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Review Article

DOES RESPIRATORY VARIATION IN INFERIOR VENA CAVA DIAMETER PREDICT FLUID RESPONSIVENESS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT—**Background:** The aim of fluid resuscitation is to increase stroke volume, yet this effect is observed in only 50% of patients. Prediction of fluid responsiveness may allow fluid resuscitation to be administered to those most likely to benefit. The aim of this study was to systematically review the test characteristics of respiratory variation in inferior vena cava (IVC) diameter as a predictor of fluid responsiveness in patients with acute circulatory failure. **Methods:** Electronic searches combined with reference review of identified studies. Prospective observational studies of all patient groups and ages that used a recognized reference standard, stratified participants into fluid responders and fluid non-responders, and used summary statistics to describe their results were selected for inclusion. Study design, size, setting, patient population, use of mechanical ventilation and tidal volume, definition of fluid responsiveness, fluid challenge strategy, and summary statistics were abstracted. Quality assessment was performed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) domains. **Results:** Seventeen studies involving 533 patients were included, in whom 253 (47%) were fluid responders. The pooled sensitivity and specificity for a positive IVC ultrasound as a predictor of fluid responsiveness were 0.63 (95% confidence interval [CI]: 0.56–0.69) and 0.73 (95% CI: 0.67–0.78), respectively, with a pooled area under the receiver operating characteristic curve of 0.79 (standard error 0.05). In subgroup analysis, respiratory variation in IVC diameter was a better predictor of fluid responsiveness in mechanically ventilated patients. **Conclusions:** Respiratory variation in IVC diameter has limited ability to predict fluid responsiveness, particularly in spontaneously ventilating patients. A negative test cannot be used to rule out fluid responsiveness. Clinical context should be taken into account when using IVC ultrasound to help make treatment decisions.

KEYWORDS—Circulatory failure, echocardiography, fluid therapy, resuscitation, sepsis, shock

INTRODUCTION

Fluid resuscitation is the universal initial therapy for hospitalized patients with acute circulatory failure, the most common cause for which is sepsis (1). The incidence of septic shock in adults in the United States is reported as 300 cases per 100,000 population (2), and 770 cases per 100,000 population in children (3). Sepsis accounts for 2% of all adult hospital admissions (4), and 3% of all pediatric hospital admissions (5). The mortality rate for adults with septic shock is 30% to 40% (6), and for children is 5% to 17% in industrialized countries (7, 8), and 20% to 30% in low and middle-income countries (9).The annual hospital cost for the care of adult patients with sepsis in the United States is estimated at $14 billion (10), with an additional $4.8 billion spent on children (11).

The aim of fluid resuscitation is to increase stroke volume and improve vital organ perfusion and oxygen delivery (12). Despite being commonly used, however, only about 50% of hospitalized children and adults who receive fluid resuscitation for acute circulatory failure have an associated increase in stroke volume, and are considered fluid responsive (13–20). The remainder have no increase in stroke volume, at the expense of an increase in right atrial pressure (RAP) (21). This may lead to fluid shifts into the extravascular space and cause harm through end-organ oedema and dysfunction (22, 23). Large volume fluid resuscitation and a positive net fluid balance have been associated with worsening renal function, acute respiratory distress syndrome, prolonged intensive care unit and hospital length of stay, and mortality when corrected for disease severity (22, 24–30). The importance of predicting fluid responsiveness lies in minimizing the risks of over-resuscitation with intravenous fluids in patients with acute circulatory failure (31).

Fluid responsiveness is defined as an increase in stroke volume of >10% following a fluid challenge (32). A fluid

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challenge may be an intravenous bolus of 500 mL (10 mL/kg) of fluid, or a passive leg raise (PLR) test. The fluid content used may be a crystalloid or colloid, both have similar immediate hemodynamic effects (33). The PLR test uses an autotransfusion of venous blood pooled in the legs that can be ''withdrawn'' at the end of the test by lowering the legs, and has a global area under the receiver operating characteristic curve (AUROC) of 0.95 (95% confidence interval [CI]: 0.92–0.97) for predicting fluid responsiveness in adults, using fluid challenge as a gold standard (34).

Respiratory variation in inferior vena cava (IVC) diameter has been reported as a noninvasive, easily obtained measure that may be used to predict fluid responsiveness in multiple patient settings (35). IVC ultrasound has the advantage over other measures of fluid responsiveness that it is noninvasive, inexpensive, widely available, can be obtained with minimal training, and can be combined with ultrasound of the heart and lungs to give a complete sonographic picture of any individual patients underlying physiology (36).

Systematic reviews of respiratory variability in IVC diameter as a predictor of fluid responsiveness have been variable in their methodology and conclusions. Mandeville and Colebourn identified two studies involving 62 patients using change in IVC diameter as an index test for predicting fluid responsiveness (37). Heterogeneity precluded meta-analysis. Zhang et al. (38) identified 8 studies involving 235 patients examining respiratory variation in IVC diameter to predict fluid responsiveness. Despite heterogeneity in the patient populations, definition and measurement technique for defining fluid responsiveness, volume of fluid challenge, predictive test used, and threshold change in IVC diameter, the pooled AUROC was calculated as 0.84 (95% CI: 0.79–0.89). Several subsequent original articles have questioned the predictive ability of IVC ultrasound.

