Ultrasonographic inferior vena cava diameter response to trauma resuscitation after 1 hour predicts 24-hour fluid requirement

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BACKGROUND: Identification of occult hypovolemia in trauma patients is difficult. We hypothesized that in acute trauma patients, the response of ultrasound-measured minimum inferior vena cava diameter ($IVCD_{MIN}$), IVC Collapsibility Index (IVCCI), minimum internal jugular diameter ($IJVD_{MIN}$) or IJV Collapsibility Index (IJVCI) after up to 1 hour of fluid resuscitation would predict 24-hour resuscitation intravenous fluid requirements (24FR).

METHODS: An NTI-funded, American Association for the Surgery of Trauma Multi-Institutional Trials Committee prospective, cohort trial was conducted at four Level I Trauma Centers. Major trauma patients were screened for an IVCD of 12 mm or less or IVCCI of 50% or less on initial focused assessment sonographic evaluations for trauma. A second IVCD was obtained 40 minutes to 60 minutes later, after standard-of-care fluid resuscitation. Patients whose second measured IVCD was less than 10 mm were deemed nonrepleted (NONREPLETED), those 10 mm or greater were repleted (REPLETED). Prehospital and initial resuscitation fluids and 24FR were recorded. Demographics, Injury Severity Score, arterial blood gasses, length of stay, interventions, and complications were recorded. Means were compared by ANOVA and categorical variables were compared via χ^2. Receiver operating characteristic curves analysis was used to compare the measures as 24FR predictors.

RESULTS: There were 4,798 patients screened, 196 were identified with admission IVCD of 12 mm or IVCCI of 50% or less, 144 were enrolled. There were 86 REPLETED and 58 NONREPLETED. Demographics, initial hemodynamics, or laboratory measures were not significantly different. NONREPLETED had smaller IVCD (6.0 ± 3.7 mm vs. 14.2 ± 4.3 mm, $p < 0.001$) and higher IVCCI (41.7% ± 30.0% vs. 13.2% ± 12.7%, $p < 0.001$) but no significant difference in IJVD or IJVCCI. REPLETED had greater 24FR than NONREPLETED (2503 ± 1751 mL vs. 1,243 ± 1,130 mL, $p = 0.003$). Receiver operating characteristic analysis indicates $IVCD_{MIN}$ predicted 24FR (area under the curve [AUC], 0.74; 95% confidence interval [CI], 0.64–0.84; $p < 0.001$) as did IVCCI (AUC, 0.75; 95% CI, 0.65–0.85; $p < 0.001$) but not $IJVD_{MIN}$ (AUC, 0.48; 95% CI, 0.24–0.60; $p = 0.747$) or IJVCI (AUC, 0.54; 95% CI, 0.42–0.67; $p = 0.591$).

CONCLUSION: Ultrasound assessed $IVCD_{MIN}$ and IVCCI response initial resuscitation predicts 24-hour fluid resuscitation requirements. (*J Trauma Acute Care Surg.* 2020;88: 70–79. Copyright © 2019 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Diagnostic tests or criteria, level II.

KEY WORDS: Trauma; ultrasound; shock; resuscitation; vena cava.

Determining which major trauma patients have occult hypovolemia and will have an increased initial intravenous fluid resuscitation requirement is often difficult in the absence of overt hypotension. Both clinical assessment and invasive measures, such as central venous pressure, have a reliability in predicting fluid responsiveness only slightly better than chance.[1,2] Concern over inadequate resuscitation has led in the past to guidelines supporting aggressive fluid administration with a risk of overresuscitation. Current approaches recommend early balanced blood transfusion in overt shock[3] but observing the response to crystalloid administration when uncertainty exists. Ultrasound (US) has emerged as a noninvasive, rapid, point of care test that may be an attractive option to assess volume status and fluid responsiveness.

US assessment of the IVC diameter (IVCD) and its variation or collapsibility with respiration (IVCCI) is a reproducible and usually easy to perform US examination.[4] The US assessment of the minimum IVCD ($IVCD_{MIN}$), maximum IVCD ($IVCD_{MAX}$) or IVCCI can be difficult or unobtainable in some cases due to obesity, increased abdominal pressure, bowel gas, air in tissues or if wounds or dressings intervene. The US assessment of the internal jugular vein (IJV) and its minimum ($IJVD_{MIN}$) and maximum diameter (IJV_{MAX}) and respiratory variation or collapsibility (IJVCI) are more recently proposed measures in ventilated and septic intensive care unit (ICU) patients[5,6] and blood donors,[7,8] but has not been described in initial resuscitation of trauma patients.

We hypothesized that in major trauma patients, ultrasonic assessment of the IVC diameter response to initial resuscitation would predict fluid requirements in the first 24 hours after admission. The primary objective of this study is to determine if repeated ultrasound assessment of $IVCD_{MIN}$, IVCCI, $IJVD_{MIN}$, and IJVCI after standard of care resuscitation in major trauma patients presenting with small or collapsible IVCs will predict total intravenous fluid requirements at 24 hours after admission (24FR). The secondary objective is to compare $IVCD_{MIN}$, IVCCI, $IJVD_{MIN}$, and IJVCI to determine the best measure or best combination of measures in predicting 24FR in major trauma patients.

