, we conducted a systemic review of all these studies and performed a meta-analysis, with hypothesis that ΔIVC performs well in predicting fluid responsiveness.

2. Materials and Methods

2.1. Clinical Research Question

The clinical research question was: What is the sensitivity and specificity of the ΔIVC when using it to predict fluid responsiveness?

2.2. PICO Statement [10]

The PICO statement is as the following:

P-patient, problem or population: patients with acute circulatory failure in whom the effect of volume expansion (VE) is unknown and needs to be predicted.

I-intervention: Inferior vena cava (IVC) diameter was examined subcostally and measured in M-mode or 2D mode, 2 cm before the IVC joined the right atrium. The IVC respiratory variation (ΔIVC) was calculate by recordingthe largest and smallest IVCdiameter at end-inspiration or end-expiration.

C-comparison, control, and comparator: Fluid responsiveness was defined as a significant increase of stroke volume (SV), cardiac output (CO) or other surrogates during a VE.

O-outcomes: Ability of the ΔIVC to predict fluid responsiveness.

2.3. Searching Strategy, Study Identification and Data Extraction

Our aim was to identify all studies evaluating the ability of the ΔIVC to predict fluid responsiveness compared to the increase in SV, CO or other surrogates induced by subsequent VE.

We searched the MEDLINE, EMBASE, Cochrane and Web of Science databases for relative studies published in English from inception to July 2016. The key words we used consist of term related to IVC ("inferior vena cava", "caval index", "collapsibility" and "distensibility") and terms related to volume status ("fluid or volume or preload responsiveness", "fluid or preload challenge", "preload dependence or independence or dependency or independency", "functional haemodynamic monitoring" and "fluid therapy or management"). These key words were searched separately by two groups using different combination strategy. We also looked for relevant articles cited in review articles, commentaries and editorials. The search was performed repeatedly until no new studies could be found.

Study identification was performed in two steps. Step 1 comprised screening for titles and abstracts, and step 2, review of full texts of studies obtained in step 1. We only included studies investigating the accuracy of the ΔIVC that were published in full text or accepted for publication in indexed journals. Excluded criteria were 1) studies using central venous pressure or right atrial pressure as the reference standard, because these static parameters cannot predict fluid responsiveness accurately; 2) studies measuring IVC with techniques other than ultrasonography; 3) studies involving animals and healthy volunteers. Two reviewers process searching independently, disagreement was settled by a third opinion. The quality of the included studies was evaluated by using the QUADAS-2 scale [11]. The meta-analysis was performed according to the PRISMA statement.

Important information was extracted from the included articles using a standardized data form by two reviewers. Extracted data include the name of the first

author, publication year, characteristics of the investigated population, sample size, respiratory pattern, the device for IVC measurement, formula for the calculation of ΔIVC, definition of fluid responsiveness and volume challenge strategy, the number of true positives, true negatives, false positives and false negatives, sensitivity, specificity, the area under the receiver operation characteristics curve (AUROC) and the best threshold of ΔIVC which is used to predict the fluid responsiveness.

2.4. QUADAS-2 Quality Assessment in Included Studies

Included studies were assessed for their quality based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) protocol. QUADAS-2 scale [11] was made up of 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. For the "patient selection" domain, we examined whether patients were consecutively included and whether inappropriate exclusions were avoided. For the "index test" domain, we examined whether the threshold used to define volume responsiveness was pre-specified. For the "reference standard" domain, we examined whether the result of VE on SV, CO or surrogates was assessed without knowledge of ΔIVC result. Finally, for the "flow and timing" domain, the authors examined whether there was an appropriate interval between IVC measurement and VE, whether patients received the same VE and whether all patients were included in the analysis. For each criterion, the risk was judged as high, low and unclear.

2.5. Statistical Analysis

We performed a meta-analysis in order to determine the pool sensitivity, specificity and diagnostic odds ratio (DOR). In addition, the pooled area under the ROC curve (AUROC) and threshold for ΔIVC as a predictor of fluid responsiveness was also evaluated. To investigate a threshold effect, we calculated the Spearman correlation coefficient between sensitivity and specificity. Homogeneity between studies was tested by the Chi squared test and I^2 index. According to heterogeneity, we adopted a random effect model by using the method of DerSimonian-Laird from the Mantel-Haenszel model. We compared studies with ICU setting versus non-ICU setting making the hypothesis that ΔIVC could be more reliable in ICU patients. We compared studies with adults versus children making the hypothesis that ΔIVC could be more reliable in adults. We compared studies with different devices for measuring IVC making the hypothesis that one device is better than the others. We compared studies with three different formulas for the calculation of ΔIVC making the hypothesis that one formula is better than the others. We compared studies with patients on mechanical ventilation versus studies with spontaneously breathing patients, testing the hypothesis that the reliability of ΔIVC is better in patients on mechanical ventilation. We compared studies where fluid responsiveness was defined by an increase in SV,