The aim of this review is to systematically review the test characteristics of respiratory variation in IVC diameter as a predictor of fluid responsiveness.

Target condition being diagnosed

Fluid responsiveness in hospitalized patients with acute circulatory failure—Acute circulatory failure may be caused by relative or real hypovolaemia, cardiac dysfunction, and maldistribution of intravenous fluid (1). Patient groups with acute circulatory failure that may be administered fluid resuscitation include those with acute fluid or blood loss, sepsis, cardiomyopathy, valvular heart disease, myocarditis, cardiac tamponade, or anaphylaxis.

Index test

IVC volume (diameter) changes with respiration occur due to cyclic changes in venous return as intrathoracic pressure, and thus RAP, fluctuates over the respiratory cycle (39). Change in IVC diameter has been studied in both spontaneously ventilating patients, using the decrease in diameter during inspiration (termed collapsibility index), and mechanically ventilated patients, using the increase in diameter during positive pressure ventilation (termed distensibility index) (40, 41). A collapsing IVC during inspiration in spontaneously ventilating patients, or a distending IVC during inspiration in mechanically ventilated patients is thought to predict fluid responsiveness.

Inferior vena cava ultrasound is performed using a low-frequency (2–5 MHz) curved array transducer and a subxiphoid view. Using the liver as an acoustic window, a long-axis view of the IVC including the right atrial (RA) junction and the confluence of the hepatic veins is obtained. The measurement of IVC diameter is taken 1 cm caudal to the confluence of the hepatic veins. In this location, M-mode measurement may be inaccurate due to motion artefact and a 2D view is preferred. Measurement near the IVC-RA junction may be in-accurate due to diaphragmatic contraction in spontaneously ventilating patients (42). Criteria for a positive test are different for mechanically ventilated and spontaneously ventilating patients, with distention of the IVC >12%–18% in the former or collapse of >40%–50% in the latter considered predictive of fluid responsiveness (36).

Clinical pathway

Published international consensus guidelines universally recommend fluid resuscitation as the initial therapy for acute circulatory failure (43–47). Assessment for volume responsiveness prior to fluid resuscitation is recommended in some international guidelines (48).

Alternative tests

Multiple devices allow fluid responsiveness to be predicted based on dynamic heart-lung interactions (49–52). The majority of these, however, are invasive, require the patient to be mechanically ventilated with large tidal volumes, not spontaneously triggering the ventilator, and in sinus rhythm. Only 5% of the intensive care unit (ICU) population meet these criteria (53), and an even smaller percentage in the emergency department (ED).

Systematic reviews of noninvasive or minimally invasive cardiac output monitors in adults and children highlight the heterogeneity in precision of both index and reference techniques, study methodology, and reporting (54–57). The gold standard for static measurement of cardiac output is by thermodilution using a pulmonary artery catheter. This has been associated with complications from placement (58) and questionable impact on clinical outcome (59), and is therefore not routinely used in clinical practice. Trans-pulmonary thermodilution (TPTD) requires central venous catheterization and a thermistor-tipped arterial line, and has become the ''practical'' gold standard for static measurement of cardiac output (57). Minimally invasive methods for predicting fluid responsiveness, such as stroke volume variation (SVV), are derived from pulse contour analysis (PCA) of the waveform from a peripheral arterial cannula during mechanical ventilation (52). Though less invasive than TPTD, PCA seems to be less reliable in low systemic vascular resistance (SVR) states and does not track changes in stroke volume accurately (55). Bioreactance (BR) is a completely noninvasive method for continuously monitoring cardiac output using the phase-shift of voltage across the thorax due to pulsatile aortic blood flow (55). BR requires minimal operator training to perform, is accurate at tracking changes in stroke volume over time, but less reliable

for measuring static values for cardiac output (60). Transthoracic echocardiography (TTE) uses a low-frequency (2–4 MHz) phased-array transducer to noninvasively measure stroke distance through an apical 5-chamber view of the heart, which may be used to derive stroke volume (using left ventricular outflow tract diameter), cardiac output (by multiplying with heart rate), and cardiac index (by dividing with body-surface area) (36).

Rationale

Respiratory variation in IVC diameter is a noninvasive, rapidly available, and easily measured index that may be used in multiple patient settings to predict fluid responsiveness. During the initial resuscitation of patients with acute circulatory failure, it may be a useful tool for assisting with clinical decision making. A positive result would be a reasonable indication to administer fluid, while a negative result may prompt the use of other hemodynamic therapies, such as inotrope of vasopressor infusion. This may reduce harm from excessive fluid resuscitation (23).

OBJECTIVES

To systematically review the evidence for respiratory variation in IVC diameter as a predictor of fluid responsiveness.

Secondary objectives

The impact of positive pressure ventilation will be evaluated in subgroup analysis.

MATERIALS AND METHODS

Criteria for considering studies for this review

Types of studies—Prospective observational studies that used a recognized reference standard for measuring change in cardiac output after a fluid challenge, stratified participants into fluid responders and fluid non-responders, and used summary statistics to describe the association between IVC ultrasound and fluid responsiveness. Only studies published in English in peer-reviewed journals were included.

Participants

Studies involving participants of any age, sex, and diagnosis who were receiving a fluid challenge for acute circulatory failure during their hospitalization, were considered for inclusion. Studies involving both mechanically ventilated and spontaneously ventilating patients were included. Studies taking place in any hospital setting were included.

