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Accuracy of Ultrasonographic Measurements of Inferior Vena Cava to Determine Fluid Responsiveness: A Systematic Review and Meta-Analysis

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Abstract

Objective: Fluid responsiveness is the ability to increase the cardiac output in response to a fluid challenge. Only about 50% of patients receiving fluid resuscitation for acute circulatory failure increase their stroke volume, but the other 50% may worsen their outcome. Therefore, predicting fluid responsiveness is needed. In this purpose, in recent years, the assessment of the inferior vena cava (IVC) through ultrasound (US) has become very popular. The aim of our work was to systematically review all the previously published studies assessing the accuracy of the diameter of IVC or its respiratory variations measured through US in predicting fluid responsiveness. **Data Sources:** We searched in the MEDLINE (PubMed), Embase, Web of Science databases for all relevant articles from inception to September 2017. **Study Selection:** Included articles specifically addressed the accuracy of IVC diameter or its respiratory variations assessed by US in predicting the fluid responsiveness in critically ill ventilated or not, adult or pediatric patients. **Data Extraction:** We included 26 studies that investigated the role of the caval index (IVC collapsibility or distensibility) and 5 studies on IVC diameter. **Data Synthesis:** We conducted a meta-analysis for caval index with 20 studies: The pooled area under the curve, logarithmic diagnostic odds ratio, sensitivity, and specificity were 0.71 (95% confidence interval [CI]: 0.46-0.83), 2.02 (95% CI: 1.29-2.89), 0.71 (95% CI: 0.62-0.80), and 0.75 (95% CI: 0.64-0.85), respectively. **Conclusion:** An extreme heterogeneity of included studies was highlighted. Ultrasound evaluation of the diameter of the IVC and its respiratory variations does not seem to be a reliable method to predict fluid responsiveness.

Keywords

inferior vena cava, fluid responsiveness, review, meta-analysis

Introduction

In critically ill patients demonstrating an absolute or relative reduction in circulating volume (for sepsis, acute blood loss, anaphylaxis, etc), increased cardiac output (CO) to improve tissue perfusion is essential. However, gathered evidence shows excessive fluid administration may result in a worst outcome, through pulmonary or peripheral edema, compartmental syndrome, and reduced oxygen diffusion. Unfortunately, clinical evaluation alone is not able to distinguish which patients will benefit from an increase in intravenous fluids and which patients may instead worsen.[1-4]

Cardiac output is the product of systolic output and heart rate. Within certain boundaries, the relationship between preload and CO is described by Frank-Starling curve. When the hemodynamic system exceeds the maximum slope of the curve, an increase in preload does not correspond to an equal increase in stroke volume. The speed at which this flat part of the Frank-Starling curve is reached depends on cardiac contractility and afterload.[1-4]

A hemodynamically compromised patient is usually hypovolemic, but the responsiveness to fluid resuscitation is scarcely predictable. Only about 50% of patients receiving fluid resuscitation for acute circulatory failure increase their stroke volume (not only for preexisting cardiac conditions but also for acutely acquired dysfunctions such as sepsis-related cardiomyopathy),[1] so it is essential to be able to accurately predict

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the fluid responsiveness of our patient. Invasive methods, such as the Swan-Ganz catheter (able to directly measure capillary wedge pressure), and noninvasive methods, such as peripheral arterial pulse wave analysis, were developed. However, these methods are not completely capable to predict fluid responsiveness, especially in certain circumstances, such as arrhythmias or spontaneously breathing patients.[5-9] Transthoracic echocardiography (TTE) currently is probably the most used method to evaluate the fluid responsiveness. However, this tool can determine the effect of increase in circulating volume only once a fluid load has already been administered.[10] For these reasons, besides the need of easy and ready-to-use methods also from nonhighly skilled staff, several methods that can potentially predict fluid responsiveness were studied.

In order to predict fluid responsiveness, one of the most popular methods is assessing the diameter of the inferior vena cava (IVC) or its respiratory variation through ultrasound (US). In spontaneously breathing patients, the IVC diameter decreases due to the increase in the thoracic volume which reduces the intrathoracic pressure. This collapsibility effect may be indexed, dividing the difference of the 2 diameters for the maximum diameter (inferior vena cava collapsibility). This measure is called "caval index." In mechanically ventilated patients, the inspiratory flow is administered by the ventilator and is therefore at a positive pressure. The increase in the intrathoracic pressure causes a distension of the IVC, the meaning of which is similar to the caval index (inferior vena cava distensibility).

The aim of our study was to systematically review all previously published studies that evaluated the accuracy of the IVC diameter or its respiratory variations assessed through US in predicting fluid responsiveness.

Methods

Searching Strategy and Study Selection

We searched the MEDLINE, Embase, and Web of Science databases from inception to September 2017. The searched item consisted of terms related to volume status (including "fluid," "volume," and "fluid responsiveness"), "inferior vena cava," and "ultrasound." We searched also citations of relevant primary and review articles. Conference abstracts, review articles, non-English studies, nonhuman studies, protocols or policy statement, and guidelines were excluded. We included studies considering a wide type of adult and pediatric patients (eg, from sepsis to subarachnoid hemorrhage). Studies involving both mechanically ventilated and spontaneously breathing patients were included. Studies in any hospital departments or setting were included.

We considered the studies on IVC diameter and/or collapsibility/distensibility of IVC measured by US. We included studies reporting any measure to define the fluid responsiveness (stroke index, CO, cardiac index, etc); we considered studies using TTE, transpulmonary thermodilution, bioreactance (BR), and any other techniques as standard references. We are aware that not all standard references are equally accurate, but we took this issue into account in the qualitative assessment of the included studies.

Critical Appraisal

Two independent reviewers (D.O. and I.P.) read all papers and scored them according to the QUADAS2 checklist.[11] Any disagreement was discussed. If no agreement was reached even after discussion, a third person (T.P.) was involved. A criterion by majority was adopted. In the systematic review, we considered all relevant studies that passed quality selection. In the meta-analysis, we considered only the studies which declared sensitivity, specificity, and prevalence of fluid responsiveness.

Data Extraction and Data Synthesis

Data about type of study; publication year; target population; setting; ventilation mode; eventual tidal volume; fluid challenge content and volume; standard reference device, measurement, and threshold; IVC detection method; index test threshold; and prevalence of fluid responsiveness were extracted from studies.

Statistical Analysis

All statistical analyses were performed using the R-CRAN project version 3.4.0 (R Core Team [2017]. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/). The R packages "meta4diag" and "INLA" were implemented. Quantitative variables were expressed as median and 95% confidence interval (CI). Due to the threshold effect, we did not consider appropriate using I^2 as heterogeneity measurement. Knowing the high level of heterogeneity a priori, we used summary receiver operating characteristic (SROC) curve and funnel plot to identify the degree of heterogeneity. For construing SROC curve, we used a Bayesian inference method using integrated nested Laplace approximations for bivariate meta-analysis.[12-16] We implemented a hierarchical approach through the model of Rutter and Gatsonis.[17] We investigated heterogeneity through subanalyses of the setting in which the studies were conducted, the type of study population, the ventilation mode, and the adopted standard reference.