CO or surrogate ≥ 15% versus studies with other definitions of fluid responsiveness, testing the hypothesis that the reliability of ΔIVC is better when fluid responsiveness is defined by a larger increase. We compared studies where SV, CO or surrogate were measured by echocardiography versus studies where they were measured by other methods, testing the hypothesis that the reliability of ΔIVC is better when SV, CO or surrogate were measured by echocardiography. Finally, we compared studies where VE was performed with versus studies where it was performed by colloids, testing the hypothesis that the reliability of ΔIVC is better when VE is performed with colloids. Causes of heterogeneity were also investigated by meta-regression based on the Littenberg and Mose linear model.

Results are expressed as mean (95% confidence interval) or as mean ± standard deviation. The meta analysis was performed with Meta-Disc v.1.4 (Universidad Complutense, Madrid, Spain). The additional statistical analysis was performed with MedCal 15.2.2 (MedCal Software, Mariakerke, Belgium). A two-tailed $p < 0.05$ was considered to statistical significance.

3. Results

3.1. Characteristics of Included Studies

A flow chart of the study selection is provided in Figure 1. Our initial search identified 399 citations. 379 of them were excluded: 320 for not relating to the subject, 49 for being reviews, letters, guidelines, case reports and editorials, 3 for not writing in English, 4 for not using proper reference standard, 3 for being animal experiments. Finally, a total of 20 studies [12]-[31] reported the ability of ΔIVC to predict fluid responsiveness were included in our analysis.

Characteristics of included studies are listed in Table 1. Sample sizes were

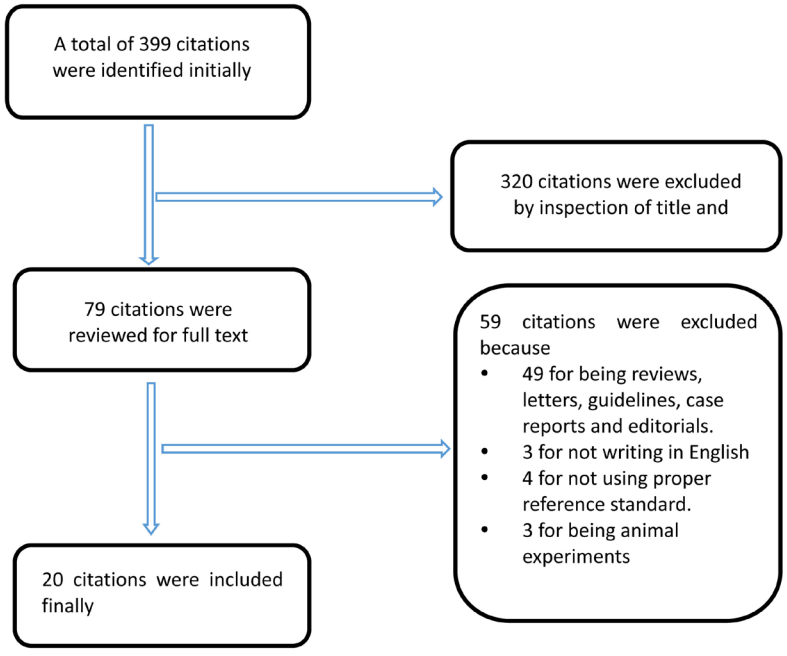


Figure 1. Flow chart of study selection.

Table 1. Characteristics of the studies included.

Study	Type of patients	Sample size	Setting	Type of device	Method for reference standard	Respiratory pattern	Index formula	reference standard	volume expansion
Barbier *et al.* 2004 [12]	adults	20	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8.5 ± 1.5 mL/kg; PEEP = 4 ± 2 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CI > 15%	7 ml/kg plasma
Feissel *et al.* 2004 [13]	adults	39	ICU	Not mention	Echocardiography	Mechanical ventilation (TV = 8 - 10 mL/kg)	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	CO > 15%	8 ml/kg 6% hydroxyethlstarch
Moretti and Pizzi 2010 [14]	adults	29	ICU	Esaote MyLab 30 CV	Transpulmonary, thermodilution	Mechanical ventilation (TV = 8 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CI > 15%	7 ml/kg 6% hydroxyethlstarch
Deok *et al.* 2010 [15]	children	21	Pediatrics	Acuson Cypress Diagnostic Ultrasound System	Echocardiography	Mechanical ventilation (TV = 10 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	SV > 15%	10 ml/kg 6% hydroxyethlstarch
Machare-Delgado 2011 [16]	adults	25	ICU	M-turbo, Sonosite, Bothell	Echocardiography	Mechanical ventilation (TV = 8.6 mL/kg)	(IVCmax − IVCmin)/IVCmin	SVI > 10%	500 ml saline
Corl *et al.* 2012 [17]	adults	26	ED	M-turbo, Sonosite, Bothell	ICG	Spontaneously breathing	(IVCmax − IVCmin)/IVCmax	CI > 10%	passive leg raise
Muller *et al.* 2012 [18]	adults	40	ICU	Vivid S6 machine, GE	Echocardiography	Spontaneously breathing	(IVCmax − IVCmin)/IVCmax	VTI > 15%	500 ml 6% hydroxyethlstarch
Brun *et al.* 2013 [19]	adults	23	Anesthesiology and obstetrics	Philips	Echocardiography	spontaneously breathing	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	SVI > 15%	500 ml normal saline

