Title

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Journal

Journal of Acute Medicine, 11(4)

ISSN

2211-5587

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Publication Date

2021-12-01

DOI

10.6705/j.jacme.202112_11(4).0002

Peer reviewed

Journal of Acute Medicine 11(4): 129-140, 2021
DOI:10.6705/j.jacme.202112_11(4).0002
Original Article

Shock Management Without Formal Fluid Responsiveness Assessment: A Retrospective Analysis of Fluid Responsiveness and Its Outcomes

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Background: In order to quantify fluid administration and evaluate the clinical consequences of conservative fluid management without hemodynamic monitoring in undifferentiated shock, we analyzed previously collected data from a study of carotid Doppler monitoring as a predictor of fluid responsiveness (FR).

Methods: This study was a retrospective analysis of data collected from a single tertiary academic center from a previous study. Seventy-four patients were included for post-hoc analysis, and 52 of them were identified as fluid responsive (cardiac output increase > 10% with passive leg raise) according to NICOM™ bioreactance monitoring (Cheetah Medical, Newton Center, MA, USA). Treating teams provided standard of care conservative fluid resuscitation but were blinded to independently performed FR testing results. Outcomes were compared between fluid responsive and fluid non-responsive patients. Primary outcome measures were volume fluids administered and net fluid balance 24- and 72-hour post-FR assessment. Secondary outcome measures included change in vasopressor requirements, mean peak lactate levels, length of hospital/intensive care unit stay, acute respiratory failure, hemodialysis requirement, and durations of vasopressors and mechanical ventilation.

Results: Mean fluids administered within 72 hours were similar between fluid non-responsive and fluid responsive patients (139 mL/kg [95% confidence interval [CI]: 102.00–175.00] vs. 136 mL/kg [95% CI: 113.00–158.00], $p = 0.92$, respectively). We observed an insignificant trend toward higher 28-day mortality among fluid non-responsive patients (36% vs. 19%, $p = 0.14$). Volume of fluids administered significantly correlated with adverse outcomes such as increased hemodialysis requirements (32 patients, 43%), (odds ratio [OR] = 1.7200, $p = 0.0018$). Subgroup analysis suggested administering ≥ 30 mL/kg fluids to fluid responsive patients had a trend toward increased mortality (25% vs. 0%, $p = 0.09$) and a significant increase in hemodialysis (55% vs. 17%, $p = 0.024$).

Conclusions: Without formal FR assessment, similar amounts of total fluids were administered in both fluid responsive and non-responsive patients. As greater volumes of intravenous fluids administered were associated with adverse outcomes, we suggest that dedicated FR assessment may be a beneficial utility in early shock resuscitation.

Key words: *fluid responsiveness, fluid resuscitation, shock, hemodialysis, hemodynamic monitoring*

Received: September 25, 2020; Revised: February 22, 2021 (3rd); Accepted: April 23, 2021.
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Introduction

While intravenous fluid administration represents one of the most substantial therapies in shock management, excessive fluids have been associated with cardiac congestion and tissue edema, increased length of hospital/intensive care unit (ICU) stay, and overall increased morbidity and mortality.[1-3] Avoiding fluid over-administration is crucial, especially knowing that only about 50% of hemodynamically unstable patients respond to fluid administration with the desired increase in cardiac output (CO).[4] Fluid responsiveness (FR) is most often defined as a > 10% increase in cardiac stroke volume (SV) in response to a fluid challenge and is an increasingly monitored parameter in the ICU used to guide fluid resuscitation in the context of shock.[5,6] Assessment of FR is critical to the management of shock, allowing for more judicious administration of fluids which has been proven to be beneficial, though there may be some limitations with static measurements of FR.[7-15] Nevertheless, managing shock with a standard of care, conservative approach of judicious fluid administration, but without formal FR testing, has not been widely evaluated in published literature.[16]

We revisited data from our previous prospective trial in a single tertiary academic center which evaluated the efficacy of carotid Doppler assessment of FR.[17] All patients had FR testing completed at the enrollment to the study, which was blinded to the caring teams. Thus, we were able to assess differences in fluid administration between patients who were fluid responsive and those who were fluid non-responsive while care teams had been unaware of the patients' hemodynamic statuses. In these retrospective analyses, we investigated whether usual care, which assumes a conservative approach to fluid management that does not encompass formal FR testing, can adequately guide fluid administration in a cohort of patients in early shock. While multiple studies have explored the outcomes in FR-based conservative vs. less conservative fluid management, our retrospective analyses evaluated FR as a sole predictor of adverse outcomes and whether clinicians could tailor fluid management accordingly without hemodynamic monitoring. We hypothesized that without formal FR monitoring, clinicians would not be able to adjust volumes of fluids administered between responsive and non-responsive patients and may cause more adverse outcomes in patients who received excessive fluid volumes as a result.