Results

Search Strategy Findings

Five hundred one articles were found through systematic search; 426 articles were excluded because they were duplicated (63), they did not meet inclusion criteria or with different end points (141), or were abstracts, case reports or letters (88), reviews (85), protocols, guidelines or policy statements (41), written in another language than English (6), or bibliographies (2). The selection process is described in Figure 1.

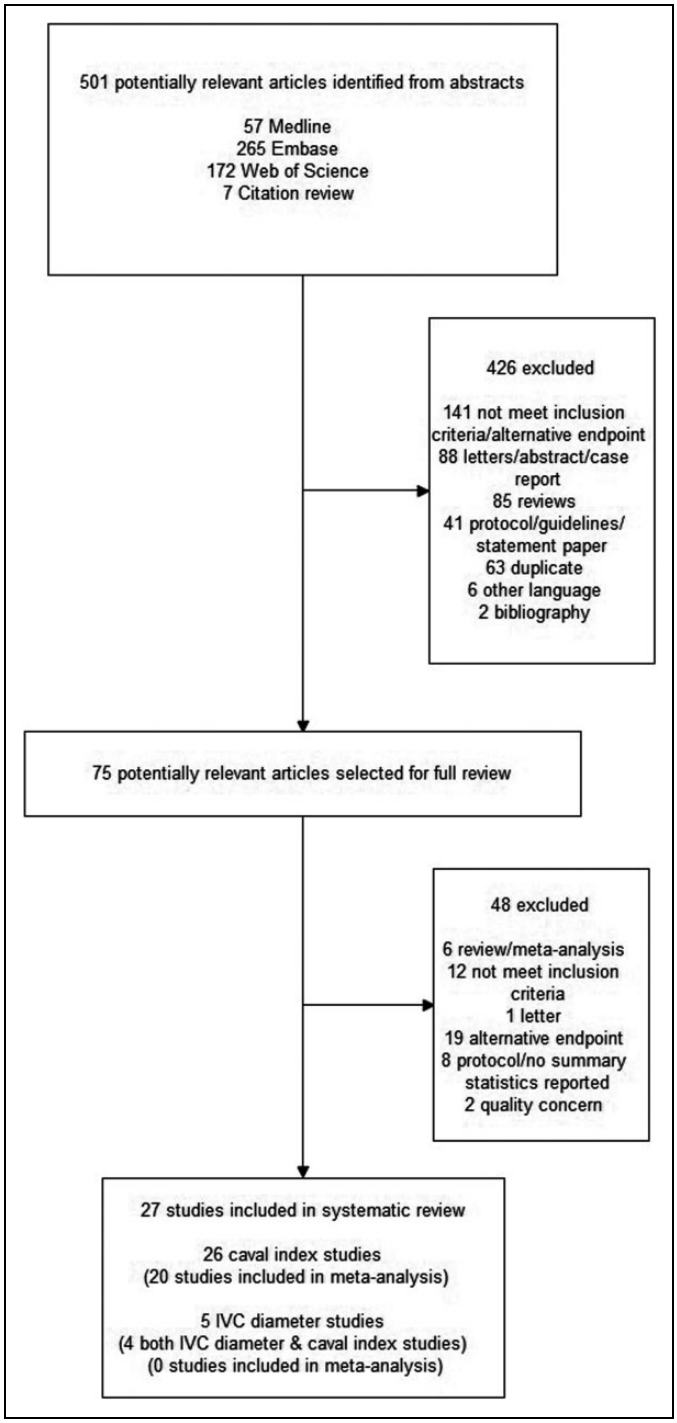

Figure 1. Flow diagram of literature search and study selection.

Of 75 studies considered for the intended purpose, 48 studies were discarded because they did not meet the inclusion criteria (12), were reviews or meta-analysis (6), were letters (1) considered alternative end points (19), were protocols or did not summarize the statistical results, (8) or because of questionable methodological quality (2).

Finally, 27 studies were included: 22 were related to the caval index,[18-39] 1 study was related to the IVC diameter,[40] and 4 studies evaluated both indexes[41-44] (Tables 1 and 2). On the basis of the included studies, we were able to achieve a meta-analysis of 20 studies[18-22,24-35,41-42,44] that evaluated the caval index. Due to the extreme heterogeneity and the small number of studies evaluating the IVC diameter, we did not conduct a meta-analysis for this index test.

Description of Included Studies

Regarding caval index studies, we considered 1709 cases. Only 1 study was multicentric. Eighteen studies were conducted in intensive care units (ICUs), 5 in operating rooms (ORs), and 3 in emergency departments (EDs). Twenty-two studies involved adult patients and 4 studies pediatric patients. Regarding the target populations, 8 studies enrolled patients with sepsis, 4 studies surgical patients, 3 studies patients with cardiac diseases, 8 studies mixed patients (the remaining studies involved neurosurgical patients, patients with subarachnoid hemorrhage, or patients with severe preeclampsia). Regarding the ventilation mode, 16 studies considered mechanically ventilated patients and 7 spontaneously breathing patients (3 studies did not declared this item). Most common tidal volumes were between 8 and 10 mL/kg/min. The most commonly used reference method was TTE (16 studies). Two studies considered transesophageal echocardiography, 2 studies BR method, 2 studies Vigileo, 2 studies pulse index continuous cardiac output, and 1 study noninvasive blood pressure (BP) measurement. Eight studies considered the cardiac index as standard reference, 5 studies CO, 8 studies stroke volume (SVi), 3 studies velocity time integral (VTI), 1 study stroke volume variation, and 1 study systolic blood pressure (SBP; Table 1).

Regarding IVC diameter studies, the pooled sample was 268 patients. All studies were conducted in ICUs. All studies involved adult patients. Two studies involved patients with sepsis, and the others considered cardiac, trauma, or mixed patients. Two studies were conducted on mechanically ventilated patients and 3 on spontaneously breathing patients. The most used standard reference method was TTE, and 1 study used BP. In 3 studies, standard reference measure was CO, in 1 was SVi, and in 1 was SBP (Table 2).

Risk of Bias

Most caval index studies were qualitatively high, but some risks of bias were found in patient selection (selection of cardiac, surgical, or other categories of patients is a possible source of heterogeneity), flow and timing (some studies did not declare the delay between fluid administration and IVC evaluation), and the choice of standard reference. The high degree of heterogeneity was also revealed by funnel plot (Figure 2). A very disaggregated distribution of studies, particularly those with wider samples (which are far from the expected logarithmic diagnostic odds ratio [LDOR] average), was detected. There was not a clear publication bias, but studies with the largest sample size were extremely heterogeneous in their results.

Table 1. List of the Caval Index Studies Included in the Systematic Review and Their Characteristics.

