Journal of Critical Care 41 (2017) 130–137

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically-ill patients

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ARTICLE INFO

Keywords:
Inferior vena cava collapsibility
Fluid responsiveness
Point-of-care ultrasound
Spontaneously breathing

ABSTRACT

Purpose: Measurement of inferior vena cava collapsibility (cIVC) by point-of-care ultrasound (POCUS) has been proposed as a viable, non-invasive means of assessing fluid responsiveness. We aimed to determine the ability of cIVC to identify patients who will respond to additional intravenous fluid (IVF) administration among spontaneously breathing critically-ill patients.
Methods: Prospective observational trial of spontaneously breathing critically-ill patients. cIVC was obtained 3 cm caudal from the right atrium and IVC junction using POCUS. Fluid responsiveness was defined as a ≥ 10% increase in cardiac index following a 500 ml IVF bolus; measured using bioreactance (NICOM™, Cheetah Medical). cIVC was compared with fluid responsiveness and a cIVC optimal value was identified.
Results: Of the 124 participants, 49% were fluid responders. cIVC was able to detect fluid responsiveness: AUC = 0.84 [0.76, 0.91]. The optimum cutoff point for cIVC was identified as 25% (LR + 4.56 [2.72, 7.66], LR- 0.16 [0.08, 0.31]). A cIVC of 25% produced a lower misclassification rate (16.1%) for determining fluid responsiveness than the previous suggested cutoff values of 40% (34.7%).
Conclusion: IVC collapsibility, as measured by POCUS, performs well in distinguishing fluid responders from non-responders, and may be used to guide IVF resuscitation among spontaneously breathing critically-ill patients.

1. Introduction

Assessing fluid responsiveness is key to the successful resuscitation of critically-ill patients. While under-resuscitation is associated with worse clinical outcomes [1], there is a growing body of evidence that over-resuscitation may be harmful to patients with septic shock [2] and the acute respiratory distress syndrome [3]. As physicians re-examine the paradigm of aggressive intravenous fluid (IVF) resuscitation, there are calls for an individualized, evidence-based, IVF resuscitation strategy [4,5].

Despite the prevailing practice of early and aggressive IVF resuscitation in critically-ill patients, only 50% of patients will respond to an IVF bolus with an increase in their cardiac index [6-8]. Traditional methods of assessing fluid status, such as vital signs and physical examination, do not reliably identify fluid responders [9,10]. The use of a pulmonary artery catheter (PAC) is invasive, exposes patients to potential harm, and has questionable efficacy [11]. The Non-Invasive Cardiac Output Measurement device (NICOM™) offers an alternative to the PAC. NICOM has been validated against the PAC in multiple studies [12-14] and produces comparable hemodynamic data when compared to stroke volume variation [15]; however, its clinical use is limited to resource-rich practice environments. Consequently, an accurate, adaptable non-invasive alternative to help guide the IVF resuscitation of critically-ill patients is needed.

Emergency and critical care physicians have readily adopted point-of-care ultrasound (POCUS) for a spectrum of diagnostic and therapeutic uses [16-18]. Proficiency with POCUS among clinicians can be established with limited additional training [19,20], and the accuracy of POCUS has been demonstrated in multiple domains [21-23]. If a sonographic method of determining fluid responsiveness is shown to be valid, POCUS could obviate the need for other invasive or non-invasive methods.

POCUS can estimate central venous pressure (CVP) [24]; however, CVP is a static measure of volume status and has little clinical value in guiding the resuscitation of critically-ill patients [25]. Measurement of

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http://dx.doi.org/10.1016/j.jcrc.2017.05.008
0883-9441/

the collapsibility of the inferior vena cava (cIVC) during respiration, also known as the caval index, has been proposed as a non-invasive means to measure a patient's response to an IVF volume challenge or following a passive leg raise (PLR). Research has demonstrated that cIVC can be used to predict fluid responsiveness in mechanically ventilated patients (receiving tidal volumes of 10 ml/kg) [26-28]. However, evidence supporting the use of cIVC in spontaneously breathing critically-ill patients has been limited to smaller trials [29-31]. In 2016, the Society of Critical Care Medicine (SCCM) released updated guidelines for the use of POCUS in the evaluation of critically-ill patients. With a lack of robust evidence, the guideline panel was unable to make a recommendation for or against the use of cIVC among spontaneously breathing patients [23]. Despite this absence, the 2015 Surviving Sepsis Campaign bundle calls for an assessment of patient volume status and suggests POCUS as a clinical option [32]. Many emergency physicians and intensivists have already adopted the practice of using POCUS to guide IVF resuscitation (with or without an IVF challenge or PLR) among spontaneously breathing critically-ill patients into their practice [33,34] despite the limited evidence.

The primary aim of this study was to assess the ability of cIVC to detect fluid responsiveness among spontaneously breathing critically-ill patients undergoing resuscitation, as measured using NICOM. Secondary aims were to establish an optimum cutoff value for cIVC, compare this value to previously suggested cutoffs, and determine if incorporating a PLR with cIVC assists in detecting fluid responsiveness.