Methods

In our original study,[17] adult patients with newly diagnosed undifferentiated shock with persistent vasopressor requirements despite fluid resuscitation > 1 L were enrolled in the study after informed consent. Additionally, patients must have had evidence of new multi-organ system failure (> 2 systems) or lactate of > 40 mg/dL before study inclusion. While care teams were aware of recently published fluid resuscitation guidelines and were thus incentivized to apply conservative fluid resuscitation strategies, fluid administration was based on clinician judgment without the results of formal FR testing.[6] While there was no specific protocol for fluid administration, conservative fluid management/usual care consisted of initially administering at most 30 mL/kg followed by cautiously titrating additional fluid boluses thereafter based on the providers' discretions. Exclusion criteria included a history of known left/right-sided heart failure, pulmonary hypertension, cardiac rhythm other than sinus, significant peripheral vascular disease, suspected or known increased intracranial pressure, recent abdominal surgery, a recent history of venous thromboembolism, and body mass index (BMI) < 15 (severely underweight) or > 35 kg/m^2 (World Health Organization [WHO] class II obesity).[18]

Assessment of FR

Our chosen measure of FR assessment was the non-invasive bioreactance CO monitoring (NICOM^{TM}, Cheetah Medical, Newton Center, MA, USA) in combination with the passive leg raise (PLR) test as the fluid challenge, which is a validated method of FR assessment and employed as the "gold standard" in the original study.[19-21] Patients showing ≥ 10% increase in SV after the PLR test were deemed "fluid responsive" while those who had a < 10% increase in SV were considered "fluid non-responsive." The patients were assessed within 24 hours after their diagnosis of undifferentiated shock. As the original study protocol was non-interventional, primary teams were not made aware of both the FR-testing results and NICOM^{TM} hemodynamic measurements, allowing for usual conservative fluid management without FR comprehensive assessment.

Chart Review

All patient charts from our prospective cohort were reviewed to measure the total volume of administered fluids and net fluid balance in 24- and 72-hour periods beginning with the completion of the FR assessment. As the target patient population for the original study had BMIs that ranged from 15–35 kg/m^2, fluid volumes were corrected by the patient's weight on admission. Volumes of fluids administered and net fluid balance were then compared between fluid responsive and non-responsive patients, and the values are represented as mL/kg.

Outcomes

Our primary outcome measures were all-cause mortality within 28 days post-admission as well as fluids administered and fluid balance at 24 and 72 hours. Fluid outcomes are expressed as median (IQR [interquartile range]) because of the non-normal distribution of the data. Secondary outcome measures included change in vasopressor requirements within 12 hours, peak lactate level, length of stay (LOS) in the ICU and the hospital, duration of vasopressor treatment, duration of invasive mechanical ventilation, and renal dysfunction as defined by the decrease in estimated glomerular filtration rate (eGFR) by 33%[22] and new hemodialysis requirement after the onset of shock. These data points were collected during the original study except for volumes of fluid administered and net fluid balance.[17]

Multivariate Outcomes Analyses

Given that the objectives of our analyses include elucidating the relationship between FR and adverse outcomes, we next performed multivariate logistic regression analyses to further evaluate mortality with respect to the patients' initial FR status. This allowed for the consideration of other comorbidities such as a hemodialysis requirement between fluid responsive and non-responsive patients simultaneously with FR. Additionally, secondary outcomes of LOS in the hospital/ICU were further analyzed through negative binomial regression models with consideration to hemodialysis requirement and FR status. We have selected hemodialysis requirement as an additional predictor variable to FR because of its well-defined association with increased mortality, fluid retention and overload, and edema.[23]

Subgroup Analyses

In order to explore the effect of greater fluid resuscitation in combination with the patient's FR status, responsive and non-responsive patients were further subdivided into those who received at least 30 mL/kg of fluids within 24-hour after FR assessment and those who received less within the same period. The cut-off point of 30 mL/kg was selected as it currently stands as the recommended minimum of fluid resuscitation according to the surviving sepsis campaign.[6] As emerging evidence[24] describes this dosage recommendation may lead to excessive fluid administration, the patients in our study who received more than 30 mL/kg were categorized into subgroup: "Liberal Management" while the others were categorized as subgroup: "Conservative Management." Differences in occurrence in our primary outcome measure of 28-day all-cause mortality and hemodialysis requirement within these subgroups were analyzed.