ID	Study	Population	Sampling	Sample Size	Setting	Patient Group	Mechanical Ventilation	Tidal Volume	Fluid Challenge Content	Fluid Challenge Volume	Ref. St. Device	Ref. St. Measure	Ref. St. Threshold (%)	ΔIVC (%)
1	Corl et al[18]	Adults	Convenience	124	ED	Mixed	No	NA	NS	500 mL	BR	CI	10	25
2	Lu et al[19]	Adults	NR	49	ICU	Sepsis	Yes	8-10	0.9% saline	200 mL	PiCCO	CI	10	23.3
3	Preau et al[41]	Adults	Consecutive	90	ICU	Sepsis	No	NA	4% gelatin	500 mL	TTE	SVi	10	47
7	Murthi et al[23]	Adults	Convenience	199	ICU	Surgical	Unclear	NA	NS	500-1000 mL	TTE	SVi	15	50
8	Soboczyk et al[24]	Adults	Consecutive	35	ICU	Cardiac	Yes	8	0.9% saline	500 mL	TTE	CO	15	18
9	Theerawit et al[25]	Adults	NR	29	ICU	Sepsis	Yes	8	HES	500 mL	PCA	CO	15	10
10	Zhang et al[26]	Adults	NR	40	OR	Surgical	Yes	NA	HES	7 mL/kg	Vigileo	SVV	16	46
11	Zhao and Wang[36]	Adults	Consecutive	42	ICU	Sepsis	Unclear	NA	HES	500 mL	PiCCO	CI	15	12.9
12	Airapetian et al[42]	Adults	Consecutive	59	ICU	Mixed	No	NA	0.9% saline	500 mL	TTE	CO	15	42
13	Soboczyk et al[43]	Adults	Consecutive	50	ICU	Cardiac	Yes	8	NS	NS	TTE	CO	15	17.6
14	Weber et al[27]	Pediatric	NR	31	ICU	Mixed	Yes	7.9 ± 3.8	HES	10 mL/kg	TEE	SVi	10	16.4
15	Charbonneau et al[28]	Adults	Consecutive	44	ICU	Sepsis	Yes	7	HES	7 mL/kg	TTE	CI	15	12
16	de Valk et al[29]	Adults	Consecutive	45	ED	Mixed	No	NA	0.9% saline	500 mL	BP	SBP	10	36.5
17	Brun et al[30]	Adults	Consecutive	23	OR	Severe preeclampsia	Unclear	NA	0.9% saline	500 mL	TTE	SVi	15	NR
18	Byon et al[37]	Pediatric	NR	33	OR	Neurosurgical	Yes	10	HES	10 mL/kg	TTE	SVi	10	NR
19	Lanspa et al[31]	Adults	Consecutive	14	ICU	Sepsis	No	NA	Crystalloid	10 mL/kg	TTE	CI	15	50
20	Corl et al[38]	Adults	Convenience	26	ED	Mixed	No	NA	PLR	PLR	BR	CI	10	NR
21	Muller et al[32]	Adults	Consecutive	40	ICU	Mixed	No	NA	HES	500 mL	TTE	VTI	15	64
22	Machare-Delgado et al[33]	Adults	NR	25	ICU	Mixed	Yes	8.6 ± 1.7	0.9% saline	500 mL	TTE	SVI	10	12
23	Choi et al[39]	Pediatric	NR	21	ICU	Cardiac	Yes	10	HES	10 mL/kg	TTE	SVi	15	NR
24	Moretti and Pizzi[34]	Adults	Consecutive	29	OR	SAH	Yes	NA	HES	7 mL/kg	PiCCO	CI	15	16
25	Barbier et al[35]	Adults	Convenience	20	ICU	Sepsis	Yes	8.5 ± 1.5	HES	7 mL/kg	TTE	CI	15	18
26	Feissel et al[44]	Adults	Convenience	39	ICU	Sepsis	Yes	8-10	HES	8 mL/kg	TTE	CO	15	12

Abbreviations: BP, noninvasive blood pressure; BR, bioreactance; CI, cardiac index; CO, cardiac output; ED, emergency department; HES, hydroxyethyl starch; ICU, intensive care unit; NA, not available; NR, not reported; OR, operating room; PCA, pulse contour analysis; PiCCO, pulse index continuous cardiac output; PLR, passive legs raising; Ref. St. Device, reference standard device; Ref. St. Measure, reference standard measure; Ref. St. Threshold, reference standard threshold; SBP, systolic blood pressure; SVi, stroke volume indexed; SVV, stroke volume variation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; ΔIVC, IVC collapsibility/distensibility.

Table 2. List of the IVC Diameter Studies Included in the Systemic Review and Their Characteristics.

ID	Study	Population	Sampling	Sample Size	Setting	Patients Group	Mechanical Ventilation	Tidal Volume	Fluid Challenge	Fluid Challenge Volume	Ref. St. Device	Ref. St. Measure	Ref. St. Threshold	ΔIVC
1	Preau et al[41]	Adults	Consecutive	90	ICU	Sepsis	No	NA	4% gelatin	500 mL	TTE	SVi	10%	16
2	Airapetian et al[42]	Adults	Consecutive	59	ICU	Mixed	No	NA	0.9% saline	500 mL	TTE	CO	15%	17 ± 4
3	Soboczyk et al[43]	Adults	Consecutive	50	ICU	Cardiac	Yes	8	NS	NS	TTE	CO	15%	22.7 ± 16
4	Yanagawa[40]	Adults	Convenience	30	ICU	Trauma	No	NA	LR solution	1-2 L	BP	SBP	>90 mm Hg	NR
5	Feissel et al[44]	Adults	Convenience	39	ICU	Sepsis	Yes	8-10	HES	8 mL/kg	TTE	CO	15%	17 ± 6

Abbreviations: BP, noninvasive blood pressure; CO, cardiac output; ED, emergency department; HES, hydroxyethyl starch; ICU, intensive care unit; IVC, inferior vena cava; NA, not available; NR, not reported; NS, nonsignificant; Ref. St. Device, reference standard device; Ref. St. Measure, reference standard measure; Ref. St. Threshold, reference standard threshold; TTE, transthoracic echocardiography; SVi, stroke volume indexed; SBP, systolic blood pressure; ΔIVC, IVC collapsibility/distensibility.