Continued

Byon HJ 2013 [20]	children	33	Operation room	Vivid 7, Pro, GE	Echocardiography	Mechanical ventilation (PEEP = 0 cm H_2O)	(IVCmax – IVCmin)/[(IVCmax + IVCmin)/2]	SVI > 10%	10 ml/kg hydroxyethlstarch
Baker *et al.* 2013 [21]	adults	25	ICU	Philips	Echocardiography	Mechanical ventilation (TV 6 - 8 mL/kg; PEEP 5 - 8 cmH2O	(IVCmax – IVCmin)/IVCmin	SV > 15%	500 ml colloid
Lanspa *et al.* 2013 [22]	adults	14	ICU	Philips	Echocardiography	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	CI > 15%	10 ml/kg crystalloid
Charbonneau *et al.* 2014 [23]	adults	44	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 6.4 - 11.0 mL/kg; PEEP = 5- 12 cm H_2O)	(IVCmax – IVCmin)/IVCmin	CI > 15%	7 ml/kg 6% hydroxyethlstarch
de Valk *et al.* 2014 [24]	adults	45	ED	Zonare, Mountain View	Systolic blood pressure	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	SBP > 10 mmHg	500ml 0.9% NaCl
Sobczyk *et al.* 2015 [25]	adults	50	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 4.5 cm H_2O	(IVCmax – IVCmin)/IVCmin; (IVCmax – IVCmin)/IVCmax	CO > 15%	2625 ± 778 mL within the first 6 hours
Lujan,varas *et al.* 2015 [26]	adults	15	ICU	Not mention	Picco, Vigileo, Swan-Ganz	Mechanical ventilation (PEEP11.4 ± 3.74)	(IVCmax – IVCmin)/IVCmin	CO > 15%	passive leg raise
Airapetian *et al.* 2015 [27]	adults	59	ICU	Philips	Echocardiography	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	CO > 10%	500 ml saline
Weber *et al.* 2015 [28]	children	31	PICU	Vivid S6; GE	Echocardiography	Mechanical ventilation (TV = 7.9 ± 3.8 mL/kg; PEEP = 6.8 ± 1.8 cm H_2O)	(IVCmax – IVCmin)/IVCmin	SVI > 10%	10 ml/kg 6% hydroxyethlstarch

Continued

Achar *et al.* 2016 [29]	children	42	Operation room	Vivid e; GE	Echocardiography	Mechanical ventilation (TV = 10 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/IVCmin	SVI > 15%	10 ml/kg 1% dextrose Ringer's lactate
Sobczyk *et al.* 2016 [30]	adults	35	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 4.5 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CO > 15%	250 ml saline
de Oliveira *et al.*2016 [31]	adults	20	ICU	Samsung Medison	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 5 - 6 cm H_2O)	(IVCmax − IVCmin)/IVCmin	VTI > 15%	500 crystalloid