Statistical Methods

Twenty-eight-day mortality and other binary outcomes were analyzed using Fisher's exact chi-square tests. Non-normally distributed continuous outcomes such as the volume of fluids administered and net fluid balance were analyzed by Wilcoxon rank-sum. Relationships between total fluid volume administered and secondary outcomes were analyzed with linear regression for continuous outcomes. Additionally, correlations between the volume of fluids administered and binomial outcomes such as mortality and acute respiratory failure were analyzed with simple logistic regressions.

Results

The baseline characteristics of patients who were enrolled in the study are displayed in Table 1. Of the 74 patients, 52 (70.3%) were fluid responsive, while 22 (29.7%) patients were fluid non-responsive. During study inclusion, patients were newly diagnosed with undifferentiated shock with the persistence of systolic blood pressure < 90 or mean arterial pressure (MAP) < 65 or ongoing requirement for vasopressor medications to maintain MAP > 65 or systolic blood pressure > 90. Most of our cohort of patients experienced septic shock (82.0%); however, every patient had evidence of new multi-organ system fail-

Table 1. Baseline patient characteristics

Patient characteristic	Total (N = 74)	Fluid non-responsive (n = 22)	Fluid responsive (n = 52)	*p*
Age, mean ± SD, years	60.0 ± 17.0	59.3 ± 17.0	60.4 ± 17.0	0.80
Female, n (%)	36.0 (49.0)	8.0 (36.0)	28.0 (55.0)	0.20
Body mass index, mean ± SD, kg/m^2	24.0 ± 8.0	24.3 ± 6.0	24.8 ± 6.0	0.75
Hematocrit, mean ± SD, %	29.2 ± 7.0	28.8 ± 6.0	29.4 ± 7.0	0.72
End-stage renal disease (ESRD), n (%)	13.0 (18.0)	3.0 (14.0)	10.0 (19.0)	0.56
Total fluids received from onset of shock, 72 hours, mean ± SD, L	8.0 ± 5.0	8.3 ± 4.5	8.4 ± 5.4	0.94
Mechanical ventilation, n(%)	43.0 (58.0)	13.0 (59.0)	30.0 (58.0)	0.80
Passive ventilation, n (% of ventilated patients)	21.0 (49.0)	6.0 (33.0)	15.0 (31.0)	1.00
PEEP > 5 mmHg, n (%)	18.0 (26.4)	2.0 (11.0)	16.0 (33.0)	0.07
Etiology of shock				
Distributive/septic, n (%)	61.0 (82.0)	19.0 (86.0)	42.0 (81.0)	0.56
Hypovolemic, n (%)	2.0 (3.0)	0.0	2.0 (4.0)	1.00
Cardiogenic, n (%)	2.0 (3.0)	0.0	2.0 (4.0)	1.00
Neurogenic, n (%)	1.0 (1.0)	0.0	1.0 (2.0)	1.00
Unknown, n (%)	8.0 (11.0)	3.0 (14.0)	5.0 (10.0)	0.69
Vasopressor used				
Norepinephrine, n (%)	53.0 (74.0)	16.0 (72.0)	37.0 (74.0)	1.00
Dopamine, n (%)	4.0 (6.0)	3.0 (14.0)	1.0 (2.0)	0.08
Vasopressin, n (%)	1.0 (1.0)	0.0 (0.0)	1.0 (2.0)	1.00
Phenylephrine, n (%)	5.0 (7.0)	1.0 (5.0)	4.0 (8.0)	1.00
Combination, n (%)	9.0 (13.0)	2.0 (9.0)	7.0 (14.0)	0.71
APACHE II, mean ± SD	27.00 ± 7.40	25.00 ± 7.30	27.00 ± 7.50	0.53

APACHE: acute physiology and chronic health evaluation; PEEP: positive end-expiratory pressure; SD: standard deviation.

ure (> 2 systems) or a lactate of > 40 mg/dL. Patients with a known history of left or right heart failure were excluded from the original study.

The Relationships Between Initial FR, Hemodialysis Requirement, and 28-Day Mortality

Within the entire cohort, 18 patients (24%) had died within 28 days. There was a trend toward higher 28-day mortality among the fluid non-responsive group (36% vs. 19%, $p = 0.14$), though this did not reach statistical significance.