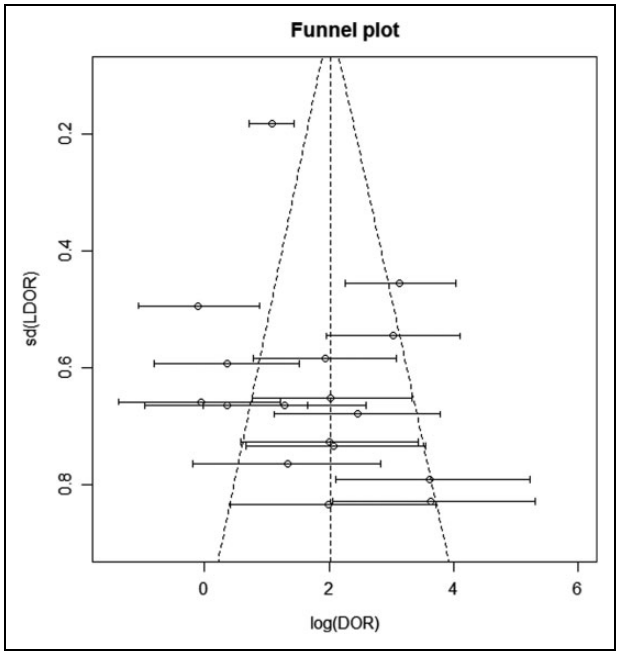

Figure 2. Funnel plot for the caval index studies. A scatter plot of the effect estimates from individual studies against logarithmic diagnostic odds ratio (LDOR). Standard deviation is plotted on the vertical axis. The effects estimated by smaller studies spread lower on the bottom; larger studies are distributed along the narrower, triangular upper part.

The quality of the IVC diameter studies was quite high. One study used SBP as standard reference: This choice was considered a high risk of bias and the applicability of the obtained results was rather uncertain (Tables 3 and 4).

Results of Meta-Analysis

Regarding caval index studies, the sensitivity ranged from 0.39 (95% CI: 0.23-0.57) to 0.86 (95% CI: 0.71-0.95) and the specificity ranged from 0.28 (95% CI: 0.18-0.41) to 0.91 (95% CI: 0.72-0.99). Logarithmic diagnostic odds ratio ranged from −0.10 (95% CI: −1.07 to 0.86) to 3.61 (95% CI: 2.03-5.32). The pooled sensitivity, specificity, and LDOR were 0.72 (95% CI: 0.63-0.80), 0.75 (95% CI: 0.64-0.84), and 2.02 (95% CI: 1.29-2.83; Figures 3 and 4; Figure 7 in Supplemental Digital Content), respectively. The pooled area under the curve was 0.71 (95% CI: 0.46-0.83; marginal likelihood ratio = −125.41; Figure 5).

By dividing the pooled sample on the basis of the considered populations (adults vs pediatric patients), the sensitivity, specificity, and LDOR of the studies on adults were 0.71 (95% CI: 0.62-0.80), 0.75 (95% CI: 0.64-0.85), and 2.04 (95% CI: 1.26-2.89), respectively. The sensitivity, specificity, and LDOR of the studies on pediatric populations were 0.74 (95% CI: 0.44-0.92), 0.68 (95% CI: 0.27-0.92), and 1.81 (95% CI: −0.60 to 4.28), respectively.

Table 3. Assessment of Quality and Risk of Bias of Individual Caval Index Studies.

	Risk of Bias				Applicability Concerns		
Study	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Corl et al[18]	L	L	?	L	L	L	?
Lu et al[19]	L	L	L	?	L	L	L
Preau et al[41]	L	L	L	L	L	L	L
Vignon[20]	L	L	L	L	L	L	L
de Oliveira[22]	?	L	L	?	L	L	L
Murthi et al[23]	L	L	L	L	L	L	L
Soboczyk et al[24]	H	L	L	L	H	L	L
Theerawit et al[25]	L	L	?	H	L	L	L
Zhang et al[26]	H	L	?	?	H	L	L
Zhao and Wang[36]	L	L	L	?	L	L	L
Airapetian et al[42]	L	L	L	L	L	L	L
Soboczyk et al[43]	L	L	L	L	?	L	L
Weber et al[27]	?	L	L	L	?	L	L
Charbonneau et al[28]	L	L	L	L	L	L	L
de Valk et al[29]	L	L	H	L	L	L	H
Brun et al[30]	L	L	L	?	?	L	L
Byon et al[37]	L	L	L	L	?	L	L
Lanspa et al[31]	L	L	L	L	L	L	L
Corl et al[38]	?	L	?	?	L	L	?
Muller et al[32]	L	L	L	L	L	L	L
Machare-Delgado et al[33]	?	L	?	L	L	L	?
Choi et al[39]	?	L	L	L	?	L	L
Moretti and Pizzi[34]	L	L	L	L	?	L	L
Barbier et al[35]	L	L	L	L	L	L	L
Feissel et al[44]	L	L	L	L	L	L	L

Abbreviations: H, high risk; L, low risk; ?, uncertain risk.

Table 4. Assessment of Quality and Risk of Bias of Individual IVC Diameter Studies.

	Risk of Bias				Applicability Concerns		
Study	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Preau et al[41]	L	L	L	L	L	L	L
Airapetian et al[42]	L	L	L	L	L	L	L
Soboczyk et al[43]	L	L	L	L	?	L	L
Yanagawa[40]	L	L	H	L	L	L	?
Feissel et al[44]	L	L	L	L	L	L	L

Abbreviations: IVC, inferior vena cava; H, high risk; L, low risk; ?, uncertain risk.