METHODS

A prospective, multi-institutional, observational cohort human trial in adult major trauma patients presenting to four U.S. Level I trauma centers was conducted. Institutional Review Board (IRB) and U.S. Army Human Research Protections Office (HRPO) approvals were obtained at participating centers. The study was entered in the ClinicalTrials.gov registry with identifier NCT01989273. Because of the short time available to obtain necessary ultrasound images at admission, IRB (UCSD IRB 100326) and HRPO (HSRRB Log Number A-18698) approval was obtained to complete delayed patient consent to participate in

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the study after the required study imaging was obtained. Patients who refused consent were withdrawn from the study and their study images and data not used. Data were collected in a secure electronic database via the American Association for the Surgery of Trauma Multi-Institutional Trials Committee study data website.

Enrollment and Data Collection

The trial was conducted in two phases, the first 18-month phase starting June 2012, and a second 18-month phase starting July 2016. Enrollment was completed in March 2018. The gap between phases was due to slow recruitment and acquisition of further funding. Focused assessment sonographic evaluations for trauma (FAST) including views of the inferior vena cava (FAST-IVC) were performed on major trauma victims as part of standard resuscitation within 30 minutes of admission. Major trauma victims who had evidence of increased IVC collapsibility: (IVC-CI ≥ 50%) or an IVC diameter of ≤12 mm on the initial FAST-IVC examination were candidates for enrollment. Exclusion criteria were pregnancy after 20 weeks gestation, patients under 18 years of age, prisoners or others prohibited from participating in clinical trials and patients with severe traumatic brain injury who at admission were deemed by treating surgeons as having nonsurvivable brain injuries.

Patients received standard-of-care intravenous crystalloids and blood products during the initial hour of resuscitation. Repleted (REPLETED) and nonrepleted (NONREPLETED) cohorts were selected on IVC diameter (IVCD) response to interventions in the Trauma Bay on a follow-up FAST-IVC obtained within 60 minutes of admission but more than 20 minutes after the first FAST-IVC examination." The REPLETED group had restoration $IVCD_{MIN}$ to 10 mm or greater after 1 hour of standard of care resuscitation. The NONREPLETED group were those with an $IVCD_{MIN}$ of less than 10 mm after 1 hour of standard of care resuscitation. During the first 18-month phase starting June 2012, IVC video clips only were obtained. In the second 18-month phase starting July 2016, video clips of right and left internal jugular veins were also obtained at the same time as the FAST-IVC video clips.

Although the ultrasound images obtained were by necessity not blinded to all team members, the actual measurement of the IVC and IJV was performed by the investigators only after patient discharge. No interventions were based on the assigned group, all resuscitation and subsequent treatments were those performed as the standard of care for that trauma center.

The primary dependent variables included hospital mortality, need for hemostatic interventions, such as surgery or angiography; need for ICU admission; need for ventilation; requiring more than typical maintenance crystalloid intravenous fluids at 24 hours (greater than 2400 mL); and blood product transfusion requirements within 24 hours and complications. Other variables collected included vital signs, Injury Severity Score (ISS), and admission arterial blood gases obtained in the first hour of admission including arterial blood gas base deficit.

Sonographic Technique and Equipment

The participating trauma centers routinely utilize clinician-performed FAST at admission. Sonographers were either clinician-sonographers or registered diagnostic sonographers who perform FAST routinely at their centers, including sonographic technicians, attending surgeons, attending emergency medicine physicians, fellows, or senior residents. Patients undergoing FAST-IVC diameter measurement were examined in the supine position (0 degrees). All examinations were done in a 0-degree flatbed position and except for standard of care fluid resuscitation, no provocative maneuvers, such as bed tilting, straight-leg raising, deep breathing, or sniffing were performed. Two FAST-IVC serial examinations were performed—the first within 30 minutes of admission and a second within 60 minutes of admission but more than 20 minutes after the first FAST-IVC examination.

Sonographic evaluation of IVC diameters was performed according to a methodology described by the study authors in written and video training materials provided to sonographers participating in the study. The IVC views were obtained in longitudinal and sagittal planes using a phased-array multifrequency probe via an initial B-mode paramedian or subxiphoid window of the IVC about 2 cm below level of the hepatic veins, within 2.5 cm to 5 cm from the right atrium. Alternately, especially if gas obscured the paramedian window, visualization via a liver window along the right posterior axillary line was used. Details of these techniques have been outlined elsewhere.[4] Images were marked by the sonographer with patient identification, time, laterality and orientation. Images were stored as video clips through at least two respiratory cycles.

Internal jugular vein (IJV) views were obtained by high frequency linear transducer probe. The left and right IJV were imaged in short and long axis in the neck at the level of the cricoid cartilage with the patient supine (0 degrees). The maximal and minimal diameter as a result of respiratory variation was assessed at both positions from the short and long axis view. Patients in cervical collars were not excluded, but in cases where the attending surgeon deemed it too unsafe to remove the cervical collar in cases of suspected spine injury, only IVC views were obtained without IJV views. Ultrasound machines used varied by center, these included the M-Turbo (Sonosite, Bothell, WA), CX-50 (Phillips, Andover, MA), Logiq-e (General Electric, Boston, MA), and the Z.One Pro (Mindray, Mahwah, NJ).