2. Methods

2.1. Study setting and population

This prospective observational investigation was performed in the emergency departments and medical intensive care units (ICUs) of two urban adult academic hospitals in the United States. From August 2014 until July 2016, we enrolled a convenience sample of spontaneously breathing patients with signs of acute circulatory failure being admitted to the ICU. Patients were enrolled within 36 h of presentation to the emergency department during the resuscitative phase of care. Acute circulatory failure was defined as hypotension (systolic blood pressure < 90 mmHg, or a mean arterial pressure < 65 mmHg for ≥30 min); decreased urine output (<0.5 ml/kg/h); persistent tachycardia (heart rate > 120 bpm for ≥30 min); and/or serum markers suggesting organ hypo-perfusion (acidosis with a serum pH < 7.3 or lactic acid >2 meq/l) as previously described by Muller et al. and Airapetian et al. [29,30]. Exclusion criteria were primary traumatic, cardiogenic, obstructive, or neurogenic shock; age < 18 years old; incarceration; pregnancy; and/or hospitalization for >36 h. Patients also were excluded if they were receiving non-invasive positive pressure ventilation, if the clinical team felt that they had active pulmonary edema, or that believed that further IVFs might pose a clinical risk. The local institutional review board approved the study protocol (204,814 45CFR 46.110), and all patients or their surrogates gave written consent prior to study involvement.

2.2. Study protocol

Following enrollment, the NICOM™ (Cheetah Medical, Tel Aviv, Israel) device leads were applied to the study participant according to manufacturer specifications. The patient's cardiac index was recorded at one-minute intervals throughout the study. Patients were placed supine for a three-minute NICOM calibration period. Following NICOM calibration, two baseline ten-second videos of the IVC were recorded one minute apart. A three-minute PLR was performed, after which the research sonographer recorded a 10-s IVC video. The patient was then returned to the supine position for a minimum of 3 min. Finally, a 500 ml normal saline fluid bolus was administered with the assistance of a pressure bag through the participant's largest gauge IV. Immediately upon completion of the fluid bolus, a single ultrasound video of the IVC was repeated. If a participant's clinical condition required vasopressors, they were held at a constant rate throughout the study.

2.3. Measurements

Fluid responsiveness was defined as a ≥ 10% increase in cardiac index following an IVF bolus as measured by NICOM [35]. IVC POCUS was performed using a Sonosite Edge (Bothell, WA) by one of three study physicians (AL, KC, and NG) who had completed residency, fellowship, or post fellowship training that included POCUS [21]. Ultrasound images of the IVC were obtained in a subcostal long axis view with a low frequency (1–5 Hz) phased array probe. Measurements were recorded throughout the native respiratory cycle, study participants were not asked to take a deep inspiratory breath. The junction of the IVC and the right atrium and/or presence of hepatic veins were assessed to differentiate the aorta from the IVC. Images were obtained in 2D B-mode, recorded on 10-s clips, and uploaded to a secure server for review.

Ultrasound images were reviewed using the OsiriX Imaging Software (© Pixmeo, Switzerland) platform. During review images were frozen during maximum expiratory and minimum inspiratory diameter, the IVC was measured using the software's calipers 3 cm caudal to the junction of the IVC and the right atrium, for each still image. Maximum and minimum diameters were identified by visual inspection. cIVC (or caval index) was defined as the degree to which the IVC collapses relative to its largest diameter: cIVC = (IVC expiratory diameter – IVC inspiratory diameter)/IVC expiratory diameter [24]. Ultrasound reviewers were blinded to the NICOM results.

2.4. Data analysis

We calculated a sample size of 124 patients (90% power with a one-sided type I error rate of 0.05) needed to detect a difference between the true area under the receiver operating characteristic curve (AUC) for cIVC of at least 0.88 and an AUC of 0.70 (considered to signify a fair level of discrimination). This sample size was targeted to help ensure that confidence intervals (using the normal approximation to the binomial distribution) for baseline cIVC sensitivity and specificity would have radii <10%.

Baseline patient clinical and demographic characteristics were summarized using descriptive statistics. Differences between fluid responders and non-responders were assessed using Pearson's chi-squared test, Fisher's exact test, the Student's *t*-test, and the Mann-Whitney *U* test, with two-sided *P* values less than 0.05 indicating statistical significance. The intraclass correlation coefficient (ICC) for absolute agreement using one-way random-effects analysis of variance (ANOVA) and two-way random-effects ANOVA were calculated for the baseline cIVC measurements to determine intra- and inter-rater reliability. The ICCs for intra- and inter-rater reliability of cIVC were found to be 0.92 (95% CI [0.89, 0.95]) and 0.67 (95% CI [0.56, 0.76]), respectively.

The relationship between the baseline cIVC and change in cardiac index was examined, and ROC analysis was employed to evaluate the baseline cIVC's ability to predict fluid responsiveness. We considered four functions of sensitivity and specificity for producing a cIVC cutoff value for optimally predicting fluid responsiveness (the sum and product of the sensitivity and specificity, maximizing the minimum of sensitivity and specificity, and minimizing the distance between the ROC curve and the point associated with 100% sensitivity and 100% specificity). We repeated these analyses to determine if IVC inspiratory or expiratory diameter, or if the change in cIVC before and after a PLR or a 500 ml IVF bolus, were predictive of fluid responsiveness. To assess if the addition of a PLR aided in the baseline cIVC's ability to detect fluid responsiveness, we created algorithms for using cIVC in conjunction with PLR. For these algorithms, we first assessed the prediction of fluid responsiveness by cIVC and PLR separately. Next, we evaluated if following a PLR there was a 5% change in cIVC that would reclassify

individuals as fluid responsive or non-responsive. Lastly, we evaluated the ability of a PLR to predict fluid responsiveness using the change in cardiac index (as measured by NICOM) before and after a PLR.

