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Positive fluid balance was associated with mortality in patients with acute-on-chronic liver failure: A cohort study

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ABSTRACT

Purpose: We aimed to study the effect of FB in the outcomes of critically-ill patients with cirrhosis.
Materials: Retrospective analysis of all adult consecutive admissions of patients with cirrhosis and organ failures to the Intensive Care Unit (ICU) at Curry Cabral Hospital (Lisbon, Portugal) and University of Alberta Hospital (Edmonton, Canada) on 08/2013–08/2017. Primary exposure was FB at 3 and 7 days post ICU admission. Primary endpoint was hospital mortality.
Results: Amongst 333 patients, median age was 56 years and 67.6% were men. Median MELD, APACHEII, CLIF-SOFA, and CLIF-C-ACLF scores on ICU admission were 27, 28, 14, and 54, respectively. ICU and hospital mortality rates were 33.0% and 49.2%, respectively. While median FB at 3 days post ICU admission (+5.46 l vs. +6.62 l; $P = 0.74$) was not associated with hospital mortality, higher median FB at 7 days post ICU admission (+13.50 l vs. +6.90 l; $P = 0.036$) was associated with higher hospital mortality. This association remained significant (OR 95%CI = 1.04 [1.01;1.07] per each l) after adjustment for confounders (age, ascites, infection, lactate, and number of organ failures).
Conclusions: FB may be a therapeutic target that helps to improve the outcomes of patients with acute-on-chronic liver failure. This data may inform future clinical trials.

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1. Introduction

Patients with cirrhosis and organ failures (acute-on-chronic liver failure (ACLF)) admitted to the intensive care unit (ICU) have high short-term mortality rates, especially if they do not receive a liver transplant (LT) [1-3].

Virtually all critically-ill patients receive variable amounts of fluid therapy during their ICU stay. Fluid resuscitation of critically-ill patients encompasses 4 phases: rescue, optimization, stabilization, and de-escalation [4]. The duration and sequence of these phases varies widely amongst different patients.

During resuscitation, intravenous fluids are generally administered as early as possible and targeted to appropriate physiologic endpoints, commonly a mean arterial pressure of ≥65-70 mmHg and a serum lactate of ≤2 mmol/L. However, following achievement of hemodynamic stability, patients often continue to receive variable amounts of fluid therapy which ultimately may lead to fluid overload (FO). This additional fluid has the potential to accumulate in the tissues, especially in the context of increased capillary permeability such as in sepsis, and lead to end-organ edema and dysfunction [5]. In fact, several studies have shown that a persistent cumulative positive fluid balance (FB) negatively impacts the outcomes of critically-ill patients [6-8]. For example, in patients with sepsis, a positive FB was associated with worse 28-day survival [6]. Furthermore, in patients with acute lung injury, a positive FB was associated with further impaired oxygenation and prolonged need for mechanical ventilation [7]. Finally, in patients with acute renal failure, a positive FB was associated with worse 60-day survival [8].

In patients with cirrhosis and portal hypertension, the hemodynamic assessment has specific features. The splanchnic vasodilatation often results in effective hypovolemia which leads to the activation of the renin-angiotensin-aldosterone system causing further sodium and water retention [9]. The ensuing renal vasoconstriction, coupled with the potentially increased intra-abdominal pressure due to the ascites,

Abbreviations: ACLF, acute-on-chronic liver failure; aOR, adjusted odds ratio; CCH, Curry Cabral Hospital; CLIF, chronic liver failure consortium; FB, fluid balance; FO, fluid overload; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; UAH, University of Alberta Hospital.

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may lead to acute renal failure and further contribute to the fluid accumulation. In the context of critical illness, circulatory failure in these patients often results in greater reduction in the mean arterial pressure and tissue impaired perfusion [10]. Therefore, the resuscitation of patients with cirrhosis and portal hypertension is often challenging, especially when it comes to monitor early signs of FO.

There is lack of data about the impact of FB on the outcomes of patients with ACLF. We hypothesized that FO may contribute to higher short-term mortality in patients with ACLF. Accordingly, the objectives of this study were: (1) characterize the FB of patients with cirrhosis and organ failures admitted to the ICU; and (2) study the association of FB with these patient's outcomes.