IVC and IJV Collapsibility Index

The inferior vena cava's diameter was measured at its largest diameter (usually at end-expiration, IVCDe) and at its smallest diameter (usually at the end of inspiration (IVCDi). Since some patients would be intubated and on positive pressure ventilation which may invert the relationship between respirations and IVC size, instead of using IVCDe and IVCDi, the maximal ($IVCD_{MAX}$, $IJVD_{MAX}$) and minimal ($IVCD_{MIN}$, $IJVD_{MIN}$) vessels sizes seen on the recorded video were used. Collapsibility Index (IVCCI) was calculated as ($IVCCI = [(IVCD_{MAX} - IVCD_{MIN}) / IVCD_{MAX}] \times 100\%$). Similarly, IJV Collapsibility Index (IJVCI) was calculated as ($IJVCI = [(IJVD_{MAX} - IJVD_{MIN})/ IJVD_{MAX}]$-100%). Because of the variation of internal jugular sizes between sides in the same patient, the left and right IJVs were recorded as separate images for each patient and treated as separate measurements for each patient.

Data Interpretation and Statistical Analysis

After 18 months, an interim analysis was performed to determine the feasibility of the study and measurements and to consider modification by adding the IJV measurements. To determine interobserver variability, three different reviewers (two

clinician-sonographers and one registered diagnostic sonographer clinician-sonographer) analyzed images from 50 randomly selected patients and the interrater reliability was determined via two-way mixed consistency average-measures intra-class correlation (ICC) for $IVCD_{MIN}$, IVCCI, $IJVD_{MIN}$, and IJVCI.[9]

Sample size was derived from published data indicating that ultrasound measurement of IVC diameter for a 450-mL blood loss in blood donor volunteers is highly sensitive.[5] It was anticipated about 5% of patients admitted to Level I trauma centers present would have significant IVC collapsibility on initial FAST-IVC. The four participating trauma centers admit 8,000 trauma patients per year, which would mean approximately 400 patients should be admitted annually with IVC collapsibility. A Power calculation determined that to detect a difference of 10% in binary outcomes such as mortality, need for transfusion or 24FR greater than 2400 mL between REPLETEDs and NONREPLETEDs groups with a beta-error of 20% or less, and alpha of 0.05, about 492 study patients would be required. At the 18-month interim analysis, there were 33 REPLETED and 32 NONREPLETED evaluable cases and 11 nonevaluable cases. A 24FR greater than 2400 mL was seen in 13 of 33 REPLETED cases and 9 of 32 NONREPLETED cases ($p = 0.243$), a recalculation of Power yielded 0.32 and the new sample size estimate was 210 enrollees, accounting for nonevaluable cases.

Frequencies of categorical variables for the groups (i.e., gender, mortality, need for surgery) were analyzed by χ^2 test. Continuous variables were analyzed by ANOVA. Correlation using Pearson correlation coefficient for total 24FR was obtained for ISS, base deficit, $IVCD_{MIN}$, $IVCD_{MAX}$, $IJVD_{MIN}$, $IJVD_{MAX}$, IVCCI, and IJVCI. To test the association between the measurements and 24FR, generalized linear mixed models were used. According to literature and clinical practice, we selected fixed factors of age, gender, ISS, admission shock index (heart rate divided by systolic blood pressure [SBP]), SBP on leaving the resuscitation bay, arterial blood gas base deficit, $IVCD_{MIN}$, $IVCD_{MAX}$, and IVCCI. To account for possible clustering effects, the subject's hospital was used as a random effect.

Receiver operating characteristic (ROC) curves were used to determine the ability of ISS, base deficit, $IVCD_{MIN}$, $IVCD_{MAX}$,