3. Results

3.1. Study population and fluid administration

Fig. 1 illustrates the recruitment, enrollment, and final study sample ($n = 124$). Table 1 provides patient demographic characteristics, clinical characteristics, and discharge diagnoses. Sixty-one participants (49.2%) were fluid responders. There were no differences between fluid responders and non-responders at baseline, except patients with COPD were more likely to be fluid responders while patients with pulmonary hypertension were more likely to be non-responders. The median time from ED triage to the first study ultrasound was 17 h (IQR [11-23]). The mean amount of IVF administered prior to study enrollment was 4060 ml (95% CI [3738, 4381]). Accounting for all maintenance fluids and the 500 ml bolus fluid, the mean amount of fluid given during the study was 525 ml. The IVF bolus took on average 8.2 min to administer (IQR [6-10]).

3.2. Primary outcome

A baseline measurement of cIVC was able to detect fluid responsiveness with an AUC of 0.84 [0.76, 0.91] (Fig. 2). Of the functions examined to maximize sensitivity and specificity, the optimal cIVC was 24.6% (Table 2). Rounding to the nearest whole integer produced a clinically more practical cIVC cutoff of 25% that had similar test characteristics: sensitivity 87% [75.8, 94.2], specificity 81% [69.1, 89.8], likelihood ratios (LRs), LR + 4.56 [2.72, 7.66], LR- 0.16 [0.08, 0.31]). Figure #4 shows positive predictive values (PPVs) and negative predictive values (NPVs) as functions of the prevalence of fluid responsiveness in the patient population (e.g., PPV = 81.5%, NPV = 86.4% for a 49.2% prevalence).

3.3. Secondary outcomes

A cIVC of 25% produced a lower misclassification rate (16.1%) (Fig. 3) for determining fluid responsiveness than the previous suggested cutoff values of 40% and 42% (34.7% and 36.3%, respectively) [28,29]. Baseline maximum or minimum IVC diameters were unable to detect fluid responsiveness (Supplementary Tables 1 and 2). The change in cIVC before and after either a PLR or a 500 ml fluid bolus was also unable to detect fluid responsiveness (Supplementary Tables 3 and 4). Algorithms constructed to use a PLR in combination with a baseline cIVC did not result in better test characteristics or fewer misclassifications than using a baseline cIVC alone (Supplementary Algorithm 1–3). A baseline PLR performed poorly in detecting fluid responsiveness with an AUC of 0.68 [0.59, 0.78] (Fig. 2, Supplementary Table 5). A PLR produced a smaller change in caval index in fluid responders and a larger change in fluid non-responders when compared to a 500 ml IVF bolus, indicating that a PLR did not reliably simulate an IVF bolus among our study population (Supplementary Fig. 1). This finding was substantiated as a PLR did not reliably reduce cIVC from baseline compared to an IVF bolus (Supplementary Fig. 2).

4. Discussion

The results of this investigation support the use of cIVC measured by POCUS to predict fluid responsiveness among spontaneously breathing critically-ill patients. Our cIVC AUC of 0.84 [0.76–0.91] is similar to the