Multivariate logistic regression analyses showed that hemodialysis requirement had a significant positive association with mortality when taken into consideration with FR concurrently (odds ratio [OR]: 3.39, 95% confidence interval [CI]: 1.05–10.90, $p = 0.04$). While holding hemodialysis requirement constant, no significant association was found between FR and mortality (OR: 0.41, 95% CI: 0.12–1.35, $p = 0.14$).

Fluid Volumes Administered by Standard of Care was Not Different Between Fluid Responsive and Fluid Non-Responsive Patients

Of the total 52 identified fluid responsive patients, 6 (11.5% of fluid responsive cohort) were discharged less than 72-hour post-FR evaluation and were therefore removed from comparison for the 72-hour time point. All data points for 24-hour evaluation were available for analysis.

There was no significant difference in either fluid administration or net fluid balance between fluid responsive and non-responsive patients at both

time points of 24- and 72-hours. As shown in Table 2, median fluids administered within 72 hours after NICOM™ assessment were similar between non-responsive and responsive patients (108.00 mL/kg [67.80 to 189.00] vs. 130.00 [86.20 to 166.00], p = 0.92). Further analyzing administered fluid volume in patients who died within 28 days, there were no significant differences in neither median total fluids administered (98.00 mL/kg [66.60 to 218.00] vs. 154.00 mL/kg [126.00 to 165.00], p = 0.34) nor net fluid balance (3.91 mL/kg [–36.10 to 14.00] vs. –6.01 mL/kg [–7.89 to 33.10], p = 0.87) between non-responsive and responsive patients. These results are visualized in Fig. 1.

Volume of Fluids Administered Correlated With Adverse Outcomes

Linear regression analyses showed that greater volumes of fluids administered in 72 hours significantly correlated with increased LOS in the ICU (β = 1.77, r^2 = 0.044, p = 0.05) and in the hospital (β = 1.80, r^2 = 0.046, p = 0.047). Greater volumes of fluids administered were also significantly correlated with increased duration of vasopressor treatment (β = 13.40, r^2 = 0.160, p < 0.001) and duration of invasive mechanical ventilation (β = 1.06, r^2 = 0.120, p = 0.01). The coefficients of each simple linear regression are displayed in Table 3.

Simple logistic regression analyses described the following associations between total fluids administered over 72 hours and binomial outcomes within the entire cohort. There were no correlations between administered fluid volume and 28-day mortality, (OR = 1.10, p = 0.47), respiratory failure leading to intubation (OR = 1.21, p = 0.21), renal dysfunction (OR = 0.88, p = 0.50), or ability to wean from vasopressors within 12 hours of FR assessment (OR = 1.00, p = 1.00). However, greater total administered volumes were significantly associated with increased hemodialysis requirements (32 patients, 43%), (OR = 1.72, p = 0.0018).

FR Alone was Not Associated With Significant Differences in Outcomes

Fluid responsive patients more often had vasopressors discontinued in the first 12 hours (23% vs. 9%, p = 0.20) yet saw higher mean lactate levels, (37.3 mg/dL ± 42.9 vs. 27.9 mg/dL ± 25.0, p = 0.33), though again these findings did not reach statistical significance. Full results are available in Table 4.

FR, Hemodialysis Requirement, and Their Relationships to LOS

Negative binomial regression analyses showed that hemodialysis requirement (incidence rate ratio [IRR] = 1.71 [95% CI: 1.10–2.67], p = 0.02) has a greater effect on hospital LOS than FR (IRR = 1.16 [95% CI: 0.72–1.89], p = 0.55) when both were taken into consideration concurrently. Similar results were seen for ICU LOS: hemodialysis requirement (IRR = 1.86 [95% CI: 1.18–2.93], p < 0.01) and FR (IRR = 1.33 [95% CI: 0.81–2.19], p = 0.26).

Subgroup Analyses

Fluid responsive patients who received ≥ 30 mL/kg had a trend toward increased mortality (25% vs. 0%, p = 0.09) and a significant increase in hemodialysis requirement (55% vs. 17%, p = 0.024) when compared to fluid responsive patients who received < 30 mL/kg. The results are tabulated in Table 5.

Table 2. Volumes of fluids administered and net fluid balance between fluid non-responsive and responsive individuals

Volume	Fluid non-responsive (n = 22)	Fluid responsive (n = 52)	p
Fluids administered			
24 hours after PLR test, mL/kg, median (IQR)	38.30 (18.70 to 79.70)	45.70 (32.00 to 62.80)	0.80
72 hours after PLR test, mL/kg, median (IQR)	108.00 (67.80 to 189.00)	130.00 (86.20 to 166.00)[a]	0.92
Net fluid balance			
24 hours after PLR test, mL/kg, median (IQR)	2.65 (–6.28 to 20.70)	3.90 (–10.70 to 26.80)	0.53
72 hours after PLR test, mL/kg, median (IQR)	11.00 (–22.90 to 38.30)	2.37 (–36.30 to 36.60)[a]	0.60

[a]Six fluid responsive patients were not available for 72 hour-fluid analyses because of early discharge or death.
IQR: interquartile range; PLR: passive leg raise.