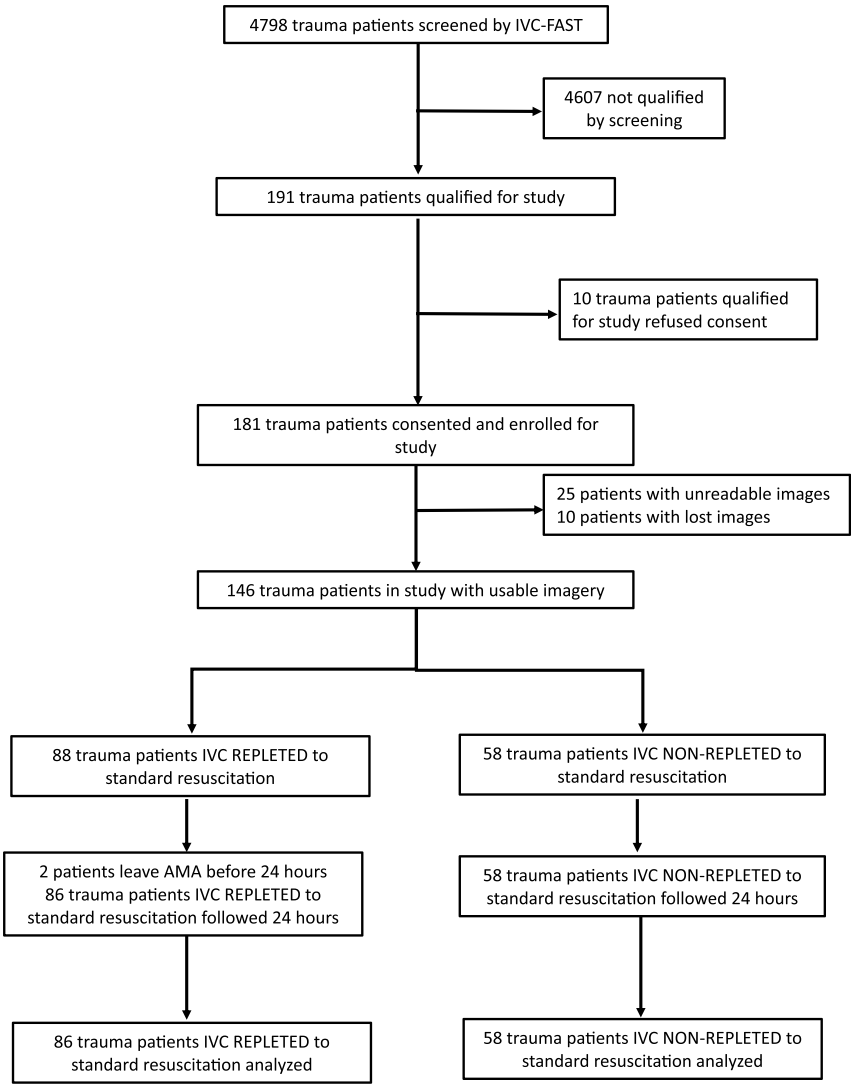

Figure 1. Consort flow diagram for the FAST-IVC trial.

$IJVD_{MIN}$, $IJVD_{MAX}$, IVCCI, and IJVCI to predict the need for 2,400 mL or more of intravenous fluid in the first 24 hours after admission. Those receiving 2,400 mL or greater were +24FR and those less than 2,400 mL were −24FR. The area under the curve (AUC) for each measure was calculated. Sensitivity, specificity, with 95% confidence intervals were calculated for each measure. The Youden index (=Sensitivity + specificity − 1) was used to determine the optimal sensitivity and specificity for each measure. Evaluation of these ROC criteria was used to identify upper and lower cutoff values for each measurement. The gray zone approach described by Coste et al.[10] for ROC curves was used to determine the inconclusive range of measurement values.[10,11] The gray zone was created between the 90% sensitivity and the 90% specificity points on the two sigma curves. The percentage of patients not falling into the gray zone was determined for each predictive measure. The ROC curves were created for the best combination of ultrasound measures using the predicted probabilities derived from binary logistic regression.

All statistical analyses were performed used IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, NY). A p value less than 0.05 (two-tailed) was considered significant.

RESULTS

Over the study period, 191 patients were enrolled, and 144 patients completed the study with useable images, the CONSORT patient flow diagram is shown at Figure 1. At UC San Diego, 97 patients completed the study, 89 had useable images. At Virginia Commonwealth, 33 patients, with 23 having useable images, while University of Maryland had 20 patients completing the study, 15 of which had useable images and University of Utah had 21 patients complete the study, with 17 having useable images. Needed images were lost in 10 patients, and images were found to be unusable in 25 patients. Consent was refused in 15 patients after image acquisition. Two patients left against medical advice before 24 hours had elapsed. There were no significant differences in age, ISS, gender, body mass index, mechanism of injury, hemodynamics, prehospital, and initial fluid volumes given, mortality, need for surgery, ICU or hospital length of stay (LOS), or ventilator days between REPLETEDs and NONREPLETEDs (Table 1). Bilateral internal jugular views were obtained in 52 patients. The interrater reliability as ICC was good overall (0.92, 95% C.I.: 0.949–0.972, $p < 0.001$) and was also good for $IVCD_{MIN}$ (0.853; 95% CI, 0.717–0.929; $p < 0.001$), IVCCI (0.851; 95% CI, 0.851–0.925; $p < 0.001$), $IJVD_{MIN}$ (0.951; 95% CI, 0.897–0.979; $p < 0.001$), and IJVCI (0.862; 95% CI, 0.714–0.941; $p < 0.001$).

After initial resuscitation, REPLETEDs did have a significantly larger $IVCD_{MIN}$ than NONREPLETEDs. The NONREPLETEDs received significantly more intravenous fluids by 24 hours. The need for transfusion between groups did not achieve significance. $IJVD_{MIN}$ and IJVCI were not significantly different between the groups.

Correlation tests for 24FR with predictive measures are shown in Table 2. Base deficit, ISS, $IVCD_{MIN}$, $IVCD_{MAX}$, and IVCCI were all significantly correlated with 24FR, but $IJVD_{MIN}$