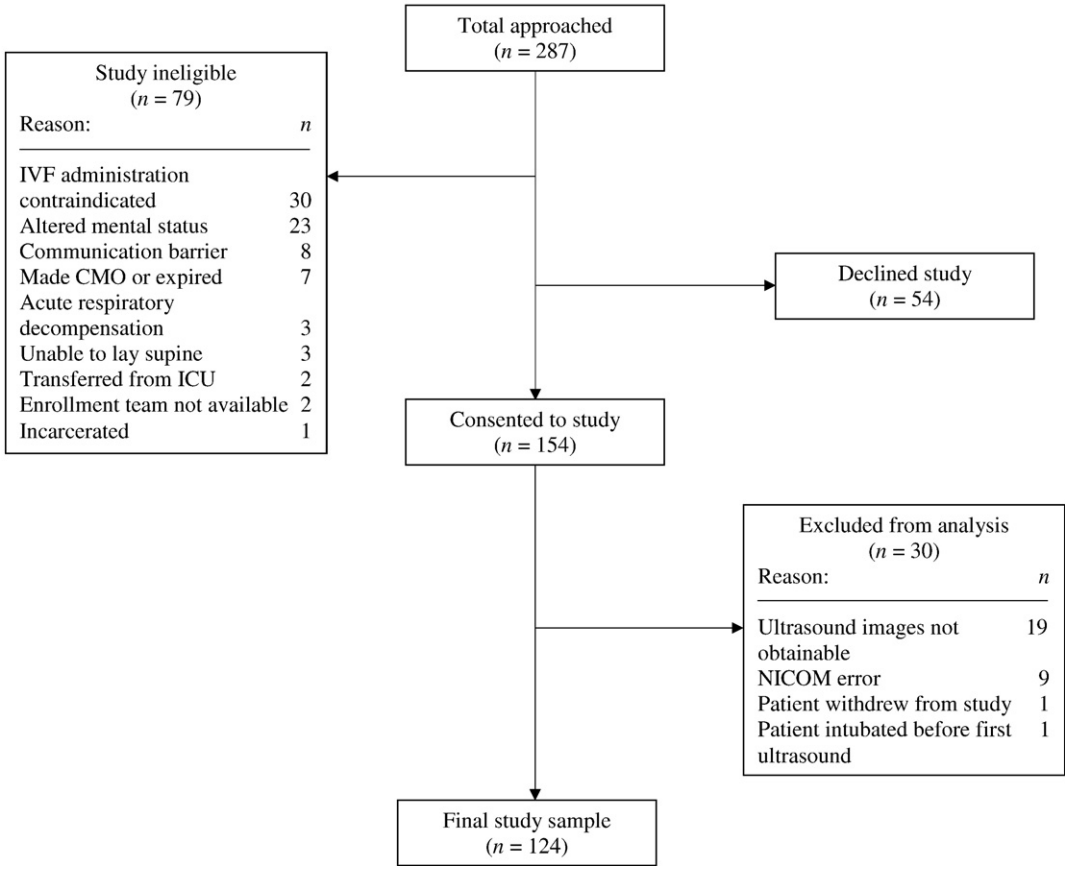

Fig. 1. Title: Flow diagram of participant enrollment Legend: CMO = comfort measures only, ICU = intensive care unit, IVF = intravenous fluid, NICOM = non-invasive cardiac output monitor.

Table 1
Patient characteristics at baseline, stratified by fluid responsiveness.

Patient characteristics	Fluid responders by NICOM ($n = 61$)	Fluid non-responders by NICOM ($n = 63$)	p
Demographic and clinical characteristics			
Age (years), median (IQR)	59.0 (38.0–74.0)	55.0 (41.0–73.0)	0.869[g]
Female gender, n (%)	36 (59.0)	32 (50.8)	0.358
BMI (kg/m^2), median (IQR)	24.1 (20.8–27.1)	24.4 (21.4–29.3)	0.529[g]
APACHE II (score), median (IQR)	21.0 (13.0–26.0)	17.0 (14.0–22.0)	0.132[g]
Time to study enrollment (hours), median (IQR)	16.0 (10.9–23.5)	18.9 (11.0–23.0)	0.327[g]
Fluid and other resuscitation			
IVF prior to ultrasound (ml), median (IQR)	4000 (3000–5000)	4000 (3000–5061)	0.754[g]
IVF administered during study (ml), median (IQR)	500 (500–550)	500 (500–500)	0.483[g]
Duration of fluid bolus (min), median (IQR)	7.0 (6.0–10.0)	7.0 (6.0–10.0)	0.216[g]
Received transfusion, n (%)	4 (6.6)	6 (9.5)	0.744[h]
Number of PRBC received, mean (SD)	2.5 (1.0)[a]	4.5 (2.9)[b]	0.235[i]
Required vasopressor, n (%)	10 (16.4)[c]	14 (22.2)[d]	0.411
Medical history, n (%)			
Hypertension	31 (50.8)	35 (55.6)	0.597
Diabetes mellitus	33 (54.1)	33 (52.4)	0.848
Cardiomyopathy	18 (29.5)	23 (36.5)	0.407
COPD	11 (18.0)	1 (1.6)	0.002[h]
Pulmonary embolism	0 (0.0)	0 (0.0)	NA
Pulmonary hypertension	1 (1.6)	5 (7.9)	0.208[h]
Hospital discharge diagnosis, n (%)			
Severe sepsis/septic shock	31 (50.8)	24 (38.1)	0.154
DKA/HHS	20 (32.8)	24 (38.1)	0.537
Gastrointestinal hemorrhage	6 (9.8)	8 (12.7)	0.615
Other	4 (6.6)[e]	7 (11.1)[f]	0.373

All *P* values are for the chi-squared test for equality of proportions, unless otherwise specified.
APACHE II Acute Physiology and Chronic Health Evaluation II, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DKA* diabetic ketoacidosis, *HHS* hyperosmolar hyperglycemic state, *IQR* interquartile range, *IVF* intravenous fluids, *NA* not applicable, *NICOM* non-invasive cardiac output monitor, *PRBC* packed red blood cells, *SD* standard deviation.
[a] $n = 4$.
[b] $n = 6$.
[c] 10 norepinephrine.
[d] 1 dopamine; 11 norepinephrine; 2 norepinephrine and vasopressin.
[e] 2 alcohol ketoacidosis; 2 hypovolemic.
[f] 1 alcohol ketoacidosis; 1 hypovolemic; 1 shock nos; 1 heart failure; 1 hypothyroid; 1 liver cancer; 1 rhabdomyolysis.
[g] Mann-Whitney test with correction for ties *p* value.
[h] Fisher's exact test *p* value.
[i] Student's *t*-test *p* value.

AUC of 0.84 [0.81–0.87] reported in a meta-analysis of stroke volume variation, an alternative more invasive method, to detect fluid responsiveness [36]. A comparison of results from studies using similar techniques as ours shows that a cIVC of 25% produced fewer misclassified patients than previously suggested supine cutoff values [29,30]. Recently published research by Preau et al. that examined cIVC in spontaneously breathing semi-upright (30°- 45°) septic patients reported an AUC of 0.82 [0.73–0.91] for a cIVC cutoff of 31% [37]. Their observed cIVC of 31% is larger than our clinically practical cIVC cutoff of 25% and is likely secondary to patient positioning. Laying a patient supine, as per our study protocol, will return more venous blood to the right heart, decreasing the cIVC. Preau et al.'s results are complementary to the findings of our study and suggest that cIVC may be utilized under a variety of clinical circumstances, however clinicians should account for patient positioning.