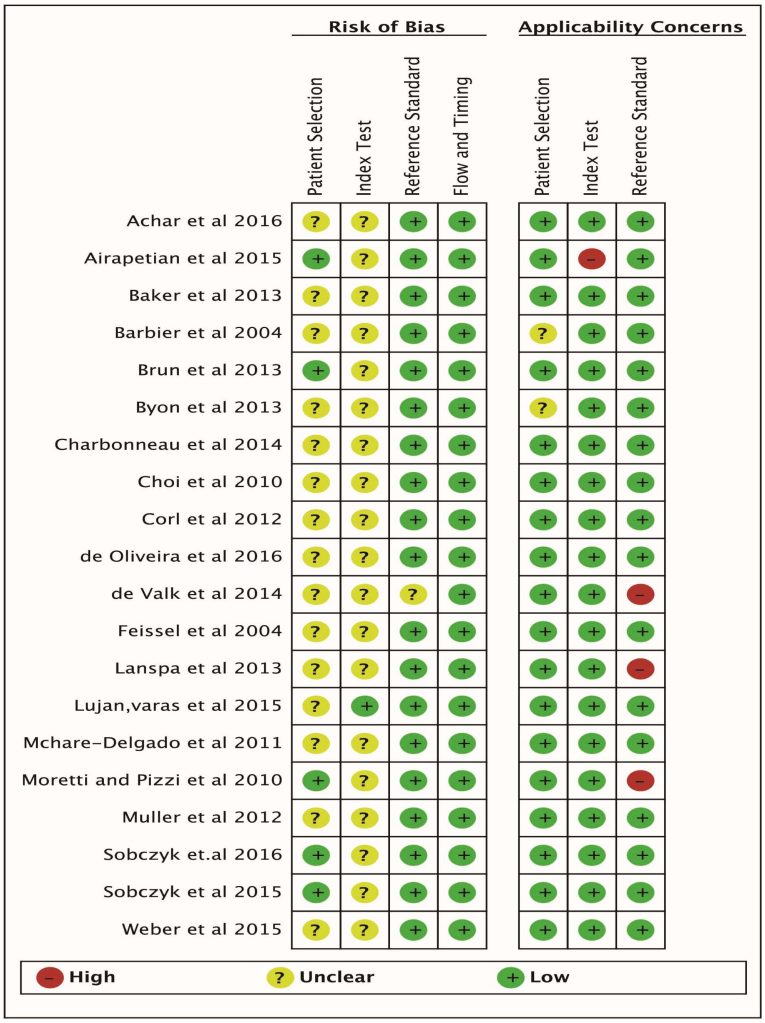
IVCmax and IVCmin = maximum and minimum diameter of inferior vena cava during a complete respiratory cycle; CI = cardiac index; CO = cardiac output; VTI = velocity-time index; SV = stroke volume; SVI = stroke volume index; SBP = systolic blood pressure; TV = tidal volume.

small, ranging from 14 to 50 patients. A total of 635 patients were included. 16 studies [12] [13] [14] [16] [17] [18] [19] [21]-[27] [30] [31] enrolled adults, and 4 studies [15] [20] [28] [29] enrolled pediatric patients. 14 studies [12] [13] [14] [15] [16] [20] [21] [23] [25] [26] [28] [29] [30] [31] enrolled patients on mechanical ventilation, and 6 studies [17] [18] [19] [22] [24] [27] enrolled spontaneously breathing patients. The formulas for the calculation of ΔIVC during the respiratory cycle were different. (IVCmax − IVCmin)/IVCmin was used in 11 studies [12] [14] [16] [21] [23] [25] [26] [28] [29] [30] [31], (IVCmax − IVCmin)/IVCmax was used in 5studies [17] [18] [22] [24] [27] and (IVCmax − IVCmin)/[(IVCmax + IVCmin)/2] was used in 4 studies [13] [15] [19] [20]. Interestingly, the 11 studies using the formula (IVCmax − IVCmin)/IVCmin allfocused on mechanically ventilatedpatients, and the 5 studies using the formula (IVCmax − IVCmin)/IVCmaxall focused on spontaneously breathing patients. In the 4 studies using (IVCmax − IVCmin)/[(IVCmax + IVCmin)/2] as the formula, one study focused on spontaneously breathing patients, while the other three studies focused on mechanically ventilated patients. With respect to reference standard, fluid responsiveness was defined as an increase in SV, CO or surrogate by more than 15% in 14 studies [12] [13] [14] [15] [18] [19] [21] [22] [23] [25] [26] [29] [30] [31], 10% in 5 studies [16] [17] [20] [27] [28], and increase in SBP by more than 10 mmHg in 1 study [24]. 16 studies [12] [13] [15] [16] [18]-[23] [25]-[31] used echocardiography to measured SV, CO or surrogate, 2 studies [14] [26] used transpulmonary thermodilution technique to measure CO, 1 study [17] used bioimpedance to measure cardiac index (CI) and the last study [24] used arterial catheter to measure SBP. VE was performed by

crystalloids in 8 studies [16] [19] [22] [24] [27] [29] [30] [31], by colloids in 10 studies [12] [13] [14] [15] [18] [20] [21] [23] [25] [28], passive leg raise in 2 studies [17] [26]. Quality assessment according to QUADAS-2 criteria is outlined in Figure 2.