TABLE 1. Demographics and Outcome Variables

	REPLETED 50% (n = 86)	NONREPLETED (n = 58)	*p*
Age (y)	50.8 ± 22	50.1 ± 23	0.597
Gender (% male)	65% M	69% M	0.533
BMI	27.5 ± 6.1	27.8 ± 9.5	0.817
Blunt/Penetrating	78/10 (88.6)	53/5 (91.3)	0.233
ISS; IQR	8; 4–12	8; 4–12	0.795
Base deficit	0.76 ± 3.8	1.2 ± 4.6	0.050
Heart rate (bpm)	91 ± 18	88 ± 21	0.433
Admission Sys BP (mm Hg)	138 ± 26	133 ± 22	0.064
Prehospital IV fluids (mL)	227 ± 538	191 ± 421	0.663
Initial resus fluids (mV)	433 ± 519	410 ± 466	0.308
Median ICU LOS; IQR (days)	0; 0–1	0; 0–2.75	0.420
Median ventilator Days; IQR (days)	0; 0–0	0; 0–0	0.935
Median hospital LOS; IQR (days)	2; 1–6.75	2; 1–6.5	0.986
Intubated	7/86 (8.1)	5/58 (8.6)	0.367
Post-resus $IVCD_{MIN}$ (mm)	14.2 ± 4.3	6.0 ± 3.7	<0.001*
Post-resus $IJVD_{MIN}$ (mm)	6.2 ± 3.5	5.6 ± 3.7	0.572
Post-resus IVCCI (%)	13.2 ± 12.7	41.7 ± 30.0	<0.001*
Post-resus IJVCI (%)	24.5 ± 22.6	26 ± 22.9	0.631
24-h Fluids (mL)	1243 ± 1130	2503 ± 1751	0.003*
24-h Fluids >2400 mL (%)	10/86 (11.6)	27/58 (46.5)	<0.001*
Received transfusion by 24 h (%)	15/86 (17.4)	8/58 (13.8)	0.499
Mean transfusion volume (mL)	1023 ± 952	1832 ± 2308	0.277
Laparotomy performed (%)	4/86 (4.7)	1/58 (1.7)	0.841
Mortality (%)	4/86 (4.7)	1/58 (1.7)	0.841

*$p < 0.05$.
BMI, body mass index; BP, blood pressure; IV, intravenous; Resus, resuscitation area; IQR, interquartile range.

TABLE 2. Correlation Analysis With 24-Hour IV Fluid Requirement

	n	r	*p*
Base deficit	120	−0.132*	0.032
ISS	123	0.366*	0.020
$IVCD_{MIN}$	144	−0.422**	0.0001
$IVCD_{MAX}$	123	−0.340**	0.0001
IVCCI	115	0.440**	0.0001
$IJVD_{MIN}$	103	−0.135	0.372
$IJVD_{MAX}$	78	−0.066	0.401
IJVCI	77	−0.107	0.789

r, Pearson correlation coefficient.
*$p < 0.05$, **$p < 0.01$(Pearson correlation analysis).

and IJVCI were not. The $IVCD_{MIN}$, $IVCD_{MAX}$, and IVCCI had a moderate correlation with 24-hour fluid requirement and were comparable to ISS but stronger than the weak correlation with base deficit.

The general linear mixed model analysis is shown in Table 3. The ISS, $IVCD_{MIN}$, and IVCCI were significant independent predictors of 24FR. Random-effect modeling demonstrated no significant effect from intra-hospital clustering on these predictors.

Comparison of the ROC analyses in Figure 2 shows that IVCCI was the most predictive measure for +24FR with an AUC of 0.75 of the single tests. The $IVCD_{MIN}$ has a comparable AUC at 0.74 (95% CI, 0.65–0.84). The $IJVD_{MIN}$ and IJVCI were not significantly sensitive or specific to have a useful AUC. Injury Severity Score was also moderately predictive of +24FR at a lower AUC of 0.65 (95% CI, 0.54–0.76). A binary logistic regression model was used to combine the $IVCD_{MIN}$ and IVCCI measures to attempt to create a more predictive measure, called Logistic($IVCD_{MIN}$ + IVCCI). This which yielded an AUC of 0.75 (95% CI, 0.66–0.85), a very slight increase in AUC over $IVCD_{MIN}$ but not over IVCCI.

Gray zone plots for +24FR were plotted for $IVCD_{MIN}$, IVCCI, and Logistic($IJVD_{MIN}$ + IVCCI) (Fig. 3). The IVCCI at 89% had the most patients outside a gray zone (95% CI, 41–51%). Both $IVCD_{MIN}$ and the Logistic($IJVD_{MIN}$ + IJVCI) combined model had 55% of patients outside the gray zone (Table 4), with the combined model having increased positive predictive value (PPV) but a lower negative predictive value (NPV) compared with IVCCI and $IVCD_{MIN}$. The IJVCI had a high PPV at 81%, but only 27% of the patients were outside the gray zone.

DISCUSSION

This study of ultrasound used in major trauma patients during initial resuscitation shows that US assessment can be used to identify failure of repletion of the IVC minimum diameter and collapsibility, associated with increased intravenous fluid requirements at 24 hours, with limitations. Ultrasound assessment to detect intraabdominal and intrathoracic injuries is well established,[12–14] but the use of ultrasonic measures to determine fluid responsiveness is newer and several US examinations and maneuvers have been proposed. Five studies that demonstrated an association of decreased IVC diameter with shock in patients with shock or gastrointestinal bleeding have been subjected to meta-analysis.[15] This showed that there was an overall reduction of IVC diameter in shock states. However, only a small percentage of trauma patients present in overt Class III or IV shock. In patients with lower grades of shock, clinicians have about the same efficacy as a coin-toss in determining fluid responsiveness from physical examination or central venous pressure alone,[1,2,16] and concerns regarding the adverse effects of crystalloid overresuscitation has recently caused the Advanced Trauma Life Support to reduce the initial fluid crystalloid bolus for adult trauma patients from 2 L to 1 L.[3]