2. Materials & methods

2.1. Study design, participants, and data collection

This was a retrospective analysis from a prospective registry of patients with cirrhosis and organ failures consecutively admitted to the ICUs of 2 regional LT centers, University of Alberta Hospital (UAH) in Edmonton, Canada, and Curry Cabral Hospital (CCH) in Lisbon, Portugal, between August 2013 and August 2017.

Patients were included if fulfilling the following criteria: age ≥ 18 years; diagnosed with cirrhosis and organ failures (see Definitions, exposures, and endpoints); and on first admission to the ICU during the inclusion period. Exclusion criteria were the following: diagnosis of acute liver failure; diagnosis of decompensated cirrhosis without organ failures; or previous LT.

Data on patients' characteristics were retrieved from manual and electronic medical records and collected in an anonymous and protected database. As this was a non-interventional study, local ethics committees waived the need for individual informed consent. All study procedures followed the principles of the Declaration of Helsinki [11]. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [12].

2.2. Definitions, exposures, and endpoints

Cirrhosis was defined as bridging fibrosis on previous liver biopsy or a composite of clinical signs and findings provided by laboratory tests, endoscopy, and radiologic imaging [13]. Organ failures and ACLF criteria were defined based on CLIF-SOFA score as per European Foundation for the Study of Chronic Liver Failure (CLIF) Consortium [14].

The following data were retrieved on ICU admission (and some at 3 days post ICU admission): age, sex, and actual weight; etiology and complications (ascites and hepatocellular carcinoma) of cirrhosis; precipitant event of acute illness; number and severity of organ failures and their level of support; general laboratory parameters (initial arterial blood samples); and severity of illness systems (MELD, APACHEII, CLIF-SOFA, and CLIF-C-ACLF scores) [14-17].

Primary exposures were FB from ICU admission to days 3 and 7 post ICU admission or until ICU discharge or death in the ICU. Cumulative FB during the ICU stay was calculated as follows: total volume in (oral fluids and feeds and intravenous fluids and medications) – total volume out (urine, stool, and drainages including following thoracentesis, paracentesis, or surgery) in liter (l). As in previous studies about the impact of FB on the outcomes of critically-ill patients, insensible losses (i.e. loss of water through the respiratory system and skin) were not accounted for in the cumulative FB calculations [18-20]. FO was defined as in previous literature: FB / actual body weight on ICU admission x 100 [20,21].

The primary endpoint considered was all-cause mortality within the index hospital stay (irrespective of LT status). The secondary endpoints defined were: all-cause mortality within the index ICU stay (irrespective of LT status); length of index ICU and hospital stays; and ICU readmission.

2.3. Statistical analysis

Continuous and categorical variables were initially described as median (interquartile range [IQR]) and frequency (percentage [%]), respectively. Univariate comparisons were done using Mann-Whitney and Chi-square or Fisher's Exact tests where appropriate. Missing data across all variables was 3.0% therefore no multiple imputation was performed.

The association of FB and endpoints was studied using logistic and linear regression. Adjusted analysis included variables based on clinical judgment and a univariate analysis $P < 0.10$. Modelling was performed using a conventional stepwise backward approach. Collinearity was avoided where appropriate.

Statistical significance was defined as $P < 0.05$ (2-tailed). Statistical analysis was performed using IBM SPSS Statistics, version 20 (IBM Corp, North Castle, NY, US).

3. Results

3.1. Baseline characteristics

Between August 2013 and August 2017, there were 336 adult patients with cirrhosis and organ failures consecutively admitted to both ICUs, 239 at UAH and 97 at CCH. Amongst those patients, 3 were excluded due to lack of bilirubin levels, therefore the overall number of patients included was 333. Baseline characteristics are depicted in Table 1.

Amongst all patients, 226 (67.3%) were men and median (IQR) age was 56 (50;62) years. Alcohol was the most prevalent etiology of cirrhosis (56.8%). The most frequent precipitants of cirrhosis decompensation leading to ICU admission were infection (29.4%) and gastro-intestinal bleeding (20.7%). The majority of patients (62.5%) had ascites on ICU admission.