3.2. Prediction of Fluid Responsiveness by ΔIVC

The diagnostic performance of ΔIVC in each study is showed in Table 2. The



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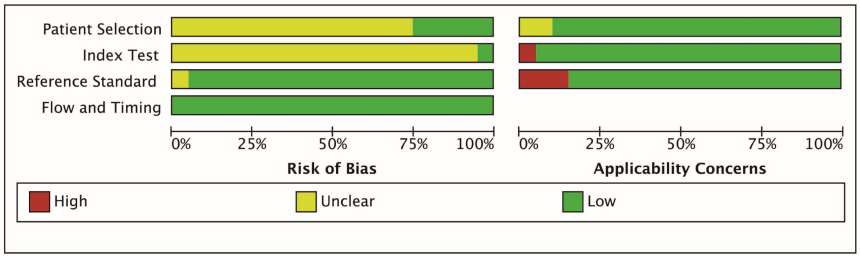

(b)

Figure 2. QUDAS-2 results and summary.

Table 2. Sensitivity and specificity of ΔIVC in predicting fluid responsiveness.

Study	TP	FP	FN	TN	Cutoff value	Sensitivity (%)	Specificity (%)	AUROC (95% CI)
Barbier *et al.* 2004	9	1	1	9	18%	90.00	90%	0.91 (0.84, 0.98)
Feissel *et al.* 2004	14	1	2	22	12%	-	-	-
Moretti and Pizzi 2010	12	0	5	12	16%	70.59%	100%	0.902 (0.733, 0.979)
Deok *et al.* 2010	-	-	-	-	-	-	-	0.85 (0.69, 1.00)
Machare-Delgado 2011	8	8	0	9	12%	100.00	53%	0.81 (0.64, 0.99)
Corl *et al.* 2012	-	-	-	-	-	-	-	0.46 (0.21, 0.71)
Muller *et al.* 2012	14	4	6	16	40%	70	80%	0.77 (0.60, 0.88)
Brun *et al.* 2013	-	-	-	-	-	-	-	0.57 (0.32, 0.82)
Byon HJ 2013	-	-	-	-	-	-	-	0.369 (0.156, 0.582)
Baker *et al.* 2013	-	-	-	-	-	-	-	0.46 (0.22 - 0.69)
Lanspa *et al.* 2013	5	3	0	6	15%	100	66.66%	0.83 (0.58 - 1.0)
Charbonneau *et al.* 2014	10	7	16	11	21%	38	61%	0.43 (0.25, 0.61)
de Valk *et al.* 2014	10	11	2	22	36.5	83	67%	0.741
Sobczyk *et al.* 2015	-	-	-	-	-	-	-	-
Lujan, varas *et al.* 2015	2	2	1	10	18%	-	-	-
Airapetian *et al.* 2015	9	1	20	29	42%	31	97%	0.62 ± 0.07 (0.49 - 0.74)
Weber *et al.* 2015	-	-	-	-	-	-	-	0.502 (0.29, 0.71)
Achar *et al.* 2016	22	2	2	16	23.5%	91	89%	0.94
Sobczyk *et al.* 2016	20	3	4	8	18%-	82.35%-	72.72%-	0.739
de Oliveira *et al.* 2016	6	0	3	11	16%	66.67	100%	0.84 ± 0.10 (0.63 - 1.0)

TP = true positive; FP = false positive; FN = false negative; TN = true negative; AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

sensitivity and specificity was reported in 14 studies [12] [13] [14] [16] [18] [19] [22] [23] [24] [26] [27] [29] [30] [31]. The pooled sensitivity, specificity and DOR was 0.68 (0.62 - 0.75), 0.80 (0.75 - 0.85) and 14.2 (6.0 - 33.6), respectively. (**Table 2**, **Figure 3**). The area under the corresponding ROC curve was reported in 17 studies [12] [14]-[24] [27] [28] [29] [30] [31]. In 9 studies [12] [14] [15] [16] [18] [22] [24] [29] [31], the AUROC of ΔIVC were more than 0.7, and in the other 8 studies [17] [19] [20] [21] [23] [27] [28] [30], ΔIVC showed low diagnostic value. The pooled AUROC was 0.86 (0.78 - 0.93) (**Table 2**, **Figure 4**). The threshold of ΔIVC was reported in 13 studies [12] [13] [14] [16] [18] [22] [23] [24] [26] [27] [29] [30] [31], the values varied across studies, ranging from 12% to 42% (**Table 2**).