Index tests

Studies of IVC ultrasound using a variety of techniques and measurements were included. It was expected that the site of IVC measurement and the reporting method to describe IVC collapsibility or distensibility would vary between studies. The timing of IVC ultrasound to the time of fluid challenge was deemed acceptable if less than 30 min.

Target conditions

Studies reporting change in stroke volume, stroke index, cardiac output, or cardiac index following a fluid challenge were included. Heterogeneity in defining fluid responsiveness was expected and therefore no threshold value for inclusion was set *a priori*.

Reference standards

Changes in stroke volume using TPTD, TTE, PCA, and BR were considered reference standards for this review. TPTD has a reported precision of ±10% (61). Newer technologies for measuring stroke volume are compared using bias and precision statistics (62), which provide a mean difference (bias) between paired measurements. Limits of agreement (LOA) may be expressed as percentage error (proportion of the mean CO), and are considered acceptable if <30% (63). Compared with TPTD, TTE has a bias of 0.8 L/min (95% CI: 0.14–3.04), with LOA 3.4 ± 1.27 L/min (63). Compared with TPTD, PCA has LOA 0.32 ± 0.64 L/min, with a percentage error of 33% to 41% (54, 56). Compared with TPTD, BR has a bias of 0.16 L/min, with LOA of 1.04 L/min with a relative error of 9% (54, 64).

Search methods for identification of studies

Electronic searches—A search strategy based on methods outlined in The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy was performed to identify clinical studies evaluating the association between respiratory variation in IVC diameter and fluid responsiveness (http://methods.cochrane.org/sdt/handbook-dta-reviews). The study protocol was registered prospectively on PROSPERO. The Cochrane Database for Systematic Reviews, National Institute for Health and Care Excellence (NICE), National Institute for Health Research (NIHR), and Health Technology Assessment (HTA) were searched for existing reviews using the following search terms: fluid resuscitation, and inferior vena cava. Medline (1946–) and EmBase (1974–) and were searched using the medical subject headings (MeSH) ''fluid therapy'' and ''inferior vena cava.''

Searching other resources—Citation review of relevant primary and review articles was performed. Conference abstracts, review articles, non-English studies, and non-human studies were excluded.

Data collection and analysis

The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy guidelines were followed.

Selection of studies

Study eligibility and quality assessment—All abstracts from the initial search were checked for relevance (EL). After abstracts had been screened, full papers were retrieved for all remaining articles (EL, FEB). Disagreements regarding study eligibility were resolved by a third party (TD).

Data extraction and management—Data were abstracted on study design, study size, study setting, patient population, use of mechanical ventilation and tidal volume, definition of fluid responsiveness, fluid challenge strategy, and the correlation coefficient and/or receiver operating characteristic between the baseline IVC and the change in stroke volume after a fluid challenge.

Assessment of methodological quality—Included studies were evaluated for the design and reporting quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) domains (65). In addition to the 11 standard domains, the following were added: ''clearly defined positive test,'' intra-observer variation reported/acceptable,'' and ''sponsoring precluded.'' Studies were classified at low risk of bias if the answers to all signalling questions for each of the four domains were positive. Studies were classified at high risk of bias if at least one answer was unclear or negative (66, 67).

Statistical analysis and data synthesis—Abstracted summary statistics were pooled and reported as sensitivity, specificity, positive and negative likelihood ratio (PLR, NLR), and diagnostic odds ratio (68). A random-effects model was used to determine the pooled AUROC using the method of DerSimonian and Laird (69). Subgroup analysis was performed using mechanical ventilation as a moderating variable. All statistical analyses were performed using STATA 14 (College Station, Tex). Statistical significance was considered when two-tailed $P < 0.05$.

Investigations of heterogeneity—Heterogeneity was expected to be significant due to differences in patient and disease cohorts, study setting, variation in calculation and threshold values for change in IVC diameter, and variation in the reference standard used and threshold value for defining fluid responsiveness. Heterogeneity was evaluated using Q and I^2 tests, and considered significant when $Q < 0.1$ and $I^2 > 50\%$.

Sensitivity analysis—Sensitivity analysis, excluding studies deemed unclear or high risk of bias, was performed.

Assessment of reporting bias—Reporting bias was assessed using funnel plot asymmetry (70).

RESULTS

Results of the search

Two hundred and ninety-nine published studies were identified using database searches and an additional 13 identified

using citation review. After duplicates were removed, 312 potentially relevant studies were screened based on title and abstract. Of these, 42 full manuscripts were screened for eligibility, 17 of which met inclusion criteria (Fig. 1) (14, 71–86).

Methodological quality of included studies

Characteristics of included studies are summarized in Table 1. Two studies were performed in the ED setting, 3 in the operating room (OR), and 12 in ICU. Three included only children <18 years of age, the remainder included adults only. Eleven included mechanically ventilated patients only, five included non-ventilated patients only, and in one study the ventilatory status was unclear. No studies included both mechanically ventilated and non-ventilated patients. Threshold values for IVC distensibility/collapsibility index varied by study, as did the site of IVC measurement, fluid challenge volume, and content. The reference standard tests were most commonly stroke volume/stroke volume index or cardiac output/cardiac index measured using TTE, with fluid responsiveness defined most commonly as an increase in the reference standard test of >10%–15% following fluid challenge.