Guidelines from the American Society of Echocardiography support the use of IVC size and IVCCI in the assessment of volume status.[17] The IVC diameter may be a reliable indicator of volume status,[18] and IVCCI may be predictive of fluid responsiveness in the ICU.[19,20] Most of the studies of US assessment of the IVC for fluid responsiveness are based in ICU patients under mechanical ventilation, which seems to increase sensitivity.[21–24] One study of spontaneously breathing ICU patients with straight

TABLE 3. Generalized Linear Mixed Model for 24 Hour Fluid Requirement

Fixed Factor Effects	**Coefficient**	**95% CI**	***p***
Constant	1094.4	0.406–1507.3	0.460
Age	6.9	−5.6 to 19.4	0.275
Male gender	−120.0	−647.3 to 407.4	0.653
ISS	48.4	19.8–77.0	0.001*
Admission Shock Index	1138.2	−90.0 -2366	0.069
SBP on leaving resus bay	−12.1	−21.5 to 6.7	0.304
Base Deficit	−0.21	−99.4 to 56.6	0.546
IVCDMIN	−101.5	−142 to 60.9	0.024*
IVCDMAX	−86.2	−214.2 to 42.3	0.186
IVCCI	26.5	7.3–45.6	0.007*
Random factor effects			
Covariance Estimate	Z-statistic	95% CI	*p*
Hospital	91,087	0.519	2085.9–3,977,505	0.604

* $p < 0.05$.

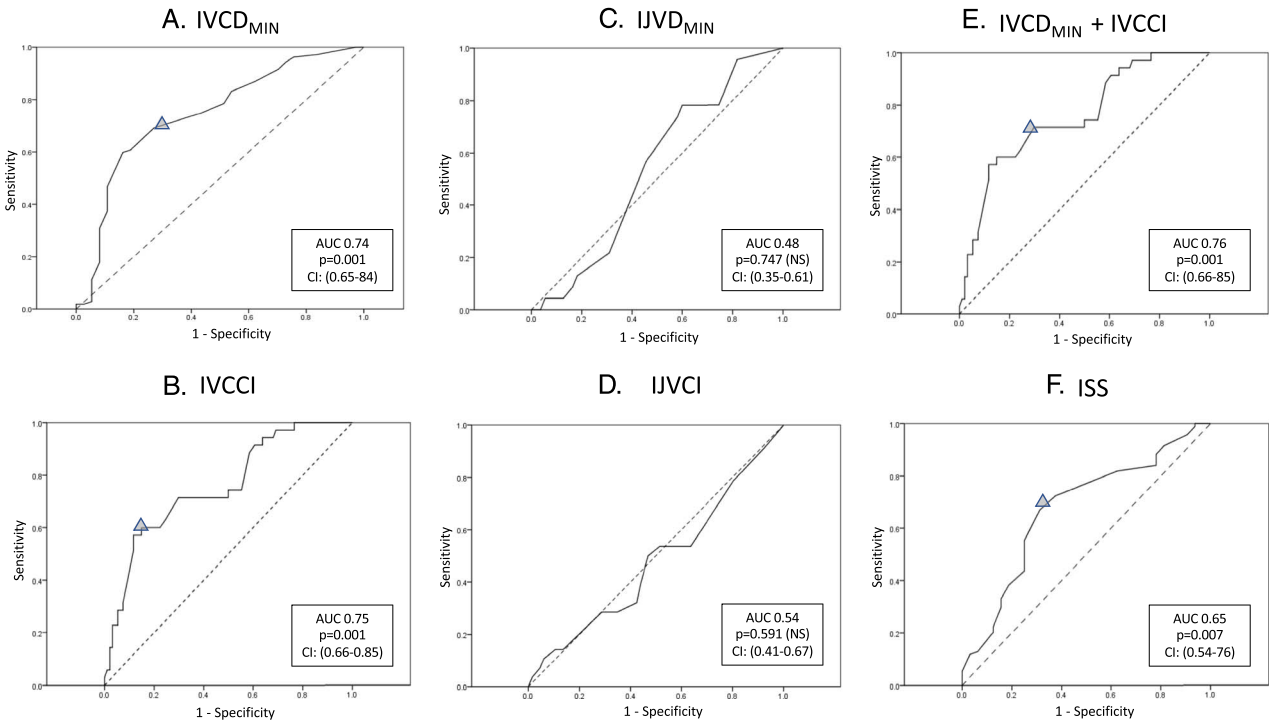

Figure 2. ROC curves for ultrasound measures and ISS.

leg raising or 500-mL boluses did not show IVC respiratory variation was predictive,[25] while another study using a 500-mL bolus showed that it was predictive.[26] Similarly, five studies on the effect of a blood donation analogous to Class I shock on IVC respiratory variation were contradictory.[27–31] The accuracy of IVC respiratory variation in determining fluid responsiveness was questioned in a study using straight leg raising in a heterogeneous ER patient population.[32] However, these studies did not include major trauma victims who may have ongoing bleeding.