Patients were enrolled midway through their resuscitation, following a mean of 4060 ml of IVF, when clinicians often question the utility of further IVF resuscitation. When applying the study results clinically to direct resuscitation a LR- of 0.14 tells the physician those patients whose IVC collapses less than 25% are very unlikely to respond to further IVF (reflected by a NPV of >86% for a population with an approximate 50% prevalence of fluid responders; Fig. 4). This finding suggests a potential clinically meaningful endpoint for resuscitation. In practice a clinician could use IVFs to resuscitate a patient until a cIVC of <25% is reached, and thereafter elect to achieve target blood pressure goals with vasopressors instead of further, potentially harmful, IVF boluses. Conversely, a LR+ of 4.56 indicates that patients whose IVC collapses ≥25% are likely to be fluid responders (PPV of 81%) (Fig. 5). Clinicians however, must recognize that there will be a subset of patients who have collapsing IVCs but fail to respond to IVFs. Analysis of misclassifications revealed 4 patients with a documented low ejection fraction (≤35%) or pulmonary hypertension with a cIVC >25% but failed to respond to IVF. These patients have the venous capacitance to receive a fluid bolus, yet were unable to augment their stroke volume and improve perfusion with additional fluid.

We found that a PLR was not clinically useful. Coupling a PLR with non-invasive hemodynamic monitoring is advocated as a reliable way of determining fluid responsiveness. A recent meta-analysis found a pooled AUC of 0.95 [0.92, 0.98] for a PLR coupled with a variety of non-invasive hemodynamic monitoring techniques, including echocardiography, pulse contour analysis, esophageal doppler, and bioreactance [8]. We found that a PLR underperformed expectations with an AUC of 0.68 [0.59, 0.78]. In our cohort, PLR frequently did not produce the same increase in cardiac index observed following a 500 ml fluid bolus in fluid responders and conversely often overestimated the change in cardiac index among non-responders. Constructing multiple step algorithms using a PLR were not clinically helpful. Per our protocol, a patient's maximum cardiac index was measured within 5 min following a PLR and used to determine fluid responsiveness. A review of previous research indicates that there is no standard protocol for timing when fluid responsiveness is measured following a PLR. Some authors measure the maximum change in a selected hemodynamic measure immediately following a PLR [38,39], while others take the maximum change over a ten-minute period [40]. This lack of standardization may explain the disparate data for PLR and why a previous pilot study that compared cIVC and PLR to fluid responsiveness

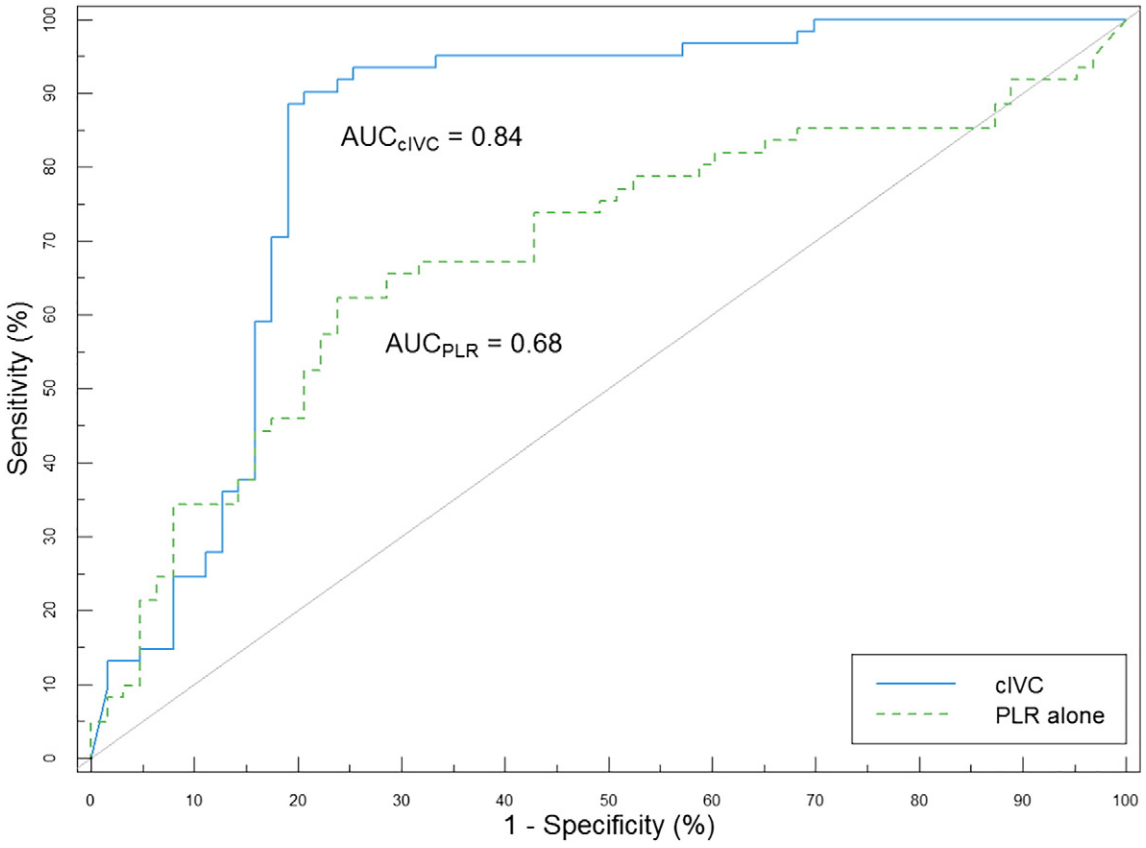

Fig. 2. Title: Receiver operator characteristic curves for baseline cIVC and for a PLR to detect fluid responsiveness Legend: AUC$_{cIVC}$ = area under curve for baseline cIVC, cIVC = inferior vena cava collapsibility, PLR = passive leg raise.