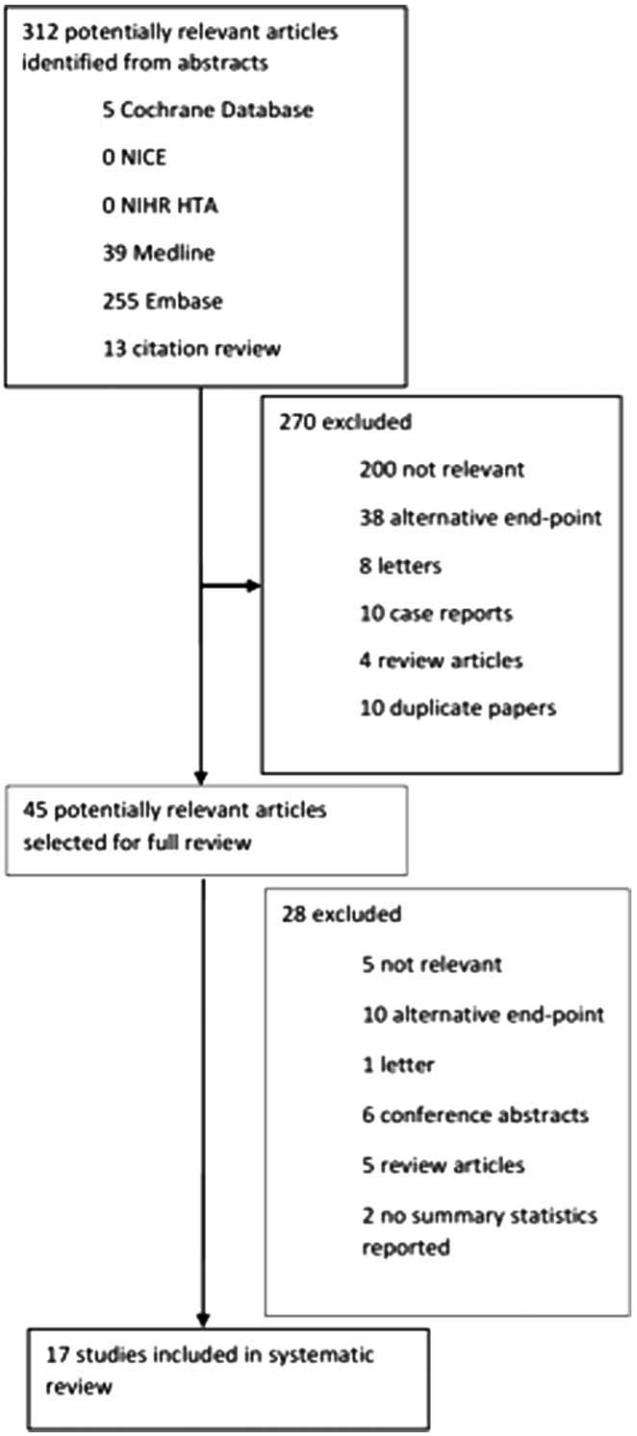

FIG. 1. **Flow chart for study selection.** HTA indicates Health Technology Assessment; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health Research.

Quality assessments using the QUADAS-2 domains are summarized in Table 2.

All studies met the predefined disease and patient spectrum criteria, had acceptable delays between index and reference tests, performed the index and reference test in all included patients, used a reference test that was independent of the index test, had all clinically relevant information available at the time of testing, and clearly defined criteria for positive index and reference tests (Fig. 2). One study used an increase in systolic blood pressure as a reference standard. Overall there was poor reporting of blinding for the index and reference tests and poor reporting of uninterpretable tests. Inter and intra-observer variability in the index test and reference test was calculated and reported in 42% of included studies.

Findings

Overall, 533 patients were included in this review, of whom 253 (47%) were fluid responsive (Table 3). The mean threshold value for a positive IVC distensibility index was 16% and for collapsibility index was 42%.

The overall pooled sensitivity and specificity of respiratory variation in IVC diameter for predicting fluid responsiveness were 0.63 (95% CI 0.56–0.69) and 0.73 (95% CI 0.67–0.78), respectively (Table 4). The overall DOR was 7.41 (95% CI 3.02–18.22). Respiratory variation in IVC diameter performed better diagnostically in mechanically ventilated patients compared with spontaneously ventilating patients (DOR 7.51 [95% CI 1.89–29.87] vs. 5.45 [95% CI 1.87–15.89]). Four studies did not include patient level data and could not be included in the calculation of pooled summary statistics (14, 74, 76, 84).

The pooled overall AUROC was 0.79 (standard error [SE] 0.05) (Fig. 3). For studies including only mechanically ventilated patents, the pooled AUROC was 0.79 (SE 0.08), and for studies including only spontaneously ventilating patients was 0.76 (SE 0.08).

Heterogeneity between studies was assessed with an overall $Q = 0.73$ and $I^2 = 75\%$. Sensitivity analysis was not possible because all included studies met predefined criteria for high risk of bias. Funnel plot asymmetry was evident, with reporting bias favoring small studies with positive results.