The utility of a single, static ultrasound assessment of the IVC in acute trauma patients was not supported by a study of 140 acute trauma admissions found that a single ultrasonographic or computed tomographic measurement of IVC diameter did not correlate with vital signs, hemorrhage, or shock markers.[33] In our study, we also did not see differences in vital signs or shock markers based on IVC$_{MIN}$ or IVCCI at initial admission. However, the use of repeated US examinations and provocative tests may increase the predictive ability of US assessment of IVCD$_{MIN}$ and IVCCI for 24FR. We found that failure to replete IVCD$_{MAX}$ and IVCCI were significantly associated with +24FR. IVCD$_{MIN}$ and IVCCI had AUCs that were moderately predictive, 0.74 to 0.75. Our lower cutoff of 41% for IVCCI is similar to results of other studies for fluid responsiveness.[21,34,35]

The combination of a small IVCD$_{MIN}$ and high IVCCI collapsibility has been shown to be predictive of fluid responsiveness in ICU patients.[36] However, when we combined these two measures in a model as Logistic(IVCD$_{MAX}$ + IVCCI), this did not significantly increase the AUC (0.75), but did increase PPV with a lower NPV. We recommend that either failure to replete IVCD$_{MAX}$ or IVCCI can be used to predict increased 24FR after initial standard of care initial trauma resuscitation.

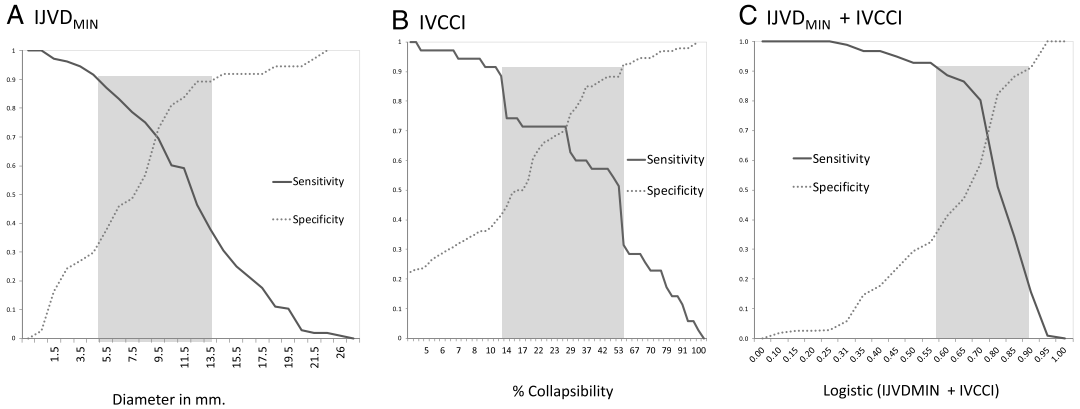

Figure 3. Gray zone analysis of IVC measures.

TABLE 4. Diagnostic Accuracy of Predictive Measures

Measure	n	−24FR	+24FR	% Measurable	PPV	NPV	AUC
Base deficit	120	≥3.1	≤ −5.3	22%	62%	17%	0.63
ISS	123	3.5	32	29%	81%	63%	0.65
$IVCD_{MIN}$	144	≤5 mm	≥13 mm	55%	55%	88%	0.74
$IVCD_{MAX}$	123	≤7.5 mm	≥20 mm	29%	55%	86%	0.69
IVCCI	115	≤41%	≥51%	89%	53%	81%	0.75
$IJVD_{MIN}$	103	≤2 mm	≥11.5 mm	31%	50%	31%	0.48
$IJVD_{MAX}$	78	≤3 mm	≥15 mm	23%	65%	24%	0.46
IJVCI	77	≤8%	≥65%	27%	81%	35%	0.54
$IVCD_{MIN}$ + IVCCI	115	≤0.56	≥0.85	55%	82%	65%	0.75

% measurable is the percent of patients not in the gray zone, but in the upper and lower threshold categories.

Our study has several limitations. The failure of our IJV measurements to predict 24FR after standard of care initial trauma resuscitation may be due to several factors. Prior studies using IJV measurements either used ventilated patients,[5,6] employed positional variation in ICU patients[21] or examined ICU patients in semirecumbent position.[5] However, less than 10% of our patients were ventilated, and we did not elevate our patient's heads by protocol and could not do so in most of our major trauma patients due to the need for a workup to rule out spinal injury. This likely compromised the utility of our IJV measures. We also only collected IJV measures in the second half of the study, thereby increasing the risk of a type II statistical error.

The fluid resuscitation volumes given were not specified by any study protocol beyond the usual practices at the center, which are informed by trauma guidelines such as the Advanced Trauma Life Support course. Other issues may have influenced decision making about intravenous fluid administration rates such as an intent to avoid excess crystalloid administration, avoid contrast nephropathy, avoid electrolytic derangement or dilutional coagulopathy. However, there was no significant difference in the volume of initial resuscitation intravenous fluids given between groups.