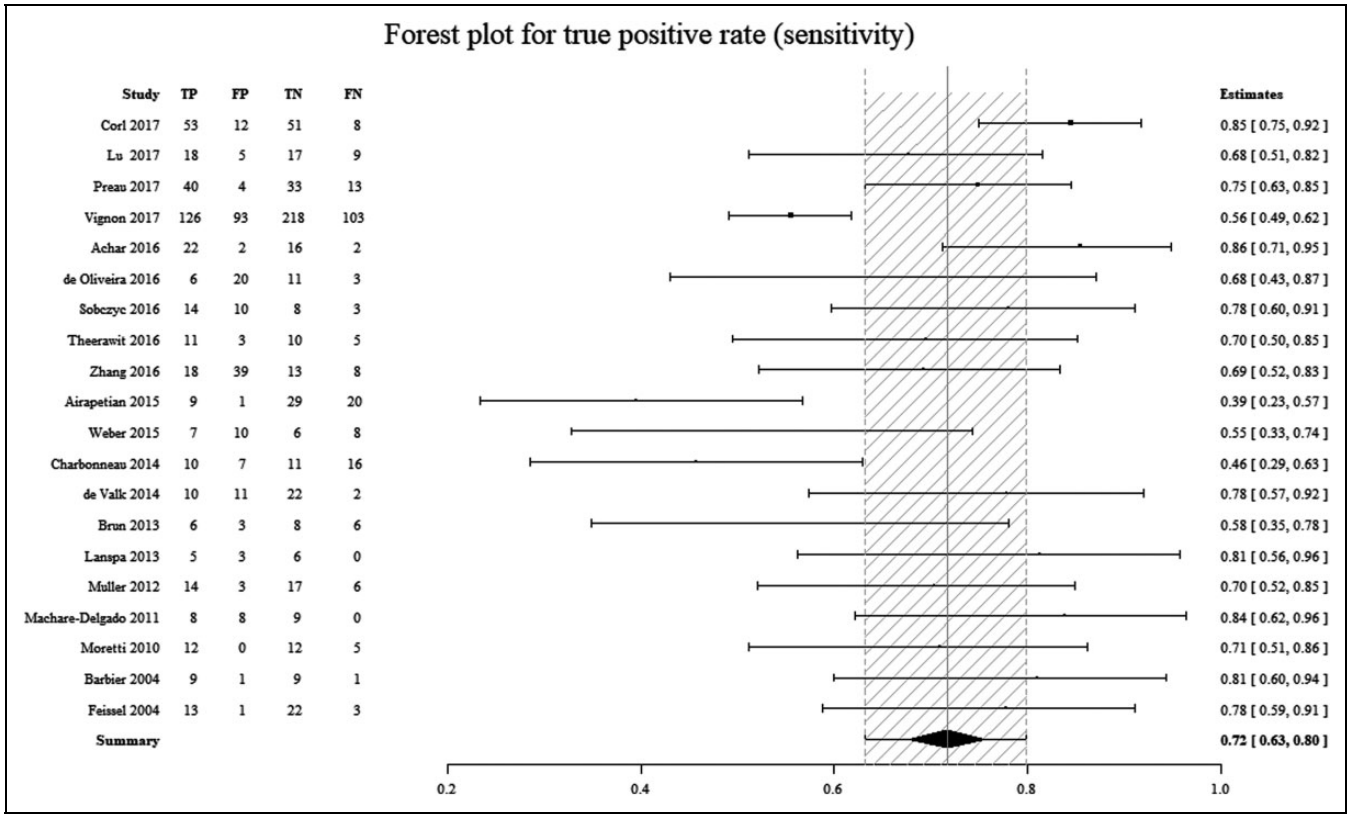

Figure 3. Comparison of the sensitivity values for the caval index studies. On the left column the individual studies. On the right column the sensitivity (95% CI). The dashed area represents the 95% CI. CI indicates confidence interval; FN, false negatives; FP, false positives; TN, true negatives; TP, true positives.

For the 14 studies conducted in ICUs, the sensitivity, specificity, and LDOR were 0.68 (95% CI: 0.58-0.78), 0.74 (95% CI: 0.60-0.85), and 1.83 (95% CI: 0.91-2.81), respectively. In ED studies (2), the results were 0.86 (95% CI: 0.65-0.96), 0.75 (95% CI: 0.35-0.94), and 2.95 (95% CI: 0.57-5.33). Finally in OR studies (4), the results were 0.74 (95% CI: 0.54-0.87), 0.76 (95% CI: 0.47-0.93), 2.19 (95% CI: 0.46-4.05).

Regarding the target populations, for patients with sepsis (7 studies), the sensitivity, specificity, and LDOR of caval index were 0.74 (95% CI: 0.57-0.87), 0.83 (95% CI: 0.68-0.92), and 2.62 (95% CI: 1.30-4.05), respectively. For mixed patients (7 studies), the results were 0.68 (95% CI: 0.51-0.83), 0.74 (95% CI: 0.57-0.86), and 1.80 (95% CI: 0.54-3.11). For surgical patients (3 studies), the results were 0.79 (95% CI: 0.54 to 0.93), 0.49 (95% CI: 0.23 to 0.77), and 1.30 (95% CI: −0.63 to 3.35).

Analyzing the different ventilation modes, 13 studies considered ventilated patients. For these studies, the sensitivity, specificity, and LDOR were 0.72 (95% CI: 0.61-0.82), 0.69 (95% CI: 0.54-0.81), and 1.73 (95% CI: 0.85-2.71), respectively. In nonventilated patients (6 studies), the results were 0.75 (95% CI: 0.58-0.87), 0.84 (95% CI: 0.68-0.93), and 2.77 (95% CI: 1.41-4.13).

Finally, on the basis of the standard reference, for CI studies (6 studies), the sensitivity, specificity, and LDOR were 0.76 (95% CI: 0.58-0.89), 0.82 (95% CI: 0.63-0.93), and 2.68 (95% CI: 1.23-4.29), respectively. For SVi studies (5 studies), the results were 0.76 (95% CI: 0.55-0.90), 0.72

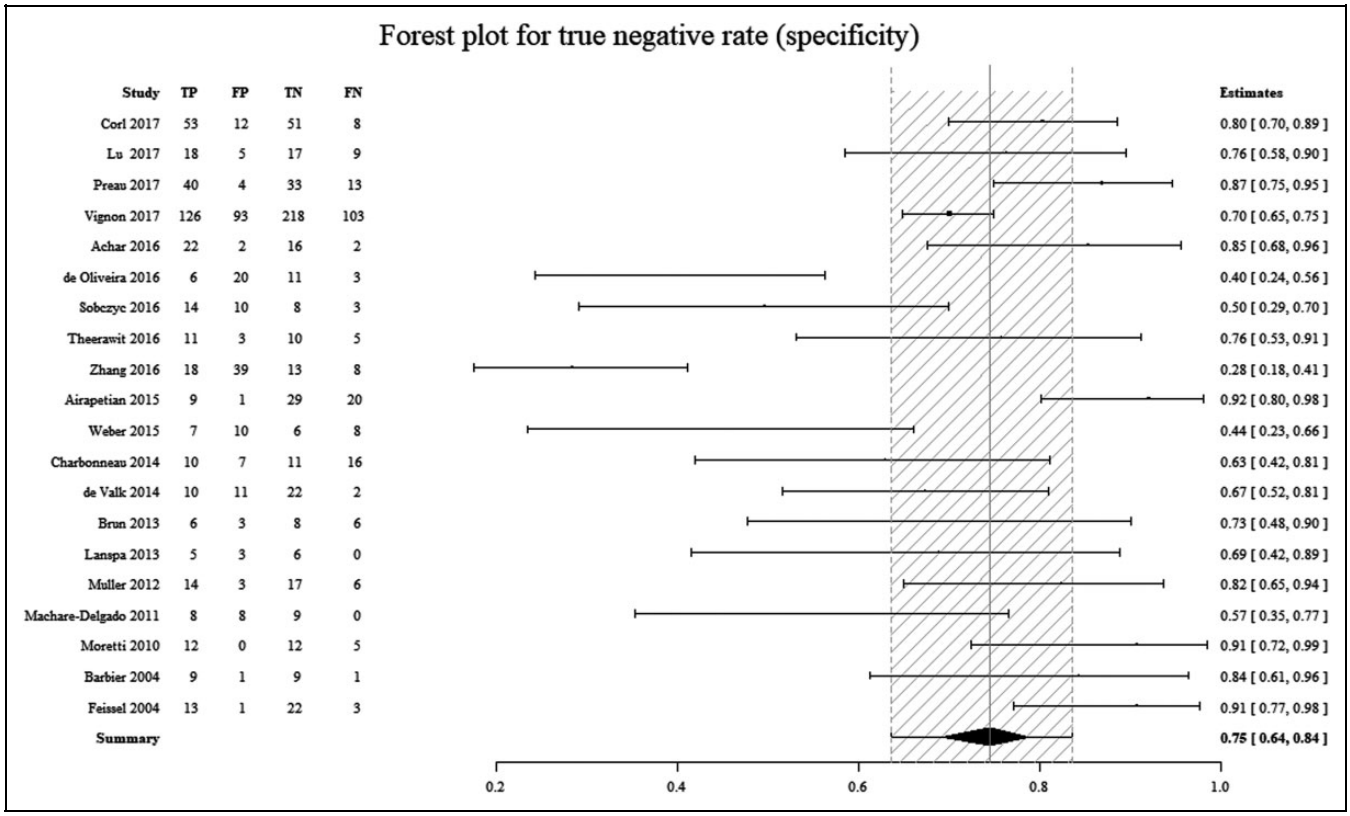

Figure 4. Comparison of the specificity values for the caval index studies. On the left column the individual studies. On the right column the specificity (95% CI). The dashed area represents the 95% CI. CI indicates confidence interval; FN, false negatives; FP, false positives; TN, true negatives; TP, true positives.