On ICU admission, median (IQR) number of organ failures (CLIF-SOFA) was 2 (1;3), with the following distribution (Table 2): liver failure in 93 (27.9%) patients; renal failure in 140 (42.0%) patients; neurological failure in 141 (42.3%) patients; coagulation failure in 103 (30.9%) patients; circulatory failure in 216 (64.9%) patients; and respiratory failure in 141 (42.3%) patients. ACLF criteria were present in 311 (93.4%) patients.

On the first day of ICU admission, the level of organ support required was: invasive mechanical ventilation in 187 (56.2%) patients (104 initially due to respiratory failure and 83 initially due to neurological failure); vasopressors in 216 (64.9%) patients; and renal replacement therapy in 33 (9.9%) patients. Median (IQR) MELD, APACHEII, CLIF-SOFA, and CLIF-C-ACLF scores were 27 (19;34), 28 (22;33), 14 (11;16), and 54 (49;61), respectively.

3.2. Outcomes

At day 3 post ICU admission ($n = 268$), all extra-hepatic organ failures improved significantly (median CLIF-SOFA of 11 vs. 14 at ICU admission), with ACLF criteria being present in 165 (61.6% vs. 93.6% at ICU admission) patients (Table 2). During the index ICU and hospital stays, 110 (33.0%) and 164 (49.2%) patients died, respectively. Median (IQR) length of ICU and hospital stays were 5.4 (3.0;10.1) and 17.8 (10.2;37.9) days, respectively. During the follow-up period, 34 (10.2%) patients were transplanted. Median (IQR) time to LT was 10.3 (4.8;22.3) days. During the follow-up period, 17 (5.1%) patients were readmitted to ICU.

3.3. Fluid balance during the ICU stay and its association with endpoints

Amongst all patients, 268 (80.5%) and 147 (44.1%) patients survived ≥2.5 and ≥ 6.5 days following ICU admission, respectively. Median (IQR) FB at days 3 and 7 post ICU admission were + 6.27 (+1.42;+15.36)l

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Table 1
Patients with cirrhosis and organ failures admitted to the intensive care unit: baseline characteristics stratified by vital status at hospital discharge.