Table 2
The ability of a baseline inferior vena cava collapsibility to detect fluid responsiveness.

Cutoff method	Baseline cIVC cutoff for fluid responsiveness (%)[a]	Fluid responders ($n = 61$)	Fluid non-responders ($n = 63$)	Sensitivity % (95% CI)[b]	Specificity % (95% CI)[b]	LR+ % (95% CI)[c]	LR- % (95% CI)[c]	Accuracy % (95% CI)[d]	Misclassification % (95% CI)[d]
Prior suggested cutoffs									
Muller et al. proposed cutoff [28]	≥40 <40	28 33	10 53	45.9 [33.1, 59.2]	84.1 [72.7, 92.1]	2.89 [1.54, 5.43]	0.64 [0.50, 0.83]	65.3 [56.5, 73.5]	34.7 [26.6, 43.5]
Airapetian et al. proposed cutoff [29]	≥42 <42	26 35	10 53	42.6 [30.0, 55.9]	84.1 [72.7, 92.1]	2.69 [1.42, 5.09]	0.68 [0.54, 0.87]	63.7 [54.8, 71.8]	36.3 [28.2, 45.2]
Analytic approaches									
Maximize the sum of sensitivity and specificity	≥24 <24	55 6	13 50	90.2 [79.8, 96.3]	79.4 [67.3, 88.5]	4.37 [2.67, 7.14]	0.12 [0.06, 0.27]	84.7 [78.2, 90.3]	15.3 [9.7, 21.8]
Maximize the minimum of sensitivity and specificity	≥24.6 <24.6	54 7	12 51	88.5 [77.8, 95.3]	81.0 [69.1, 89.8]	4.65 [2.77, 7.79]	0.14 [0.07, 0.29]	84.7 [78.2, 91.1]	15.3 [8.9, 21.8]
Maximize the product of sensitivity and specificity	≥24.6 <24.6	54 7	12 51	88.5 [77.8, 95.3]	81.0 [69.1, 89.8]	4.65 [2.77, 7.79]	0.14 [0.07, 0.29]	84.7 [78.2, 91.1]	15.3 [8.9, 21.8]
Minimize the distance between the ROC curve and the point (0, 100)	≥24.6 <24.6	54 7	12 51	88.5 [77.8, 95.3]	81.0 [69.1, 89.8]	4.65 [2.77, 7.79]	0.14 [0.07, 0.29]	84.7 [78.2, 91.1]	15.3 [8.9, 21.8]
Suggested practical cutoff based on current analysis	≥25 <25	53 8	12 51	86.9 [75.8, 94.2]	81.0 [69.1, 89.8]	4.56 [2.72, 7.66]	0.16 [0.08, 0.31]	83.9 [77.4, 90.3]	16.1 [9.7, 22.6]

CI confidence interval, *cIVC* inferior vena cava collapsibility, *LR+* positive likelihood ratio, *LR-* negative likelihood ratio, *ROC* receiver operating characteristic.
[a] ≥ baseline cIVC means that the participant is predicted to be a fluid responder.
[b] Clopper-Pearson confidence intervals.
[c] Wald confidence intervals.
[d] Confidence intervals calculated using bootstrap percentiles.