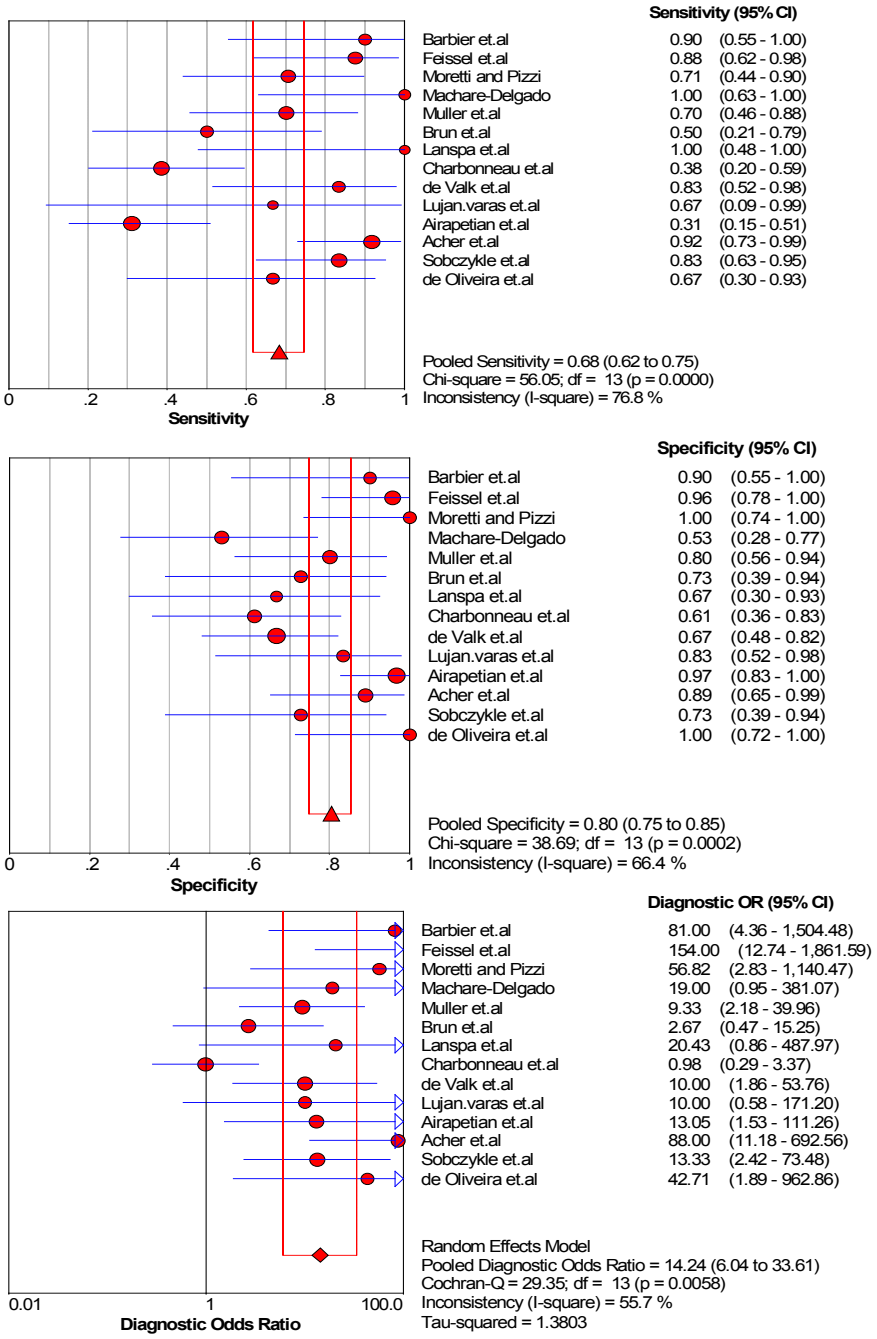

Figure 3. Pooled diagnostic accuracy of ΔIVC in whole studies.

3.3. Subgroup Analysis and Investigation of Heterogeneity

The Spearman correlation coefficient between sensitivity and specificity was 0.323 (p = 0.260), indicating no threshold effect. The heterogeneity Chi-squared was 56% for sensitivity and 39% for specificity. The I^2 statistics was 77% for sensitivity, 66% for specificity.

Meta-regression shows none of the covariates included were the significant source of heterogeneity. However, the comparison between studies with mechanical ventilation versus studies with spontaneously breathing, and between