	Total ($n = 333$)	Deceased ($n = 164$)	Alive ($n = 169$)	P
Sex (male)	225 (67.6%)	115 (70.1%)	110 (65.1%)	0.33
Age (years)	56 (50;62)	57 (51;63)	55 (49;61)	0.10
Weight (kg) ($n = 304$)	75 (67;90)	78 (70;90)	75 (65;90)	0.20
Etiology				0.70
Alcohol	177 (53.2%)	83 (50.6%)	94 (55.6%)	
HCV	16 (4.8%)	8 (4.9%)	8 (4.7%)	
Alcohol + HCV	12 (3.6%)	5 (3.0%)	7 (4.1%)	
Other	128 (38.4%)	68 (41.5%)	60 (35.5%)	
Ascites	208 (62.5%)	116 (70.7%)	92 (54.4%)	0.002
HCC	33 (9.9%)	19 (11.6%)	14 (8.3%)	0.31
Precipitant event				0.008
Infection	98 (29.4%)	59 (36.0%)	39 (23.1%)	
Bleeding	69 (20.7%)	30 (18.3%)	39 (23.1%)	
Other	139 (41.7%)	69 (42.0%)	70 (41.4%)	
Unknown	27 (8.1%)	6 (3.7%)	21 (12.4%)	
Grade III-IV HE	141 (42.3%)	80 (48.8%)	61 (36.1%)	0.019
IMV	187 (56.2%)	95 (57.9%)	92 (54.4%)	0.52
PF ratio (mmHg) ($n = 314$)	219 (144;305)	202 (142;299)	229 (153;316)	0.13
Vasopressors	216 (64.9%)	119 (72.6%)	97 (57.4%)	0.004
MAP (mmHg)	62 (55;69)	60 (53;67)	63 (57;70)	0.019
RRT	33 (9.9%)	19 (11.6%)	14 (8.3%)	0.31
Hemoglobin (g/l) ($n = 321$)	86 (78;100)	87 (78;103)	86 (78;96)	0.35
Leucocytes (10^3/μl) ($n = 332$)	10.6 (6.7;16.5)	11.1 (6.8;17.0)	10.0 (6.7;15.7)	0.20
Platelets (10^3/μl)	75 (49;120)	74 (42;119)	79 (54;128)	0.12
INR	1.9 (1.6;2.5)	2.2 (1.7;2.8)	1.8 (1.5;2.3)	<0.001
Bilirubin (mg/dl)	5.6 (2.4;14.9)	8.2 (2.9;21.3)	4.7 (2.0;9.3)	<0.001
Albumin (g/dl) ($n = 284$)	27 (22;32)	25 (20;30)	27 (24;34)	0.001
Creatinine (mg/dl)	1.77 (1.01;2.96)	1.96 (1.10;3.32)	1.49 (0.92;2.44)	0.005
Sodium (mmol/l) ($n = 221$)	136 (131;140)	136 (130;140)	136 (131;141)	0.85
Lactate (mmol/l) ($n = 317$)	3.0 (1.9;6.1)	3.7 (2.1;7.9)	2.7 (1.9;4.6)	0.003
FB at day 3 (l) ($n = 266$)	+6.27 (+1.42; +15.36)	+5.46 (+1.47; +15.61)	+6.62 (+1.28; +14.88)	0.74
FB at day 7 (l) ($n = 142$)	+9.60 (+0.86; +21.82)	+13.50 (+2.30; +24.57)	+6.90 (−0.13; +18.71)	0.036
FO at day 3 (%) ($n = 242$)	+9.3 (+2.4; +21.5)	+9.0 (+2.0; +21.5)	+9.5 (+2.5; +21.8)	0.15
FO at day 7 (%) ($n = 131$)	+13.4 (+1.2; +30.9)	+20.5 (+5.0; +32.0)	+7.9 (−0.3; +24.3)	0.030
ACLF grade				<0.001
No ACLF	22 (6.6%)	5 (3.0%)	17 (10.1%)	
Grade I	65 (19.5%)	20 (12.2%)	45 (26.6%)	
Grade II	82 (24.6%)	35 (21.3%)	47 (27.8%)	
Grade III	164 (49.2%)	104 (63.4%)	60 (35.5%)	
Organ failures (≤6)	2 (1;3)	3 (2;4)	2 (1;3)	<0.001
MELD	27 (19;34)	30 (23;36)	24 (17;30)	<0.001
APACHEII ($n = 332$)	28 (22;33)	29 (23;35)	27 (21;31)	0.013
CLIF-SOFA	14 (11;16)	15 (12;18)	12 (10;15)	<0.001
CLIF-C ACLF ($n = 314$)	54 (49;61)	57 (52;64)	52 (46;58)	<0.001

ICU: intensive care unit; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; IMV: invasive mechanical ventilation; PF ratio: arterial pressure of oxygen / fractional inspired oxygen (mmHg); MAP: mean arterial pressure (mmHg); RRT: renal replacement therapy; INR: international normalized ratio; FB: fluid balance (liter); FO: fluid overload (%); MELD: model for end-stage liver disease score; APACHEII: acute physiology and chronic health evaluation II score; CLIF-SOFA: chronic liver failure – sequential organ failure assessment score; CLIF-C ACLF: chronic liver failure consortium – acute-on-chronic liver failure score.

and + 9.60 (+0.86;+21.82)l, respectively (Table 1). Based on actual body weight on ICU admission, median (IQR) FO at days 3 and 7 post ICU admission were + 9.3 (+2.4;+21.5)% and + 13.4 (+1.2; +30.9)%, respectively (Table 1).

Table 2
Patients with cirrhosis and organ failures: characteristics at intensive care unit admission and at day 3 post admission.

	Admission (n = 333)	Day 3 (n = 268)	P
ACLF grade			<0.001
No ACLF	22 (6.6%)	103 (38.4%)	
Grade I	65 (19.5%)	18 (6.7%)	
Grade II	82 (24.6%)	71 (26.5%)	
Grade III	164 (49.2%)	76 (28.4%)	
Organ failures (≤6)	2 (1;3)	2 (1;3)	<0.001
Neurological	141 (42.3%)	67 (25.0%)	
Respiratory	141 (42.3%)	66 (24.6%)	
Circulatory	216 (64.9%)	137 (51.1%)	
Renal	140 (42.0%)	93 (34.7%)	
Liver	93 (27.9%)	76 (28.4%)	
Coagulation	103 (30.9%)	41 (15.3%)	
CLIF-SOFA	14 (11;16)	11 (8;15)	<0.001

ACLF: acute-on-chronic liver failure; CLIF-SOFA: chronic liver failure – sequential organ failure assessment score.