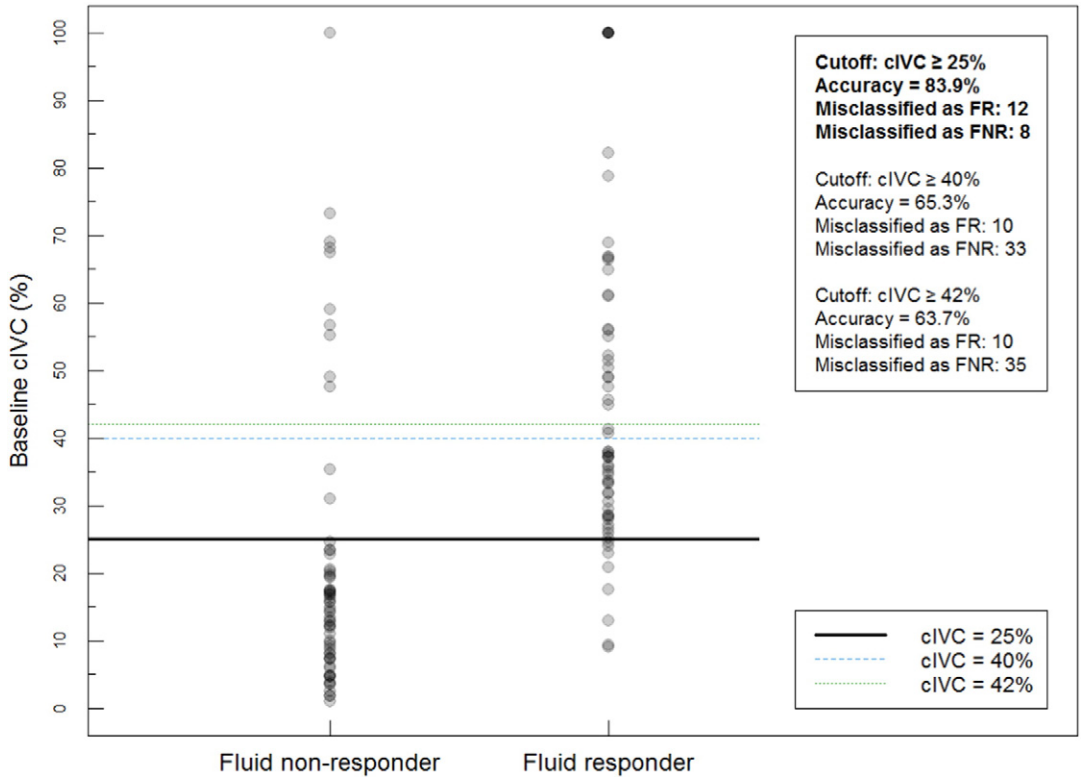

Fig. 3. Title: Baseline cIVC for fluid responders and non-responders Legend: Darker portions indicate a greater concentration of data points (circles). The horizontal lines are the optimal cutoff values for the baseline cIVC to predict fluid responsiveness according to previous and current analyses. cIVC = inferior vena cava collapsibility, FR = fluid responder, FNR = fluid non-responder.

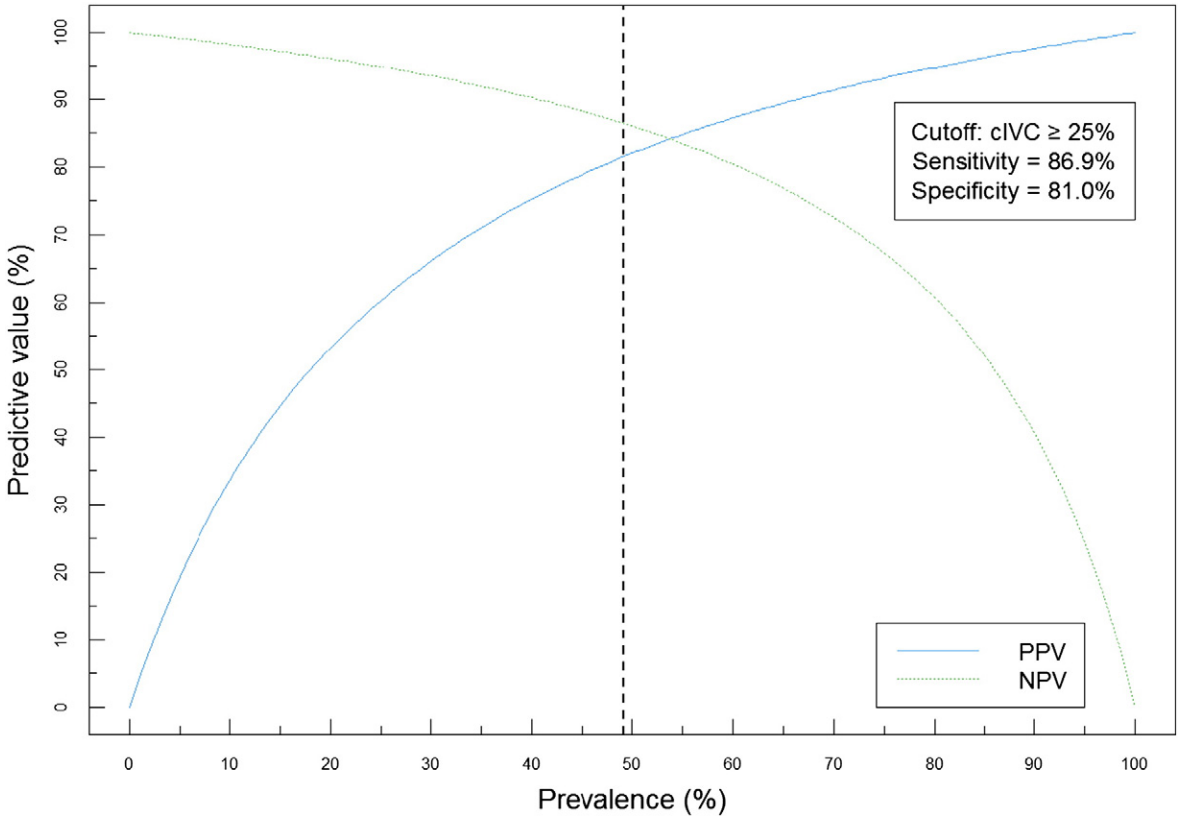

Fig. 4. Title: Positive and negative predictive values for specified prevalences using cIVC of 25% to predict fluid responsiveness Legend: The vertical dotted line is the observed prevalence of fluid responsiveness in the study population (49.2%). cIVC = inferior vena cava collapsibility, NPV = negative predictive value, PPV = positive predictive value.

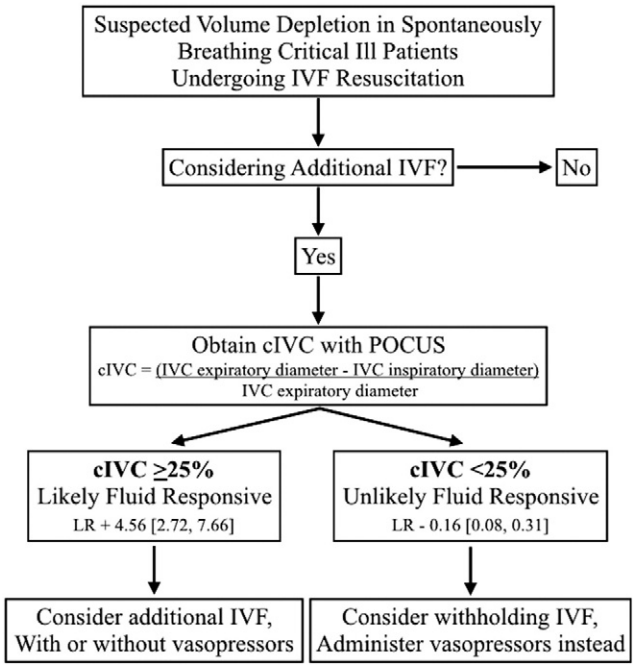

Fig. 5. Title: Decision algorithm for using cIVC to direct fluid resuscitation Legend: cIVC = inferior vena cava collapsibility, IVF = intravenous fluids, LR = likelihood ratio, POCUS = point of care ultrasound.