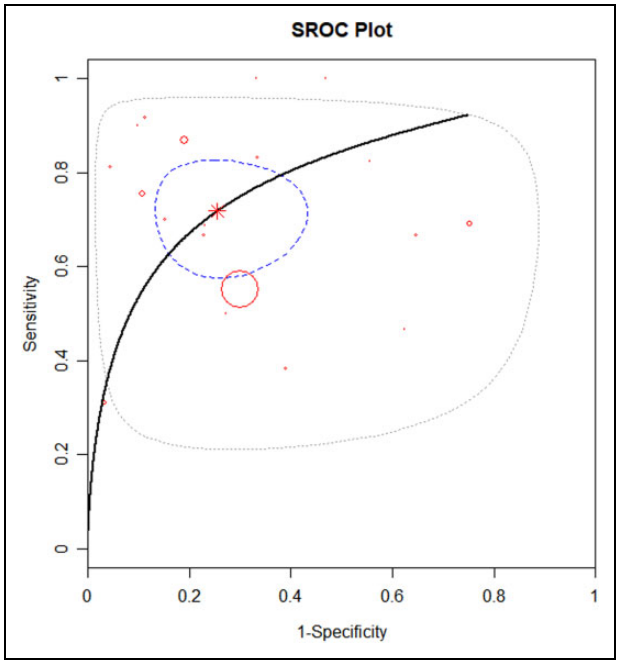

Figure 5. Receiver operating characteristics (ROC) curve for the caval index studies. Area under the curve (AUC) = 0.71 (95% CI: 0.46-0.83; marginal likelihood ratio = −125.41). Solid red circles are individual studies depicted for the sample size. Dashed blue circle represents the 95% confidence interval.

(95% CI: 0.48-0.89), and 2.13 (95% CI: 0.51-3.80). For CO studies (4 studies), the results were 0.67 (95% CI: 0.42-0.85), 0.85 (95% CI: 0.63-0.95), and 2.46 (95% CI: 0.66-4.33). For VTI studies (3 studies), the results were 0.63 (95% CI: 0.35 to 0.85), 0.65 (95% CI: 0.34 to 0.88), and 1.19 (95% CI: −0.78 to 3.20; Figure 6).

Discussion

The evaluation of the IVC diameter or the caval index seems to be a well-studied method. Nevertheless, extremely discordant results were obtained in the literature. Long and colleagues, in their meta-analysis, found a remarkable degree of heterogeneity.[4] Even if we did not find a relevant difference in the diagnostic accuracy of the caval index in predicting fluid responsiveness among studies enrolling adult or pediatric populations, there are still few studies in the literature investigating the role of IVC in pediatric populations. Gan et al found only 2 studies in this regard, with contrasting results.[45] Only 2 of 4 studies on the pediatric population could be included in our meta-analysis. Drawing conclusions from these small populations and from very different studies each other is very difficult.

The caval index seemed to gain greater accuracy in ED and OR studies than ICU studies.[46] In particular, a greater sensitivity of the caval index in ED studies than ICU ones was

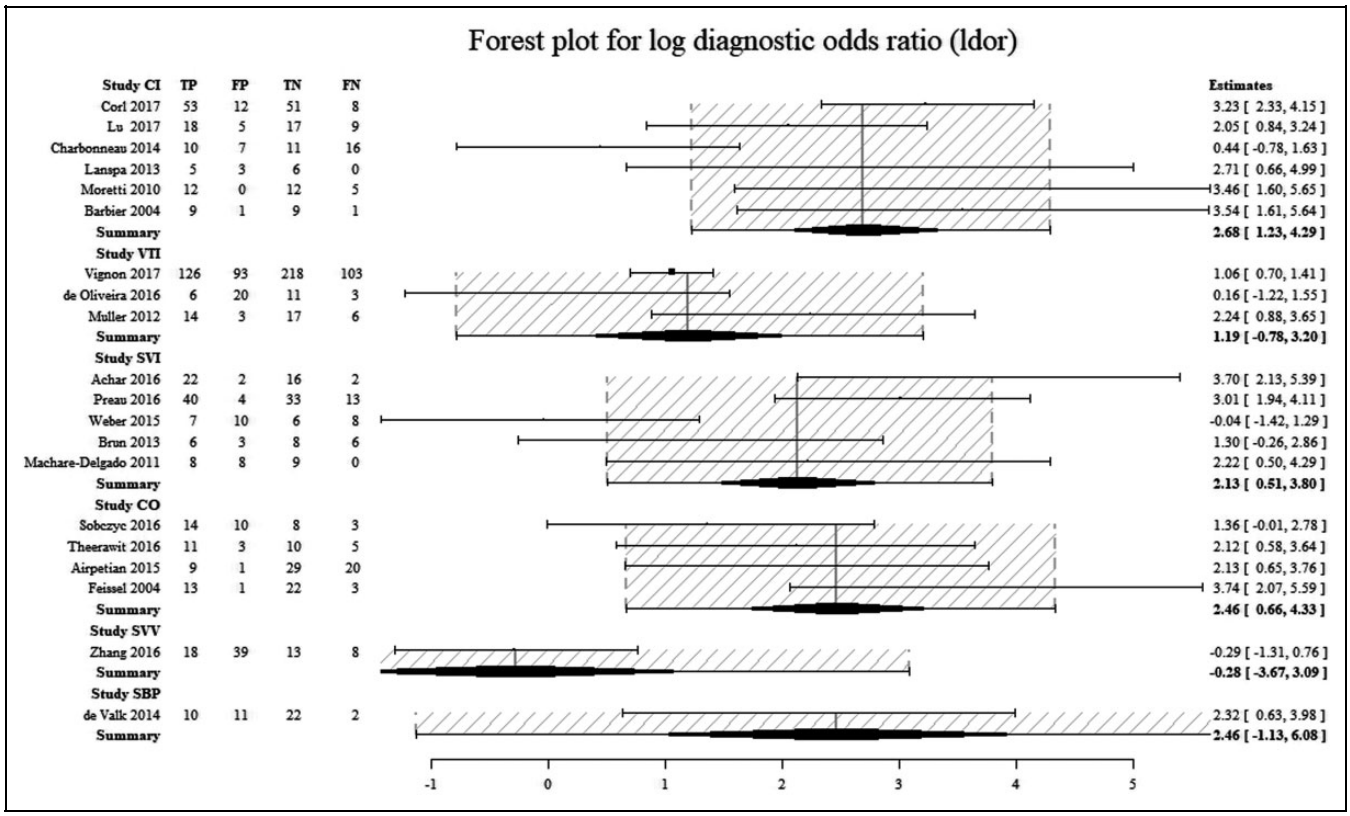

Figure 6. Comparison of the LDOR for the caval index studies for every standard reference group. On the left column the individual studies. On the right column the LDOR (95% confidence interval). The dashed area represents the 95% confidence interval. CI indicates cardiac index; CO, cardiac output; FN, false negatives; FP, false positives; LDOR, logarithmic diagnostic odds ratio; SBP, systolic blood pressure; SVI, stroke volume indexed; SVV, stroke volume variation; TN, true negatives; TP, true positives; VTI, velocity time integral.