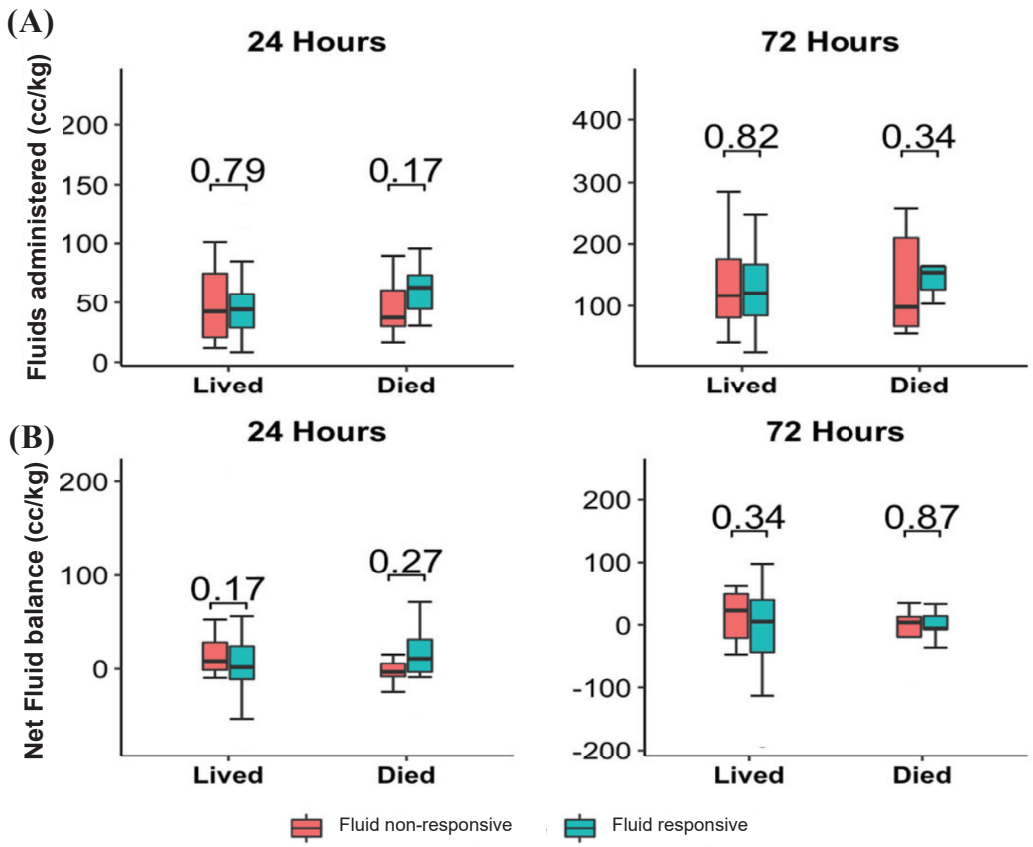

Fig. 1. Box plot representation between fluid non-responsive and responsive patients by 28-day mortality. (A) Volume of fluids administered over 24- and 72-hour time points. (B) Net fluid balance over 24- and 72-hour time points. No significant differences in fluid volumes were found between fluid non-responsive and responsive patients who died within 28 days nor those who lived.

Table 3. Linear regression coefficients: correlations of total fluids administered over 72 hours vs. secondary outcomes

Secondary outcome	df	β	Std. error	r^2	t	*p*
LOS in the ICU, days	64	1.77	0.89	0.044	1.99	0.05
LOS in the hospital, days	64	1.80	0.89	0.046	2.03	0.047
Duration of vasopressor treatment, hours	64	13.40	3.66	0.160	3.66	< 0.001
Duration of invasive mechanical ventilation, days	43	1.06	0.40	0.120	2.63	0.01

β: estimate/slope; df: degrees of freedom; ICU: intensive care unit; LOS: length of stay; Std.: standard.

Discussion

In this analysis, we evaluated the outcomes of a general conservative approach to fluid management in a population of critically ill patients with undifferentiated shock whose FR status was unknown to care providers at the time. Because FR in this population was previously determined in the original study, we were able to retrospectively assess the correlation between predetermined FR and the outcomes following standard conservative treatment.