Due to significant between-study heterogeneity, analysis of patient sub-groups that were not specified *a priori* was performed. Exclusion of studies involving children (14, 74, 83) yielded a pooled sensitivity of 0.64 (95% CI: 0.57–0.71), specificity of 0.76 (95% CI: 0.69–0.81), PLR of 2.63 (95%

Table 1. **Characteristics of included studies**

Study	Population	Setting	Patient group	Mechanical Ventilation	Tidal Volume (mL/kg)	Fluid challenge content	Fluid challenge volume	Reference standard device	Reference standard measurement	Reference standard threshold	ΔIVC (%) threshold
Airapetian 2015	Adults	ICU	Mixed	No	n/a	0.9% Saline	500 mL	TTE	SV	>10%	42
Barbier 2004	Adults	ICU	Sepsis	Yes	8.5	HES	7 mL/kg	TTE	CI	>15%	18
Brun 2013	Adults	OR	Severe pre-eclampsia	Unclean	n/a	0.9% saline	500 Ml	TTE	SVi	>15%	Not reported
Byon 2013	Children	OR	Neurosurgical	Yes	10	HES	10 mL/kg	TTE	SVi	>10%	Not reported
Charbonneau 2014	Adults	ICU	Sepsis	Yes	8–10	HES	7 mL/kg	TTE	CI	>15%	21
Corl 2012	Adults	ED	Mixed	No	n/a	PLR	PLR	BR	CI	>10%	Not reported
Choi 2010	Children	ICU	Cardiac	Yes	10	HES	10 mL/kg	TTE	SV	>15%	Not reported
de Oliveira 2016	Adults	ICU	Surgical	Yes	8	0.9% saline	500 Ml	TTE	VTI	>15%	16
de Valk 2014	Adults	ED	Mixed	No	n/a	0.9% saline	500 mL	NIV BP	SBP	>10mmHg	36.5
Feissel 2004	Adults	ICU	Sepsis	Yes	8-10	HES	8 mL/kg	TTE	CO	>15%	12
Lanspa 2013	Adults	ICU	Sepsis	No	n/a	Crystalloid	10 mL/kg	TTE	CI	>15%	50
Machare-Delgado 2011	Adults	ICU	Mixed	Yes	8.6	0.9% saline	500 mL	TTE	SVi	>10%	12
Muller 2012	Adults	ICU	Mixed	No	n/a	HES	500 mL	TTE	SV	>15%	40
Moretti 2010	Adults	OR	SAH	Yes	8	HES	7 mL/kg	TPTD	CI	>15%	16
Sobczyc 2016	Adults	ICU	Cardiac	Yes	8	0.9% saline	250 mL	TTE	CO	>15%	18
Theerawit 2016	Adults	ICU	Sepsis	Yes	8	HES	500 mL	PCA	CO	>15%	10
Weber 2015	Children	ICU	Mixed	Yes	7.9	HES	10 mL/kg	TTE	SVi	>10%	Not reported

BR indicates bioreactance; CI, cardiac index; CO, cardiac output; ED, emergency department; HES, hydroxyethyl starch; ICU, intensive care unit; NIV BP, noninvasive blood pressure; OR, operating room; PLR, passive leg raise; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SV, stroke volume; SVi, stroke volume index; TPTD, transpulmonary thermodilution; TTE, transthoracic echocardiogram.

Table 2. **Quality assessment of included studies using QUADAS-2 domains**

Study	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?	Clinical review acceptable?	Uninterpretable results reported?	Withdrawals explained?	Clearly defined positive test?	Intra-observer variation reported/ acceptable?	Sponsoring precluded?
Airapetian 2015	y	y	y	y	y	y	n	n	y	u	u	y	y	y
Barbier 2004	y	y	y	y	y	y	y	n	y	u	y	y	y	u
Brun 2013	y	y	y	y	y	y	n	n	y	u	y	y	y	u
Byon 2013	y	y	y	y	y	y	n	n	y	u	y	y	u	y
Charbonneau 2014	y	y	y	y	y	y	u	u	y	u	n	y	y	y
Corl 2012	y	y	y	y	y	y	y	y	y	u	n	y	u	y
Choi 2010	y	y	y	y	y	y	n	n	y	u	n	y	y	u
de Oliveira 2016	y	y	y	y	y	y	n	u	y	n	y	y	n	n
de Valk 2014	y	n	y	y	y	y	n	n	y	u	y	y	u	y
Feissel 2004	y	y	y	y	y	y	u	n	y	u	u	y	y	u
Lanspa 2013	y	y	y	y	y	y	u	y	y	u	u	y	u	u
Machare-Delgado 2011	y	y	y	y	y	y	n	u	y	n	y	y	u	y
Moretti 2010	y	y	y	y	y	y	n	y	y	u	y	y	y	u
Muller 2012	y	y	y	y	y	y	n	n	y	u	u	y	y	y
Sobczyc 2016	y	y	y	y	y	y	u	u	u	u	u	y	n	y
Theerawit 2016	y	y	y	y	y	y	u	u	y	u	u	y	y	u
Weber 2015	y	y	y	y	y	y	u	u	y	u	u	y	u	u

n indicates no; u, unclear; y, yes.