observed. It is difficult to understand how much this result is linked to real clinical conditions of clearly different populations or it is the result of transient effects not observed in ICU.

Compared to patients with sepsis, in surgical patients, the caval index shown a different accuracy, in particular a lower specificity. Although surgical patients are often hypovolemic, surgical interventions or conditions that increase intra-abdominal pressure can make the caval index unreliable.[47-49]

In contrast to the literature, we found a lower predictive ability of the caval index in ventilated patients than those in spontaneously breathing.[4,50] It is difficult to understand how much this is related to real clinical differences or methodological bias. In fact, the ventilatory parameters collected from the studies were not so different such as to explain this very heterogeneous result. A possible explanation may be that changes in IVC diameter in ventilated patients are less extensive and therefore more subject to approximation errors, compared to the spontaneously breathing patients.

The lack of a real gold standard is responsible for a consistent part of heterogeneity: In our analysis, nonindexed measures (eg, VTI, CO) seem to be more subject to a broad variability (wider CIs). This is reasonable considering the anthropometric variations associated with each patient. Also, small errors in transvalvular flow sampling can cause major errors in the final result. Ansari et al noted there is no substantial agreement in the literature on the definition of "fluid responsiveness." Parameters such as "precision" and "reproducibility" of a measurement do not seem to be sufficiently explicated in fluid responsiveness studies.[1] Moreover, any monitoring system has limitations related to the clinical condition of the patient, which reduces its applicability to any patient indiscriminately. In addition to this bias source, the accuracy with which measurements are made, especially in chaotic environments, is not always optimal. Ultimately, a number of minor approximations can lead to a major final error, especially when the parameters to be measured relate to critical patients requiring nearly immediate assistance.

Intra- and interobserver variability can contribute to overall heterogeneity. Only 5 studies clearly indicated the intra- and interobserver agreements. These ranged from 1.4% to 9% and from 3% to 6%, respectively.

Finally, the continuous nature of the considered variables—that were transformed into dichotomous variables in order to determine the diagnostic accuracy by SROC curve—could be a source of heterogeneity. As reported by several papers, probably there is an area of overlapping between responders and nonresponders, the so-called "gray zone" that is difficult to evaluate in a dichotomous manner.[1,4,32]

Compared to the meta-analyses reported in the literature,[4,50,51] our study revealed a high degree of heterogeneity.

All the factors analyzed so far contribute to this result. Probably, there is no "one size fits all" method able to adapt to all critically ill patients indiscriminately. It is necessary not only to know the benefits of different hemodynamic monitoring methods but also their limitations in each setting and for each clinical condition. In other words, clinicians must select the right test for the right patient at the right time.

For the high heterogeneity, we found the cumulative final considerations in our study may not be totally reliable, although we used robust statistical methods (in particular a Bayesian method through a hierarchical approach) to overcome this limitation.

Conclusions

In summary, the extreme heterogeneity of the studies considering the role of IVC to predict fluid responsiveness makes difficult to evaluate the usefulness of IVC diameter and the caval index assessed by US. For the obtained data so far, US evaluation of the diameter of the IVC and its respiratory variations does not seem to be a reliable method to predict the fluid responsiveness.

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Supplemental Material

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References

1. Ansari BM, Zochios V, Falter F, Klein AA. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review. *Anaesthesia*. 2016;71(1):94-105.
2. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(9):1538-1545.
3. Laher AE, Watermeyer MJ, Buchannan SK, et al. A review of hemodynamic monitoring techniques, methods and devices for the emergency physician. *Am J Emerg Med*. 2017;35(9):1335-1347.
4. Long E, Oakley E, Duke T, Babl FE; Pediatric Research in Emergency Departments International Collaborative. Does respiratory variation in inferior vena cava diameter predict fluid responsiveness: a systematic review and meta-analysis. *Shock*. 2017;47(5):550-559.
5. Teboul JL, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med*. 2016;42(9):1350-1359.
6. Sangkum L, Liu GL, Yu L, Yan H, Kaye AD, Liu H. Minimally invasive or noninvasive cardiac output measurement: an update. *J Anesth*. 2016;30(3):461-480.
7. Velissaris D, Karamouzos V, Kotroni I, Pierrakos C, Karanikolas M. The use of pulmonary artery catheter in sepsis patients: a literature review. *J Clin Med Res*. 2016;8(11):769-776.
8. Youssef N, Whitlock R. The routine use of PAC should be abandoned. *Can J Cardiol*. 2017;33(1):135-141.
9. Lee M, Curley GF, Mustard M, Mazer CD. The Swan-Ganz catheter remains a critically important component of monitoring in cardiovascular critical care. *Can J Cardiol*. 2017;33(1):142-147.
10. Wetterslev M, Haase N, Johansen RR, Perner A. Predicting fluid responsiveness with transthoracic echocardiography is not yet evidence based. *Acta Anaesthesiol Scand*. 2013;57(6):692-697.
11. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the qualify assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
12. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models using integrated nested Laplace approximations. *J R Statist Soc B*. 2009;71(2):319-392.
13. Martins TG, Simpson D, Lindgren F, Rue H. Bayesian computing with INLA: new features. *Comput Stat Data Anal*. 2013;67:68-83.
14. Lindgren F, Rue H, Lindstrom J. An explicit link between Gaussian fields and Gaussian Markov random fields: the stochastic partial differential equation approach. *J R Statist Soc B*. 2011;73(4):423-498.
15. Lindgren F, Rue H. Bayesian spatial modelling with R-INLA. *J Stat Softw*. 2015;63(19):1-25.
16. Rue H, Riebler A, Sorbye SH, et al. Bayesian computing with INLA: a review. *Annu Rev Stat Appl*. 2017;4:395-421.
17. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med*. 2001;20(19):2865-2884.
18. Corl KA, George NR, Romanoff J, et al. Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically-ill patients. *J Crit Care*. 2017;41:130-137.
19. Lu N, Xi X, Jiang L, Yang D, Yin K. Exploring the best predictors of fluid responsiveness in patients with septic shock. *Am J Emerg Med*. 2017;35(9):1258-1261.
20. Vignon P, Repessé X, Bégot E, et al. Comparison of echocardiography indices used to predict fluid responsiveness in ventilated patients. *Am J Resp Crit Care Med*. 2017;195(8):1022-1032.
21. Achar SK, Sagar MS, Shetty R, et al. Respiratory variation in aortic flow peak velocity and inferior vena cava distensibility as indices of fluid responsiveness in anaesthetized and mechanically ventilated children. *Indian J Anaesth*. 2016;60(2):121-126.
22. de Oliveira OH, de Freitas FGR, Ladeira RT, et al. Comparison between respiratory changes in the inferior vena cava diameter and pulse pressure variation to predict fluid responsiveness in postoperative patients. *J Crit Care*. 2016;34:46-49.
23. Murthi SB, Fatima S, Menne AR, et al. Ultrasound assessment of volume responsiveness in critically ill surgical patients: two measurements are better than one. *J Trauma Acute Care Surg*. 2017;82(3):505-511.