In the absence of formal hemodynamic monitoring, there was no difference in the volume of intravenous fluids administered between fluid responsive and non-responsive patients, even after volumes were corrected by patient weight. These findings indicated that

Table 4. Primary and secondary outcomes table

Outcome	Total (N = 74)	Fluid non-responsive (n = 22)	Fluid responsive (n = 52)	*p*
Primary outcome				
28-day mortality, n (%)	18 (24)	8 (36)	10 (19)	0.14
Secondary outcomes				
Change in vasopressor requirements in 12 hours after PLR test				
Vasopressor treatment removed, n (%)	14 (19)	2 (9)	12 (23)	0.20
Mean peak lactate levels (mg/dL), mean (SD)	34.0 (37.7)	27.9 (25.0)	37.3 (42.9)	0.33
LOS				
LOS in the ICU, median (IQR)	13.0 (7.0–31.2)	12.0 (7.0–25.0)	13.0 (7.0–36.0)	0.56
LOS in the hospital, median (IQR)	15.5 (8.0–35.0)	15.0 (8.0–26.0)	16.0 (8.0–41.0)	0.57
Duration of vasopressor treatment (hours), median (IQR)	40.0 (18.0–96.0)	43.0 (32.0–144.0)	40.0 (17.5–72.5)	0.34
Duration of invasive mechanical ventilation (days), median (IQR)	7.0 (3.5–17.5)	5.0 (3.0–20.0)	7.0 (4.0–15.0)	0.90
Acute respiratory failure requiring intubation and mechanical ventilation, n (%)	52 (70)	12 (55)	40 (77)	0.27
Renal dysfunction				
eGFR 33% decrease, n (%)	13 (18)	2 (9)	11 (21)	0.32
Hemodialysis requirement or unrecovered profound renal failure, n (%)	32 (43)	8 (36)	24 (46)	0.61

eGFR: estimated glomerular filtration rate.

Table 5. Comparison of 28-day mortality and renal dysfunction incidences between liberal and conservative management[a]

Fluid responsive	Total responsive (n = 52)	Liberal management ≥ 30 mL/kg (n = 40)	Conservative management < 30 mL/kg (n = 12)	*p*
28-day mortality, n (%)	10 (19)	10 (25)	0	0.09
Hemodialysis requirement or unrecovered profound renal failure after onset of shock, n (%)	24 (46)	22 (55)	2 (17)	0.024*
Fluid non-responsive, n (%)	**Total non-responsive (n = 22)**	**Liberal management ≥ 30 mL/kg (n = 16)**	**Conservative management < 30 mL/kg (n = 6)**	***p***
28-day mortality, n (%)	8 (36)	6 (38)	2 (33)	1.00
Hemodialysis requirement or unrecovered profound renal failure after onset of shock, n (%)	8 (36)	7 (44)[b]	1 (17)	0.34

[a] Subgroup analyses within fluid responsive and non-responsive cohorts according to the volume of fluids received (mL/kg) after fluid responsiveness-assessment.
[b] One patient was excluded from hemodialysis requirement analysis because of early inpatient mortality shortly after fluid responsiveness-assessment.
* $p < 0.05$.

clinicians did not treat non-responsive patients differently from responsive patients. Although the clinical utility of FR status is still emerging, the fact that our non-responsive patients received similar amounts of fluids as fluid responsive patients may suggest that this FR can be difficult to discern without the use of hemodynamic testing. Thus, future applications of FR may necessitate a form of hemodynamic monitoring. In contrast to past major trials, such as Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe), patients in our study had received more fluids on average over 72 hours by usual care (8.84 L, compared with 6.63 L, 6.10 L, and 5.84 L, respectively).[25-27] These discrepancies in fluids administered between our cohort and the major trials may be attributed to a quicker response in enrollment as our patients were evaluated within 24 hours after shock identification while patients in the major trials were evaluated within 12 hours. Nevertheless, the fact that our cohort ultimately received more fluids during the study period may indicate that our patients were more aggressively fluid resuscitated despite the intention of conservative management. The recent ANDROMEDA-SHOCK trial demonstrated that FR-guided management can result in a decrease in the volume of fluids administered for fluid non-responsive patients without producing any significant difference in mortality.[28] Additionally, a recent randomized trial demonstrated a reduced net fluid balance if fluid resuscitation was guided by changes in SV after PLR and the additional benefit of improved discharge to home.[29] These findings suggest that non-responsive patients in our cohort could have avoided receiving more fluids if their responsiveness status was known without the risk of producing adverse effects.