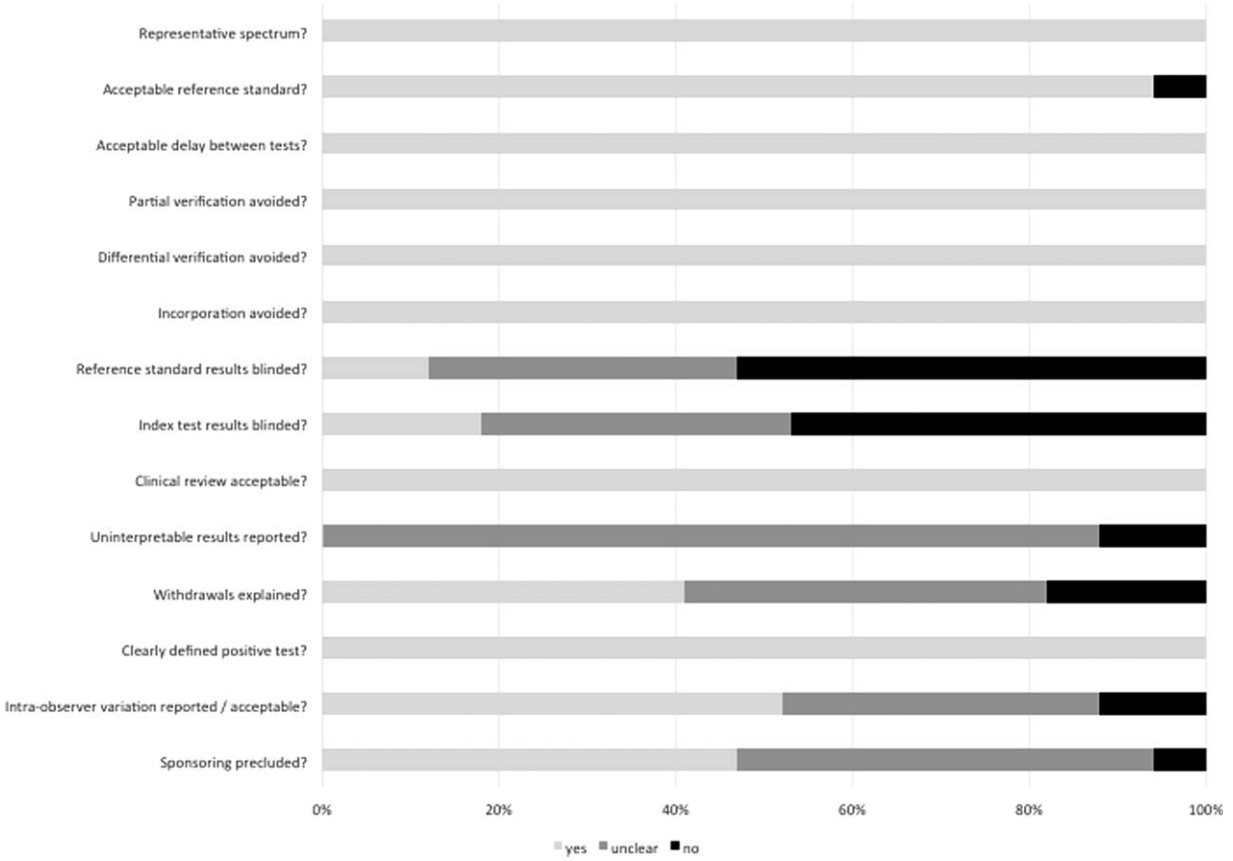

FIG. 2. **Methodological quality graph using QUADAS-2 domains.**

CI: 1.72–4.02), NLR of 0.42 (95% CI: 0.27–0.63), DOR of 9.35 (95% CI: 4.08–21.43), and AUROC of 0.81 (SE: 0.05). Inclusion of studies involving only patients with sepsis (72, 75, 77, 78, 86) yielded a pooled sensitivity of 0.65 (95% CI: 0.53–0.76), specificity of 0.79 (95% CI: 0.68–0.88), PLR of 3.24 (95% CI: 1.26–8.35), NLR of 0.32 (95% CI:0.12–0.89), DOR of 12.98 (95% CI: 1.87–89.73), and AUROC of 0.85 (SE: 0.09).

Summary of main results

This systematic review found that overall, respiratory variation in IVC diameter performs moderately well in predicting fluid responsiveness, with a pooled AUROC of 0.79 (SE 0.05). A positive IVC ultrasound is moderately predictive of fluid responsiveness, with a pooled specificity of 0.73 (95% CI: 0.67–0.78). A negative IVC ultrasound, however, could not be

TABLE 3. **Sensitivity and specificity of respiratory variation in inferior vena cave diameter in predicting fluid responsiveness**