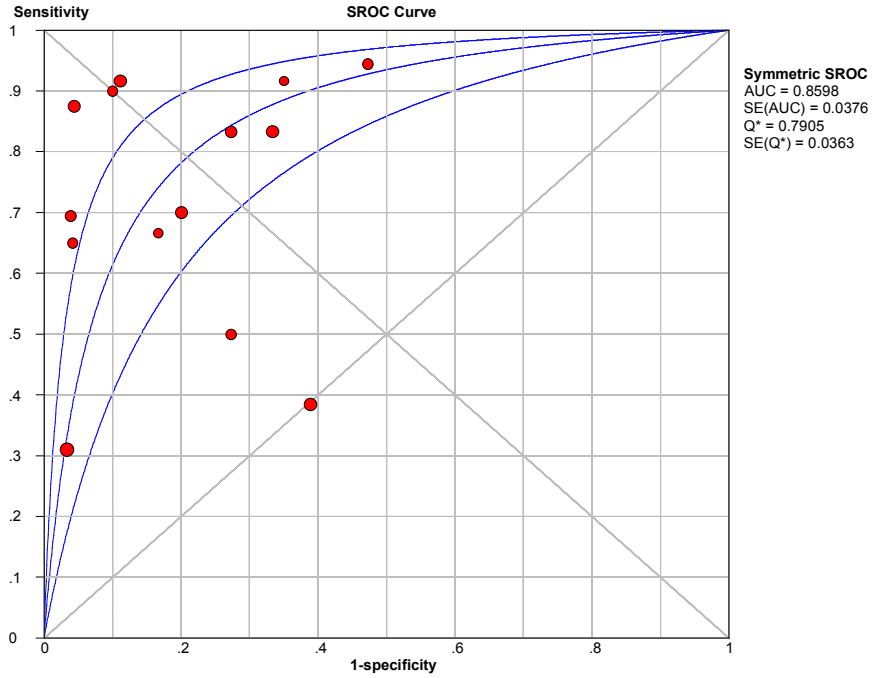

Figure 4. Summary receiver operating characteristics curve of ΔIVC in whole studies.

studies with different devices and formulas for the calculation of ΔIVC had influence on sensitivity and specificity. Diagnostically, ΔIVC performed better in patients on mechanical ventilation than in spontaneously breathing patients with higher sensitivity (0.75 vs.0.56), specificity (0.82 vs. 0.78), DOR (22.9 vs. 7.9), and AUROC (0.9 vs.0.8) (**Table 3**). In addition, 9 studies [12] [13] [14] [16] [23] [26] [29] [30] [31] with mechanical ventilation reported the threshold ranging from 12% to 23.5%, the average was 17% ± 4%; the average of the other 4 studies [18] [22] [24] [27] with spontaneously breathing was 33% ± 12%.

4. Discussion

This meta-analysis including 20 studies with a combined total of 635 patients concluded that ICU staff must be cautious of using ΔIVC, which was not so excellent to predict fluid responsiveness with pooled sensitivity (0.68) and specificity (0.80).In patients on mechanical ventilation, ΔIVC could predict fluid responsiveness moderately with acceptable pooled sensitivity (0.75) and specificity (0.82). The pooled AUROC was 0.90 (0.80 - 0.99) and the average of threshold was ΔIVC ≥ 17% ± 4%. However, in spontaneously breathing patients, ΔIVC predict fluid responsiveness with poor sensitivity (0.56) and acceptable specificity (0.78).

Point-of-care ultrasonography is a reliable monitoring technique and is becoming increasingly popular in the ICU. The IVC diameter is easily examined from a subcostal view in a longitudinal section, varying during the respiratory cycle due to the changes in intrathoracic pressure during inspiration and expiration. This variation is expressed as the ΔIVC. Recent years, ΔVC has been developed to

Table 3. Pooled diagnostic accuracy of ΔIVC in whole and subgroup studies.

Setting	Total number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic odds ratio (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95%CI)	AUROC
Overall	14	0.68 (0.62 - 0.75)	0.80 (0.75 - 0.85)	14.2 (6.0 - 33.6)	3.3 (2.1 - 5.1)	0.34 (0.21 - 0.54)	0.86 (0.78 - 0.93)
Mechanical ventilation	9	0.75 (0.67 - 0.82)	0.82 (0.74 - 0.88)	22.9 (5.6 - 93.4)	4.3 (2.0 - 9.4)	0.27 (0.13 - 0.54)	0.90 (0.80 - 0.99)
Spontaneous breathing	5	0.56 (0.45 - 0.68)	0.78 (0.70 - 0.86)	7.9 (3.5 - 18.1)	2.7 (1.8 - 4.0)	0.50 (0.29 - 0.86)	0.80 (0.71 - 0.89)

accurately predict fluid responsiveness in clinical practice. The consensus on circulatory shock and hemodynamic monitoring published by task force of the European Society of Intensive Care Medicine in 2014 recommended that ΔIVC as dynamic variables were available to predict fluid responsiveness [32].

To our knowledge, in 2014, Zhang and co-workers performed a systematic review and meta-analysis that included eight studies investigating the diagnostic performance of ΔIVC [9]. They concluded that ΔIVC is of great value in predicting fluid responsiveness, particularly in patients on mechanical ventilation compared to spontaneously breathing patients. However, since this meta-analysis, additional studies [19] [20] [21] [23] [25] [26] [27] [28] have been published, reporting ΔIVC would not be reliable in spontaneously breathing patients. In addition, G. Via *et al.* [33] have suggested ten situations where ΔIVC may fail to accurately predict fluid responsiveness. Furthermore, the threshold of ΔIVC varied widely, causing confusion of ICU staff to use it in clinical practice. Finally, the meta-analysis of Zhang *et al.* included only one study [18] investigating spontaneously breathing patients and four studies [12] [13] [14] [16] on mechanical ventilation with complete data. All these arguments justified an updated meta-analysis.