Median (IQR) FB (+5.46 l vs. +6.62 l; $P = 0.74$) or FO (+9.0% vs. +9.5%; $P = 0.15$) at day 3 post ICU admission were not associated with hospital mortality (Table 1). Conversely, higher median (IQR) FB (+13.50 l vs. +6.90 l; $P = 0.036$) or FO (+20.5% vs. +7.9%; $P = 0.030$) at day 7 post ICU admission were associated with higher hospital mortality (Table 1). Hospital mortality was 57.1% and 39.3% for patients with a FO ≥10.0% and < 10.0% (frequent cutoff used in the literature) at day 7 post ICU admission, respectively (Fig. 1: $P = 0.042$).

While lower median FB (+3.91 l vs. +7.10 l; $P = 0.048$) or FO (+5.3% vs. +10.3%; $P = 0.026$) at 3 days post ICU admission was associated with higher ICU mortality, median FB (12.17 l vs. 9.15 l; $P = 0.97$) or FO (+12.8% vs. 14.8%; $P = 0.81$) at 7 days post ICU admission was not. Median FB or FO at 3 or 7 days post ICU admission were not associated with median length of index ICU and hospital stays or ICU readmission ($P \geq 0.17$ for all comparisons).

Following adjustment for clinically and statistically relevant co-founders, namely age, ascites, infection, lactate, and the number of organ failure on ICU admission, FB at 7 days post ICU admission was independently associated with hospital mortality (Table 3: adjusted odds ratio (aOR) (95% confidence interval (CI)) = 1.04 (1.01;1.07); $P = 0.004$). Furthermore, the presence of ascites on ICU admission was also independently associated with hospital mortality (Table 3: aOR (CI) = 4.90 (2.06;11.65); $P < 0.001$).

The same adjusted analysis yielded similar results when considering other severity of illness systems as an alternative to the number of organ failures on ICU admission, namely MELD, APACHEII, CLIF-SOFA, or CLIF-C-ACLF (Table S1).

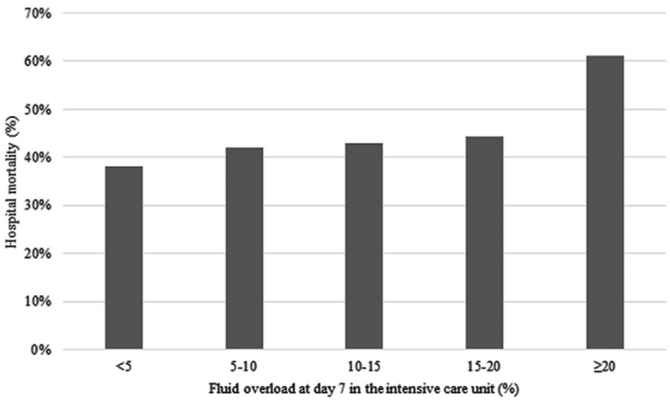

Fig. 1. Stratified fluid overload at day 7 in the intensive care unit and observed hospital mortality.

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Table 3
Fluid balance at day 7 in the intensive care unit as an independent risk factor for hospital mortality: adjusted analysis.

Model 1 (n = 135)	aOR (95%CI)	P	C-statistic (95%CI)
Age (years)	0.99 (0.96;1.03)	0.75	0.75 (0.67;0.83)
FB at day 7 (l)	1.04 (1.01;1.07)	0.004	
Ascites	4.90 (2.06;11.65)	<0.001	
Infection (vs. other)	1.80 (0.76;4.29)	0.18	
Lactate (mmol/l)	0.94 (0.85;1.05)	0.26	
Organ failures (≤6)	1.45 (0.98;2.14)	0.06	

aOR: adjusted odds ratio; CI: confidence interval; FB: fluid balance (liter)

Following adjustment for the same confounders (age, ascites, infection, lactate, and the number of organ failures on ICU admission), FB at 3 days post ICU was independently associated with ICU mortality (Table S2: aOR = 0.97 (0.95;1.00); $P = 0.029$).