Study	Number of included patients	Fluid responders (%)	TP	FP	FN	TN	Sens (%)	Spec (%)	AUROC (95% CI)
Airapetian 2015	59	29 (49)	9	1	20	29	31	97	0.62 (0.49–0.74)
Barbier* 2004	20	10 (50)	9	1	1	9	90	90	0.91 (0.84–0.98)
Brun 2013	23	12 (52)	6	3	6	8	50	73	0.57 (0.32–0.82)
Byon* 2013	33	15 (45)							0.37 (0.16–0.58)
Charbonneau* 2014	44	26 (59)	10	7	16	11	38	61	0.43 (0.25–0.61)
Choi* 2010	21	11 (52)							0.85 (0.69–1.0)
Corl 2012	26	8 (31)							0.46 (0.21–0.71)
de Oliveira 2016	20	9 (45)					67	100	0.84 (0.63–1.00)
deValk 2014	45	12 (26)	10	11	2	22	83	67	0.741
Feissel* 2004	39	16 (41)	13	1	3	22	81	96	
Lanspa 2013	14	5 (36)	5	3	0	6			0.83 (0.58–1.0)
Machare-Delgado* 2011	25	8 (32)	8	8	0	9	100	53	0.81 (0.64–0.99)
Moretti* 2010	29	17 (59)	12	0	5	12	71	100	0.90 (0.73–0.98)
Muller 2012	40	20 (50)	14	3	6	17	70	84	0.77 (0.60–0.88)
Sobczyc 2016	35	24 (68)	14	10	3	8	82	72	0.74
Theerawit 2016	29	16 (55)	11	3	5	10	75	77	0.67 (0.48–0.89)
Weber* 2015	31	15 (48)	7	10	8	6	0.47	0.37	0.50 (0.29–0.71)

*Studies involving mechanically ventilated patients.

AUROC indicates area under the receiver operator characteristics curve; CI, confidence interval. Blank data fields indicate no available data; FN, false negative; FP, false positive; sens, sensitivity; spec, specificity; TN, true negative; TP, true positive.

Table 4. **Pooled diagnostic accuracy for respiratory variation in inferior vena cava diameter in predicting fluid responsiveness**

	Overall	Mechanical ventilation	Not ventilated
AUROC (SE)	0.79 (0.05)	0.79 (0.08)	0.76 (0.08)
Sensitivity (95% CI)	0.63 (0.56–0.69)	0.67 (0.58–0.75)	0.52 (0.42–0.62)
Specificity (95% CI)	0.73 (0.67–0.78)	0.68 (0.60–0.76)	0.77 (0.68–0.84)
PLR (95% CI)	2.35 (1.52–3.64)	0.21 (1.16–3.97)	2.33 (1.40–3.86)
NLR (95% CI)	0.47 (0.32–0.70)	0.43 (0.23–0.81)	0.60 (0.39–0.92)
DOR (95% CI)	7.41 (3.02–18.22)	7.51 (1.89–29.87)	5.45 (1.87–15.89)

AUROC indicates area under the receiver-operator characteristics curve; CI, confidence interval; DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio; SE, standard error; sens, sensitivity; spec, specificity.

used to rule out fluid responsiveness, with a pooled sensitivity of 0.63 (0.56–0.69). The test characteristics of respiratory variation in IVC diameter are better in mechanically ventilated patients compared with spontaneously ventilating patients. Subgroup analysis excluding pediatric studies or including only studies in patients with sepsis did not yield significantly different pooled test characteristics.

Heterogeneity in the included studies was apparent in a high Cochrane Q test and I^2 index (0.73 and 75%, respectively). Heterogeneity was evident in the patient population (age, illness spectrum, clinical setting, ventilatory status), in reference tests used (TPTD, TTE, BR), in index test characteristics (where the IVC diameter was measured, what index test was used, what volume and fluid was used for a fluid challenge, and the threshold for a positive test). No standard method has been widely accepted for performing or reporting IVC ultrasound in research or clinical settings, which makes comparing results between studies problematic. Of particular concern are the contribution of imprecision of all reference standard tests, and inter/intra-observer variability in the index test. The ''practical'' gold standard test for monitoring changes in stroke volume is TPTD (57), with a precision of ±10% (61). If a positive response to a fluid challenge is considered an increase in stroke volume of >10%, this may occur due to imprecision of the reference standard alone regardless of the ''true'' change in stroke volume following a fluid challenge. In addition, all intermittent cardiac output monitoring devices need to be used both before and after the administration of a fluid challenge to monitor for change in stroke volume, thus doubling the risk of device imprecision contributing to any observed effect. Continuous cardiac output monitors may benefit from having the same bias in the same direction for all measurements, which may improve their ability to track changes in cardiac output despite limited precision in measuring absolute values. Inter/intra-observer variability in measuring respiratory variation in IVC diameter also contributes to the limitations of this test in predicting fluid responsiveness. When reported, inter and intra-observer variability in IVC diameter measurement were 1.5% to 8% and 6.2% to 9%, respectively (14, 73, 75, 77, 81, 82). In a research setting, where thresholds for positive and negative tests are enforced, this variability may create a ''gray zone'' around the threshold value where it is unclear whether the index test is truly positive or negative (87).