produced negative results [41]. Of interest, the PLR AUC in our study was similar to the value found by Airapetian et al. of 0.78 [0.66, 0.88] who examined a similar study cohort [30]. These findings question the contemporary role of a PLR in resuscitation, and if they are replicated in future studies, should provoke a reevaluation of currently accepted practice.

Performing multiple ultrasounds to calculate a delta cIVC was not found to be superior to a single baseline measurement. Measuring a cIVC before-and-after a PLR or before-and-after a 500 ml bolus was not useful in detecting fluid responsiveness. This finding suggests that POCUS measurements of the cIVC are unable to reliably detect smaller changes in intravascular volume. Repeated ultrasounds after larger volumes of resuscitation (1000 to 2000 ml) were not performed in the study, and it is anecdotally plausible that POCUS would be able to detect them.

Strengths of this study include that it is the largest investigation to date examining POCUS measurement of cIVC in spontaneously breathing critically-ill patients. Ultrasounds were performed by multiple emergency medicine and critical care physicians with training in POCUS, but who did not have formal ultrasound fellowship training, making the results more generalizable to practicing physicians. Additionally, patients were enrolled midway through their resuscitation when physicians often face therapeutic uncertainty in administering further IVF.

Limitations of this study include that critically-ill non-medical ICUs patients were excluded from the study sample. It is unlikely that our findings would differ significantly in a surgical population, while a cohort with a high prevalence of cardiac dysfunction (cardiac or cardiothoracic ICU) may have a higher percentage of patients misclassified as fluid responders. Respiratory effort has been shown to effect cIVC [42] and was not quantified using buccal mucosal measurements or breathing standardization. We enrolled spontaneously breathing patients who did not require non-invasive positive pressure ventilation. Non-standardization of respiratory effort may lead to increased variability of observed cIVC within and across patients; conversely non-standardization potentially allows for greater external validity of the study's findings. Twelve of 63 (19%) non-responders were misclassified as fluid responsive. While it is likely that respiratory effort contributed to this population other patient factors such as cardiac dysfunction and pulmonary hypertension contributed to misclassification as well. Clinicians should be careful when interpreting a cIVC > 25% in patients with significant respiratory distress, cardiac dysfunction, or pulmonary hypertension and administer IVF judiciously. Due to study logistical design patients were enrolled up to 36 h after emergency department triage. This produced a study cohort that on average had received approximately 4 l of IVF prior to study enrollment. This timing did not affect the prevalence of fluid responders in the study sample. In 19 patients (12.3%) the study clinician was unable to obtain adequate POCUS images of the IVC. This rate is consistent with previously reported cohorts [24]. Larger body habitus, presence of a gastric tube, and POCUS following endoscopic gastroduodenoscopy were the most cited reasons for failure to obtain adequate images; therefore POCUS measurement of cIVC may be limited in specific patient populations. Measurements of the cIVC were performed following ultrasound video review rather than in real time. The measurement process is relatively simple and unlikely to vary when performed at bedside. While the intra-rater reliability for cIVC performed 1 min apart was 0.92, the inter-rater reliability between readers was 0.67. This finding is likely because reviewers of the ultrasound videos each selected the point when they believed IVC was at a maximum and minimum by visual inspection during the 10-s clip; no fixed measuring time point was standardized. Our results suggesting a clinically practical cIVC cutoff of 25% that maximizes sensitivity and specificity, are based upon the findings of this single trial and warrant prospective validation.

5. Conclusion

cIVC, as measured by POCUS, is able to detect fluid responsiveness and may be used to guide IVF resuscitation among spontaneously breathing critically-ill patients.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.05.008.

Author's Contributions

KC: study concept and design, patient enrollment, ultrasound review, data analysis and interpretation, drafting and revision of manuscript; NG: patient enrollment, ultrasound review, and revision of manuscript; JR: data analysis and revision of manuscript; AL: patient enrollment and revision of manuscript; DC: data collection and patient enrollment; RM: study design, data analysis and interpretation, and revision of manuscript; ML: study design and revision, data interpretation, and revision of manuscript; AN: study concept and design, and revision of manuscript.

Conflicts of interests

KC has no conflicts of interest. NG has no conflicts of interest. JR has no conflicts of interest. AL has no conflicts of interest. DC has no conflicts of interest. RM has no conflicts of interest. ML has no conflicts of interest. AN has no conflicts of interest.

Funding

This work was supported by the Division of Pulmonary and Critical Care and the Department of Emergency Medicine, Alpert Medical School of Brown University.

Acknowledgements

We would like to extend a special thanks to Dr. Otto Leibmann who provided ultrasound support and Dr. Gregory Jay who provided research personnel support for the study.

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