3.4. Sensitivity analyses

Of subgroups of critically-ill patients especially susceptible to FO, the ones with infection, renal failure, or respiratory failure are to be considered. Amongst patients admitted to ICU with infection (+7.87 l vs. +11.61 l; $P = 0.19$) or renal failure (+8.93 l vs. 10.86 l; $P = 0.30$), there was a lower median FB at 7 days post ICU admission than others. Conversely, amongst patients admitted to ICU with respiratory failure, there was higher median FB at 7 days post ICU admission than others (+12.94 l vs. +8.64 l; P = 0.19). However, following adjustment solely for infection (aOR (95%CI) = 1.03 (1.00;1.05); $P = 0.027$), renal failure (aOR (95%CI) = 1.02 (1.00;1.05); $P = 0.045$), or respiratory failure (aOR (95%CI) = 1.02 (1.00;1.05); $P = 0.044$) on ICU admission, higher median FB or FO at 7 days post ICU admission remained associated with higher hospital mortality.

Amongst patients with renal failure at 3 days post ICU admission, there was a lower FB at 7 days post ICU admission than others (+8.72 l vs. +11.21 l; $P = 0.38$). Conversely, amongst patients with respiratory failure at 3 days post ICU admission, there was a higher FB at 7 days post ICU admission than others (+11.43 l vs. +9.00 l; $P = 0.14$). Following adjustment solely for renal failure at 3 days post ICU admission, FB at 7 days post ICU admission was not associated with hospital mortality (aOR (95%CI) = 1.00 (1.00;1.00); $P = 0.052$). However, if adjustment was made for creatinine (continuous variable) and not renal failure (categorical variable) at 3 days post ICU admission, higher median FB at 7 days post ICU admission remained associated with higher hospital mortality (aOR (95%CI) = 1.00 (1.00;1.00); $P = 0.033$). Following adjustment solely for respiratory failure at 3 days post ICU admission, higher median FB at 7 days post ICU admission remained associated with higher hospital mortality (aOR (95%CI) = 1.00 (1.00;1.00); $P = 0.043$).

Following exclusion of 7 patients transplanted before 6.5 days in the ICU, in order to mitigate the influence of intraoperative FB, higher FB at 7 days post ICU admission was associated with higher transplant-free hospital mortality (+13.50 l vs. 6.83 l; $P = 0.034$). Furthermore, following adjustment for the same confounders (age, ascites, infection, lactate, and the number of organ failures on ICU admission), FB at 7 days post ICU admission was independently associated with transplant-free hospital mortality (Table S3: aOR = 1.04 (1.01;1.07); $P = 0.005$).

4. Discussion

4.1. Key results and comparisons with previous literature

In our cohort, patients with cirrhosis and organ failures who died in hospital had a 2 times higher median positive FB and 2.5 times higher median positive FO at day 7 post ICU admission than patients who survived until hospital discharge.

While specific hemodynamic endpoints should be targeted during fluid resuscitation, each patient's anthropometry, underlying disease pathophysiology, and type and severity of ensuing organ failures may lead to wide variation in fluid management (including resuscitation and maintenance fluids, transfusion of blood products, medications, and others) and therefore net FB.

In patients with cirrhosis, features of portal hypertension (e.g. ascites, hepatic hydrothorax, varices, hepatorenal syndrome, or hyponatremia) may further complicate individual hemodynamic assessment and fluid management. Therefore, while patients with cirrhosis may present with clinical signs of congestion, there initial hemodynamic assessment in the ICU may find they are actually hypovolemic (e.g. sepsis or bleeding). In this scenario, aggressive fluid resuscitation is necessary to restore hemodynamic stability, with the potential to further aggravate chronic signs of congestion.

Net FB or FO at 7 days post ICU admission may have reflected the stabilization or de-escalation phases of fluid resuscitation. The extra volume of fluid we found to be present in patients deceased in hospital in comparison to survivors, whether absolute (a median excess of 6.60 l) or relative (a median excess of 12.6%), was clinically and statistically significant. This additional positive FB may have led to further end-organ edema and dysfunction (e.g. lungs or kidneys) with increased risk of mortality. While studies in critically-ill patients with cirrhosis lack, there are reports amongst other subgroups of critically-ill patients highlighting the association of positive FB or FO with worse outcomes, including prolonged ventilation, increased incidence of acute kidney injury, increased length of ICU and hospital stays, and increased mortality [22,23]. Furthermore, a FO ≥10% has been specifically associated with increased risk of poorer outcomes [20,21].