Our meta-analysis is inconsistent with the meta-analysis performed by Zhang *et al.* and concluded that ICU staff must be cautious of using ΔIVC to test fluid responsiveness. Based on the results from a large number of patients, we found that ΔIVC was not so excellent to predict fluid responsiveness with poor sensitivity (0.68) and acceptable specificity (0.80). The pooled AUROC was 0.86 but not close to each other. In addition, the threshold values for ΔIVC varied across studies, ranging from 12% to 42%, which reinforce our conclusion.

In subgroup analysis, our study indicated that in patients on mechanical ventilation, ΔIVC predict fluid responsiveness with acceptable pooled sensitivity (0.75) and specificity (0.82), which are less accurate than meta-analysis performed by Zhang *et al.*, however. This is likely due to high PEEP and/or low tidal volume invalidating the diagnostic performance of ΔIVC. High PEEP has been demonstrated to elevate right atrial pressure (RAP) and IVC pressure, while simultaneously reducing venous return, introducing an increase IVC size and false negative of ΔIVC [34]. Furthermore, the low tidal volumes less than 8 ml/kg will cause smaller variations in intrathoratic blood volume, resulting in smaller ΔIVC theoretically, irrespective of volume status. Charbonneau *et al.* [23] sug-

gested that ΔIVC predicted fluid responsiveness with low sensitivity (38%), and Baker *et al.* [21] demonstrated that ΔIVC was an inaccuracy predictor with low AUROC (0.46). The ventilation of these two studies was High PEEP > 5 cm H_2O and low tidal volumes < 8 ml/kg. However, these two studies [21] [23] were published after the meta-analysis performed by Zhang *et al.* In addition, our study indicated that in spontaneously breathing patients, ΔIVC predict fluid responsiveness with poor sensitivity (0.56) and acceptable specificity (0.78). The pooled AUROC was 0.80 (0.71 - 0.89). This is probably because of varying breath, meaning that the amplitude of intrathoracic pressure swings and size of tidal volumes are hard to quantify in spontaneously breathing patients. Study in healthy volunteers [35] shows deeper the breathing is, the larger diaphragmatic motion and ΔIVC are, regardless of volume status. This indicates that shallow breaths may minify ΔIVC and reduce its sensitivity, while inspiratory efforts may magnify ΔIVC and reduce its specificity [18]. Even if in patients on ventilation, ΔIVC is not a valid measure when patients made an inspiratory effort [36].

An important point that must be paid more attention to is the formula of calculation of ΔIVC. ΔIVC is usually expressed as the difference between expiratory IVC diameter and inspiratory IVC diameter divided by the expiratory IVC diameter, multiplied by 100%. However, in spontaneous respiration or mechanical ventilation, the changes of IVC diameter are opposite because of opposite changes of intrathoracic pressure during inspiration. In patients on mechanical ventilation, ΔIVC is calculated by (IVCmax − IVCmin)/IVCmin defined as IVC distensibility index (ΔdIVC), while in spontaneously breathing patients, it is calculated by (IVCmax − IVCmin)/IVCmax defined as IVC collapsibility index (ΔcIVC). In our meta-analysis, the best threshold of ΔIVC in patients on mechanical ventilation was ΔdIVC ≥ 17% ± 4%, compared to ΔcIVC ≥ 33% ± 12% in spontaneously breathing patients. Nowadays, the clinical use of ΔIVC is in chaos regardless of its physiology, leading to misjudgment, which need to be more accurate define and recognition.

There are some limitations that should be noted for interpreting the results. First, the heterogeneity of the included studies existed with respect to patient population, respiratory pattern, calculation formula, definition of index test and fluid responsiveness. Nevertheless, no threshold effect was detected. Furthermore, both the subgroup analyses and meta-regression were opposed to the influence of heterogeneity on the results. Second, although we performed subgroup analysis, the number of studies and sample size in each subgroup was small, the conclusion needs to be validated in future trials. Third, we did not include studies not in English, non-full-text and unpublished studies, which may increase the risk of reporting bias.

5. Conclusion

In conclusion, our meta-analysis indicated that ΔIVC is not an excellent predictor of fluid responsiveness in patients with acute circulatory failure. The pre-

dicting ability of ΔIVC was moderate in patients on mechanical ventilation, while it was poor in spontaneously breathing patients. Thus, intensivist must be cautious of using ΔIVC.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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