We had a failure rate of 19.5% to obtain usable images in qualified patients, although this is similar to similar studies.[11] Only 14% of stored images were unusable, which is better than some comparable studies. Operator experience did not affect the quality of images, as previously seen.[11] A significant issue was lost images, which usually occurred when the correct images were obtained but errors were made in saving the images to the machines' internal memory storage or to the PACS system. While we used a common protocol and training video for all sonographers, each of the centers had different ultrasound machines. Although the imaging techniques and modes were similar between machines, each machine has a different keypress sequence or required text entries to safely store and identify images. These differences should be addressed in training for any future multicenter study. Newer US machines have the ability to instantaneously and wirelessly store studies in a cloud-based PACS systems, sometimes with voice enabled dictation, which may alleviate these issues. If we had included the lost and unusable images in our statistics in the same manner as in an-intent-to-treat analysis, the usefulness of the measures would suffer. However, in clinical practice, decision making about fluid resuscitation occurs simultaneously with imaging, and so such storage problems may be less important.

Another limitation was the low prevalence of small or collapsible IVC at admission of screened major trauma patients. This rarity of IVC collapsibility at admission for major trauma patients led to a low rate of patient accrual during the study. A reason for this may be due to administration of prehospital intravenous fluid, which a large majority of the blunt trauma patients transported by EMS to our centers received but only 47% of enrolled study patients received. The mean prehospital infused volumes for study patients were also quite small, only 212 mL. Based on prior literature, we had plan to enroll patients with an initial US $IVCD_{MIN}$ of 12 mm or less or 50% or greater IVCCI, which we now recognize overlaps the gray zones for these measures and very likely reduced recruitment of useable cases.

A further limitation in applying these results is that unlike many laboratory blood tests, in practice, US does have broad true gray areas. Determining exactly 41% collapsibility may be difficult for any provider to see at the bedside. Although we had high interrater reliability when measuring recorded images, clinicians will not have the same luxury as researchers making multiple measurements of ultrasound images while seated at a large monitor. In many disciplines, ultrasonographic assessment is often semiquantitative, using grading scales and ranges to describe physiologic findings. It may be worthwhile to consider the IVCCI and $IVCD_{MAX}$ assessments in trauma resuscitation to reflect ranges of very likely, possibly and unlikely to be fluid repleted. Like FAST, US assessment is always made in the context of a dynamic situation, that is, the resuscitation of an acute major trauma patient, and other clinical and laboratory assessments for fluid responsiveness will continue to be contributory.

Another possible limitation is that administration of intravenous chloride in normal saline solutions may make the base deficit artificially lower in those receiving normal saline. While base deficit is commonly used to assess resuscitation fluid requirements, in our study, it was a weaker predictor of 24FR than $IVCD_{MIN}$ or IVCCI. There was no preference specified in the protocol for Lactated Ringer's over normal saline for each study center's standard resuscitation. However, the intravenous volumes given before the ABG samples were obtained were less than a liter, on average, and not likely to cause significant hyperchloremia.

By design, we limited our examinations to the IVC and IJV, which reflect the capacity of the venous system supplying

the right heart. Other studies have combined these measures with left and right heart echocardiographic assessments, in an attempt to improve the utility of US assessment of hemodynamics. Such techniques may also allow the operator to overcome issues with body habitus, spine precautions, bowel gas and air in tissues that may limit IVC or IJ US assessment. The most common combinations are cardiac ventricular volumes or flows by using Doppler mode velocity time integral, cardiac output or stroke volume with IVC or IJV sizes and CI.[20,21,37,38] While these techniques may improve the detection of fluid responsiveness, they require the operator-intensivist to be familiar with echocardiography and make quantitative assessments using modes, such as velocity time integral, which may limit utility with less-trained providers and in environments more austere than the academic center's ICU. Another set of combinations not requiring skills in echocardiography is to combine IVCD, IJVD, IVCCI, or IJVCI with US assessment of other vessels[39] or with other hemodynamic measurements, such as mean arterial pressure,[40] shock index or arterial line-derived stroke volume variation.[5] These have yet to undergo trials in major trauma patients.

In conclusion, US assessment of fluid repletion of IVC diameter and collapsibility provides a rapid, noninvasive way to determine the 24FR of major trauma victims within 1 hour of admission. We were unable to show that IJV diameter and collapsibility were predictive of 24FR in supine major trauma victims receiving standard of care resuscitation without other provocative maneuvers. Future clinical research should focus on rapid, reproducible, and easy-to-perform noninvasive imaging approaches that limit the harm from either unrecognized hypovolemia or overresuscitation. Already available are a second generation of low cost, handheld pocket-sized ultrasound devices that are wireless or connect to personal smartphones. These promise to make US assessment ubiquitous inside and outside the hospital by multiple disciplines and provider types. In the near future, low-cost, disposable, conformal ultrasound bandages may be worn in austere, prehospital and hospital environments to provide continuous recording of hemodynamic parameters.[41,42] We can easily predict that there will be a continuing search to find the optimal noninvasive US hemodynamic measure for occult hypovolemia.

AUTHORSHIP

J.D. participated in the literature search, study design, data collection, data analysis, data interpretation, and writing. P.F. participated in the study design, data collection, critical revision. S.M. participated in the data collection and critical revision. R.N. participated in the study design, data collection, and critical revision. S.E. participated in the data collection, data analysis, and critical revision. E.C. participated in the data collection, data analysis, and critical revision. J.H. participated in the data collection. D.H. participated in the data collection and critical revision. A.S. participated in the data collection and data analysis. K.B. participated in the data collection. G.C. participated in the critical revision. R.C. participated in the critical revision.

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DISCLOSURE

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