It is not yet clear whether FR improves the prognosis of shock patients requiring fluid resuscitation. However, in this study, we observed a trend toward increased mortality in non-responsive patients receiving standard methods of fluid resuscitation. Our multivariate analyses showed that when FR and hemodialysis requirement after shock onset were concurrently evaluated for associations with mortality or LOS in the hospital/ICU, hemodialysis had a significantly greater effect on these outcomes than the patient's FR status. This is an expected finding given the known association between renal failure and mortality.[30,31] These findings further emphasize the need for careful fluid resuscitation in patients on hemodialysis. We speculate that dedicated hemodynamic monitoring may be beneficial especially for patients with underlying kidney dysfunction though further studies within this specific patient population are warranted.[32,33]

Despite the lack of statistically significant associations between FR and mortality and LOS, there is evidence that FR may still play a role in predicting response to fluid resuscitation. In our subgroup analyses, fluid responsive individuals who received 30 mL/kg or more during the first 24 hours after FR assessment had an increased requirement for hemodialysis. Such findings are also supported by the ProCESS trial, in which the incidence of newly developed acute kidney injury was significantly higher among patients who received greater volumes of fluid, even within the protocol-based group which called for fluid management guided by central venous pressure monitoring.[34] That this association was not seen in fluid non-responsive individuals suggests that further research is needed as to whether FR may serve as an independent variable affecting the relative risk of adverse renal outcomes with over-resuscitation. However, we recognize the difficulty in determining whether fluid overload during resuscitation caused an increased incidence of hemodialysis or if the need for hemodialysis led to fluid overload.[35] While elucidating the cause-and-effect relationship between fluid overload and hemodialysis is beyond the scope of this paper, we believe that further studies are warranted on whether excessive fluid administration could have increased incidences of comorbidities, such as hemodialysis, as a function of the patient's FR status.

In addition to increased hemodialysis, we also observed an increased trend toward mortality in fluid responsive patients who received > 30 mL/kg during the study period. This observation within our fluid responsive patients may suggest that a single-point identification of the patient's initial FR status alone may not be sufficient to guide fluid administration, particularly later in the course of shock. While it is assumed that FR status suggests a propensity to improve with fluids, our findings indicate the need for a more nuanced interpretation. In addition, FR is very likely to be a dynamic characteristic that changes over time during fluid resuscitation.[4,28] Therefore, repeated assessments of FR would be warranted because of our previously discussed finding that clinicians tend

to provide comparable volumes of fluid to shock patients when the fluid responsiveness status is not known. While our study was not sufficiently powered for these subanalysis endpoints, these findings raise interesting questions as to whether FR may still be able to identify patients who are especially vulnerable to excessive fluid administration.

While the current literature has not found an association between FR-guided fluid management and a decrease in mortality, many acknowledge the need for adequately powered trials to reach a more definitive answer as to the utility of FR.[36] We feel that our preliminary observations point to a possibility that FR may play a complicated role in affecting a patient's outcomes following fluid over-resuscitation. It is important to note that our clinicians delivered the same fluid volumes to both responsive and non-responsive patients in the absence of hemodynamic monitoring. However, we find that the need for a standardized protocol for fluid resuscitation is still clear. Our results are in agreement with published data suggesting that prolonged positive net fluid balance and fluid over-administration are associated with increased mortality.[37] In this study, linear regression analysis showed an association between increased fluid volumes and increased hospital and ICU LOS, duration of vasopressor treatment, and hemodialysis requirement, strengthening the evidence for conscientious fluid management for patients in shock.

For these reasons, continuous hemodynamic monitoring may prove to be beneficial for preventing fluid over-resuscitation and potential sequelae. However, the best method of hemodynamic monitoring may need to be individualized to the patient and future studies may yet uncover a superior method of FR assessment.[38] For example, mechanically ventilated patients' FR may be assessed by measuring percent changes in the inferior vena cava diameter (caval index) using bedside ultrasound; however, factors that affect venous return, such as right-ventricular dysfunction, may decrease this method's accuracy.[38] There are also emerging methods such as measuring the partial pressure differences between venous and arterial carbon dioxide levels to monitor tissue hypoperfusion and the need for fluid resuscitation.[39] These may prove to be ideal methods because of their ease of use in the ICU setting, where patients may require continuous or repeated reassessments to guide fluid resuscitation. Our specific cohort of patients' FR statuses was initially assessed using PLR and response with CO monitoring with NICOM™ bioreactance, which we previously found to be reliably substituted with carotid corrected flow time via bedside ultrasound.[17]