Taking into account the magnitude of FO detected in our patients deceased in hospital, we could speculate that further aggressive strategies to actively remove the excess of fluid would have been potentially beneficial to at least some of them. Such strategies may have included the use of diuretics or renal replacement therapy. Moreover, in patients with ascites or hepatic hydrothorax, paracentesis or thoracentesis may have been helpful. Overall, strategies of deresuscitation for critically-ill patients have been associated with lower mortality [24,25]. Therefore, such strategies may also potentially benefit critically-ill patients with cirrhosis.

Net FB at 3 days post ICU admission is likely to reflect mainly the result of the initial rescue and optimization phases of fluid resuscitation. We found that lower median FB or FO at 3 days post ICU admission was associated with higher ICU mortality (secondary endpoint). This raises the possibility that some deceased patients could have been under-resuscitated during that initial period of time in the ICU for reasons that we were not able to identify with our data. We could speculate that early resuscitation often depends on several therapeutic strategies, such as fluids, vasopressors, blood products, and the treatment of the underlying acute disease (e.g. sepsis or bleeding). Furthermore, the number of organ failures on ICU admission was independently associated with ICU mortality but not hospital mortality. This may add that the effect of FB at 3 days post ICU admission on ICU mortality was also related to the number, and quite possibly, the severity of the ongoing organ failures.

In our cohort, median FB or FO at 3 or 7 days post ICU admission were not associated with median length of index ICU and hospital stays or ICU readmission (secondary endpoints). Other studies have suggested that FO may increase the risk of prolonged ICU and hospital stays or ICU readmission [22,26]. Therefore, while FO may increase patients' morbidity and mortality, it may also increase costs associated with their hospital stay [27].

In our cohort, the presence of ascites on ICU admission was independently associated with hospital mortality. Previous studies have shown that decompensated cirrhosis with ascites (a marker of uncontrolled portal hypertension) is associated with increased risk of mortality [28]. Therefore, it is unsurprising that ascites in context of ACLF also increased the risk of worse outcomes.

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Overall, our results signal that positive net FB or FO at 7 days post ICU admission may be associated with higher hospital mortality in patients with ACLF. This suggests that better strategies to frequently assess volume status (intra and extra-vascular compartments) and potentially de-escalate resuscitation in these patients may need to be implemented.

4.2. Limitations

Our results need to be interpreted in the context of the following limitations. Firstly, this was a retrospective analysis which may have been prone to selection bias. Nevertheless, the multicenter nature, the defined inclusion and exclusion criteria, and the use of consecutive first ICU admissions, may have minimized such risk of bias. Secondly, insensible losses through respiratory tract and skin were not accounted for. However, while this may be difficult to measure in daily ICU practice, it is reasonable to accept that their effect on FB could have been similar amongst non-survivors and survivors. Thirdly, the types and specific doses of fluids and blood products administered were not specified. While potential for volume expansion and toxicity may vary amongst different types of fluids, the overall efficacy in resuscitation has been reported as similar [29]. Furthermore, while transfusion practices may vary amongst different centers, international standards have been widely adopted during the study inclusion period, thus minimizing the effect of such variation. Fourthly, bedside strategies for hemodynamic assessment (e.g. static vs. dynamic parameters or non-invasive vs. invasive techniques) were not captured. Therefore, variations in their use may have affected clinical decisions on fluid management. However, both centers used a standard of care approach to hemodynamic assessment, including serum markers (e.g. lactate and central venous oxygen saturation), central venous pressure, echocardiography, and/or invasive monitoring (e.g. PiCCO® and Swan-Ganz cathether).

Despite these limitations, our study uses a large international cohort of patients with ACLF to provide new data about the potential impact of FB on patients' outcomes. These results may be important to inform the development of future prospective trials addressing this issue.

5. Conclusions

In patients with ACLF, higher positive FB or FO at day 7 post ICU admission was associated with increased hospital mortality. FB as a therapeutic target for patients with ACLF needs to be further studied.

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Authors' contributions

FSC and CJK developed the concept and design. All authors helped to collect data. FSC performed statistical analysis and drafted the manuscript. All authors revised and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.09.012.

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