24. Soboczyk D, Nycz K, Andruskiewicz P, Wierzbicki K, Stapor M. Ultrasonographic caval indices do not significantly contribute to predicting fluid responsiveness immediately after coronary artery bypass grafting when compared to passive leg raising. *Cardiovasc Ultrasound*. 2016;14(1):23.
25. Theerawit P, Morasert T, Sutherasan Y. Inferior vena cava diameter variation compared to pulse pressure variation as predictors of fluid responsiveness in sepsis patients. *J Crit Care*. 2016; 36:246-251.
26. Zhang X, Feng J, Zhu P, et al. Ultrasonographic measurements of the inferior vena cava variation as a predictor of fluid responsiveness in patients undergoing anesthesia for surgery. *J Surg Res*. 2016;204(1):118-122.
27. Weber T, Wagner T, Neumann K, Deusch E. Low predictability of three different noninvasive methods to determine fluid responsiveness in critically ill children. *Pediatr Crit Care Med*. 2015; 16(3):e89-94.
28. Charbonneau H, Riu B, Faron M, et al. Predicting preload responsiveness using simultaneous recordings of inferior and superior vena cavae diameters. *Crit Care*. 2014;18(5):473.
29. de Valk S, Olgers TJ, Holman M, Ismael F, Ligtenberg JJ, Ter Maaten JC. The caval index: an adequate non-invasive ultrasound parameter to predict fluid responsiveness in the emergency department? *BMC Anesthesiol*. 2014;14:114.
30. Brun C, Zieleskiewicz L, Textoris J, et al. Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. *Intensive Care Med*. 2013;39(4):593-600.
31. Lanspa MJ, Grissom CK, Hirshberg EL, Jones JP, Brown SM. Applying dynamic parameters to predict hemodynamic response to volume expansion in spontaneously breathing patients with sepsis shock. *Shock*. 2013;39(5):462.
32. Muller L, Bobbia X, Toumi M, et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care*. 2012;16(5):R188.
33. Machare-Delgado E, Decaro M, Marik PE. Inferior vena cava variation compared to pulse contour analysis as predictors of fluid responsiveness: a prospective cohort study. *J Intensive Care Med*. 2011;26(2):116-124.
34. Moretti R, Pizzi B. Inferior vena cava distensibility as a predictor of fluid responsiveness in patients with subarachnoid hemorrhage. *Neurocrit Care*. 2010;13(1):3-9.
35. Barbier C, Loubières Y, Schmitt C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med*. 2004; 30(9):1740-1746.
36. Zhao J, Wang G. Inferior vena cava collapsibility index is a valuable and non-invasive index for elevated general heart end-diastolic volume index estimation in septic shock patients. *Med Sci Monit*. 2016;22:3843-3848.
37. Byon HJ, Lim CW, Lee JH, et al. Prediction of fluid responsiveness in mechanically ventilated children undergoing neurosurgery. *Br J Anaesth*. 2013;110(4):586-591.
38. Corl K, Napoli AM, Gardiner F. Bedside sonographic measurement of the inferior vena cava caval index is a poor predictor of fluid responsiveness in emergency department patients. *Emerg Med Australas*. 2012;24(5):534-539.
39. Choi DY, Kwak HJ, Park HY, Kim YB, Choi CH, Lee JY. Respiratory variation in aortic blood flow velocity as a predictor of fluid responsiveness in children after repair of ventricular septal defect. *Pediatr Cardiol*. 2010;31(8):1166-1170.
40. Yanagawa Y, Sakamoto T, Okada Y. Hypovolemic shock evaluated by sonographic measurement of the inferior vena cava during resuscitation in trauma patients. *J Trauma*. 2007;63(6): 1245-1248.
41. Preau S, Bortolotti P, Colling D, et al. Diagnostic accuracy of the inferior vena cava collapsibility to predict fluid responsiveness in spontaneously breathing patients with sepsis and acute circulatory failure. *Crit Care Med*. 2017;45(3):e290-e297.
42. Airapetian N, Maizel J, Alyamani O, et al. Does inferior vena cava respiratory variability predict fluid responsiveness in spontaneously breathing patients? *Crit Care*. 2015;19:400.
43. Soboczyk D, Nycz K, Andruszkiewicz P. Bedside ultrasonographic measurement of the inferior vena cava fails to predict fluid responsiveness in the first 6 hours after cardiac surgery: a prospective case series observational study. *J Cardiothorac Vasc Anesth*. 2015;29(3):663-669.
44. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med*. 2004;30(9):1834-1837.
45. Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg*. 2013;117(6):1380-1392.
46. Dipti A, Soucy Z, Surana A, Chandra S. Role of the inferior vena cava diameter in assessment of volume status: a meta-analysis. *Am J Emerg Med*. 2012;30(8):1414-1419.
47. Rubinson RM, Vasko JS, Doppman JL, Morrow AG. Inferior vena cava obstruction from increased intra-abdominal pressure. Experimental hemodynamic and angiographic observations. *Arch Surg*. 1967;94(6):766-770.
48. Markou N, Grigorakos L, Myrianthefs P, et al. Venous pressure measurement in the superior and inferior vena cava: the influence of intra-abdominal pressure. *Hepatogastroenterology*. 2004;51(55):51-55.
49. Via G, Tavazzi G, Price S. Ten situations where inferior vena cava ultrasound may fail to accurately predict fluid responsiveness: a physiologically based point of view. *Intensive Care Med*. 2016; 42(7):1164-1147.
50. Zhang Z, Xu X, Ye S, Xu L. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: systematic review and meta-analysis. *Ultrasound Med Biol*. 2014; 40(5):845-853.
51. Alavi-Moghaddam M, Kabir A, Shojaee M, Manouchehrifar M, Moghimi M. Ultrasonography of inferior vena cava to determine central venous pressure: a meta-analysis and meta-regression. *Acta Radiol*. 2017;58(5):537-541.