This study has several strengths that are worth emphasizing. While several other studies identify the benefits of conservative fluid management based on FR assessment in shock, our study is unique as it focuses on the possible consequences of fluid management without hemodynamic monitoring. This approach applies the principles of conservative fluid administration under current guidelines but remains blinded to the formal FR testing results during the process of fluid resuscitation in shock. FR was tested by a well-validated method using PLR and non-invasive NICOM™ CO monitoring after the initial fluid resuscitation was completed, and we were able to analyze fluid management in later stages of fluid resuscitation, notably 24- and 72-hour after the initial FR testing. While our cohort is composed of sick patients in shock who required vasopressor support (average APACHE II score 27), it fairly balanced a ratio of patients who were fluid non-responsive (30%) in comparison to fluid responsive ones, which allows for an adequate insight into the real-life scenarios where FR testing may be of crucial importance.

We recognize, however, that our study also has several limitations. Our outcome measures showed trends but no statistically significant associations, likely because of our original prospective cohort being underpowered for this series of post hoc analyses. While most of our discussions encompassed fluid resuscitation guidelines in the context of sepsis, our cohort also included a minority of cases with neurogenic, cardiogenic, and hypovolemic etiologies of shock. However, our exclusion criteria included known right or left heart failure history, and all patients were considered to suffer from an undifferentiated shock at the time of enrollment (all patients had evidence of end-organ dysfunction or lactate > 40 mg/dL in the setting of undifferentiated shock), thus allowing for the extrapolation of our findings beyond septic shock alone. As such, our data present a preliminary assessment of the utility of FR in determining patient outcomes. We also recognize the statistical limitations of our multivariate logistic regressions and negative binomial regressions, as predictor variables were selected by clinical judgment rather than a robust stepwise

selection with univariate modeling.[40] Although our secondary outcome of hemodialysis requirement was recorded for patients who needed hemodialysis after the onset of shock, this endpoint included patients who had a history of end-stage renal disease before enrollment in the original study (13% of our entire cohort). Therefore, it is difficult to characterize the relationships between mortality, FR, and hemodialysis accurately from our findings. Furthermore, FR was not continuously monitored throughout the duration of our original study.[17] As a result, we were unable to assess whether the patients' responsiveness may have changed within 24- and 72-hour time points following the initial FR assessment. Finally, while the institutional standard of care suggests applying conservative fluid management in patients with undifferentiated shock, the volume of fluid administered in study participants was higher than expected. This observation ultimately limits the extrapolation of our findings to be applied to populations of patients who were more conservatively fluid managed.

In conclusion, in our retrospective analyses, care teams could not practically distinguish fluid responsive from non-responsive patients without hemodynamic monitoring. A lack of continuous hemodynamic monitoring may lead to fluid over-resuscitation. Excessive fluid administration was associated with an increase in LOS in the hospital and ICU, duration of vasopressor treatment, and duration of invasive mechanical ventilation. We did not find significant differences in 28-day mortality between responsive and non-responsive patients. Fluid responsive patients who were over-resuscitated had an increased trend toward mortality and a significantly greater incidence of hemodialysis after the onset of shock. For these reasons, further studies are needed to demonstrate the role of early, repeated and non-invasive hemodynamic monitoring in preventing the adverse effects of liberal fluid resuscitation.

Conflicts of Interest Statement

The original study on ultrasound carotid Doppler evaluation of fluid responsiveness was financially and logistically supported by GE Healthcare (Chicago, IL, USA); however, no funding was used for post-hoc analyses and all time was donated by research associates.

Acknowledgments

We would like to acknowledge Dr. Nicholas Jackson at the UCLA Clinical and Translational Science Institute (CTSI) for his guidance on the statistical analysis of this data. This work was supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL-1TR001881.

We would like to acknowledge the patients who participated in the original study, the UCLA CTSI Research Associates Program, and the UCLA Reagan 4ICU nursing team who made this study possible.

Author Contributions

AH performed further chart review, analysis of the datasets, and wrote the initial draft of the paper. NV crafted the study design and was a major contributor to the writing and editing of the manuscript. WT was an author of the original prospective study and offered insight into the analysis of data. IB served as principal investigator and was a major contributor to the discussion and conclusion of the study. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The dataset has also been uploaded alongside the primary manuscript.

Consent for Publication

Not applicable.

Ethics Approval and Consent to Participate

This retrospective study has been conducted on a previous prospective trial which has been approved by the IRB. All data analyzed here have been collected during the original trial. IRB#15-001768.

Funding

None.

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