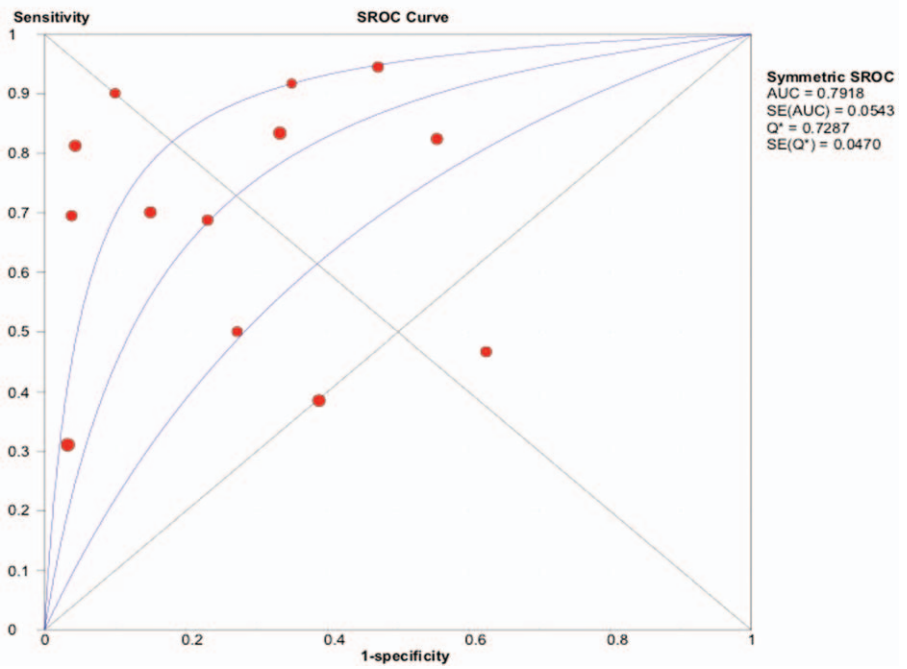

Fig. 3. **Pooled area under the receiver operator characteristics (AUROC) curve for respiratory variation in inferior vena cava diameter as a predictor of fluid responsiveness.** Each dot represents a separate study.

The limitations of respiratory variation in IVC diameter to predict fluid responsiveness may be explained through closer examination of the included study characteristics, and underlying pathophysiologic factors influencing IVC diameter. Respiratory variation in IVC diameter is determined by venous compliance, right atrial pressure, and the amplitude of intrathoracic pressure changes with respiration. Increased venous compliance (e.g., venoplegia in sepsis, hypovolaemia), a low RAP (e.g., hypovolaemia), or increased amplitude of intrathoracic pressure changes with respiration (e.g., increased respiratory effort) will increase respiratory variability in IVC diameter independent of fluid responsiveness. Likewise, decreased venous compliance (e.g., venoconstrictor infusion, abdominal compartment syndrome), a high RAP (e.g., right ventricular diastolic dysfunction, pericardial tamponade, tension pneumothorax, gas trapping, high positive end-expiratory pressure, restrictive pericarditis), or decreased amplitude of intrathoracic pressure changes with respiration (e.g., poor respiratory effort, low tidal volume ventilatory strategy, open chest) will decrease respiratory variability in IVC diameter independent of fluid responsiveness (88). These limitations may explain the poor test characteristics of respiratory variation in IVC diameter in predicting fluid responsiveness, particularly in spontaneously ventilating patients with uncontrolled and variable intrathoracic pressure changes during respiration. As such, the clinical context in which IVC ultrasound is performed has a large bearing on the result of the test, and needs to be taken into account when interpreting the result and making treatment decisions.

The primary clinical utility of respiratory variability in IVC ultrasound as a predictor of fluid responsiveness is in settings where no invasive monitoring is available. Other methods for predicting fluid responsiveness may be used when central venous access and arterial access have been obtained, or when trans-oesophageal echocardiography is available (55). This is especially pertinent in the ED, where treatment for acute circulatory failure is often initiated, and fluid resuscitation is the initial therapy. Based on the results of this systematic review, however, respiratory variation in IVC diameter in spontaneously ventilating patients has significant limitations that need to be taken into account when applying it as a predictive test for fluid responsiveness. In spontaneously ventilating patients, a positive IVC ultrasound may be used in clinical context to predict fluid responsiveness, with a pooled specificity of 0.77 (95% CI 0.68–0.84). A negative IVC ultrasound, however, cannot be used to rule out fluid responsiveness, with a pooled sensitivity of 0.52 (95% CI 0.42–0.62).

Across all studies included in this systematic review, in all settings and ages, only 47% of patients were found to be fluid responsive. Half of the patients treated with fluid resuscitation had no resulting increase in cardiac output, and may have been harmed by this intervention. It seems logical, therefore, that prior to administering fluid resuscitation, all patients should be assessed for fluid responsiveness. IVC ultrasound may have a role in this assessment, though contextual information seems necessary in interpreting this test, and in weighing the potential benefits and risks of fluid resuscitation for the individual patient.

Strengths and weaknesses of the review

This systematic review included a wide range of study participants, study settings, reference tests, and reporting methods for validating the index test. This increases the generalizability of the study findings. The large degree of heterogeneity, however, limited the ability of included studies to be compared. All included studies met predefined criteria for high risk of bias, precluding sensitivity analysis. Reporting bias potentially skewed the pooled results in favor of IVC ultrasound as a predictor of fluid responsiveness.

Applicability of findings to the review question

The findings of this systematic review were directly applicable to the review question, helping to clarify the role of respiratory variation in IVC diameter in determining fluid responsiveness.

CONCLUSIONS

Implications for practice

Respiratory variation in IVC diameter is moderately predictive of fluid responsiveness. A negative test cannot be used to rule out fluid responsiveness. Its clinical utility, particularly in spontaneously ventilating patients, is limited and should be interpreted in clinical context.

Implications for research

Standardization of the location, method, and threshold values for positive test would make comparison between studies easier. Future research may involve the use of respiratory variation in IVC diameter in combination with sonographic examination of the heart and lungs to guide fluid resuscitation in acute illness.

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