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RESEARCH ARTICLE

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The association between early fluid strategy and prognosis of acute respiratory distress syndrome: A post hoc study of CHARDS

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Abstract

We aimed to assess general fluid management in China and evaluate the association between fluid balance and survival outcomes in acute respiratory distress syndrome (ARDS) patients. A retrospective, multicenter study including ARDS patients was conducted. We described the fluid management of ARDS patients in China. Furthermore, clinical characteristics and outcomes of patients subdivided by cumulative fluid balance were also analyzed. Multivariable logistic regression analysis was performed with hospital mortality as the outcome. From June 2016 to February 2018, 527 ARDS patients were included in our study. The mean cumulative fluid balance was 1669 (−1101 to 4351) mL in the first 7 day after intensive care unit (ICU) admission. Patients were divided into four groups based on cumulative fluid balance of the first 7 day after ICU admission: Group I (≤0 L), Group II (>0 L, ≤3 L), Group III (>3 L, ≤5 L), and Group IV (>5 L). Significantly lower hospital mortality was observed in patients with a lower cumulative fluid balance on day 7 of ICU admission (20.5% in Group I vs. 32.8% in Group II, 38.5% in Group III, and 50% in Group IV, $p < 0.001$). A lower fluid balance is associated with lower hospital mortality in patients with ARDS. However, a large-scale and well-designed randomized controlled trial is needed in the future.

Ziying Chen, Xu Huang, Haining Lu, and Wang Deng are contributed equally to this study, Ziying Chen is the first co-first author.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a critical illness, especially in intensive care units (ICUs). Although researchers have attempted to improve and implement respiratory support strategies, the mortality rate still ranges from 30% to 50%. The main characteristic of ARDS is the increased permeability of capillary endothelium and alveolar epithelium, leading to edema of the lungs.[1,2] Meanwhile, shock is a common complication in ARDS patients, which worsens the prognosis.[3–5] To avoid the negative effects of hypoxemia on the body, assessing volume status and hemodynamic disturbances is important. Achieving optimal fluid management in patients with ARDS means providing adequate fluid to maintain hemodynamic stability while avoiding the occurrence or exacerbation of pulmonary edema. This task is vital and extremely challenging.

The fluid and catheter treatment trial (FACTT) showed that conservative fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care in ARDS patients,[6] which provided a theoretical basis for fluid guidance.[7] Unfortunately, no studies have yet convincingly reported the survival benefit of conservative fluid management for ARDS. Although several observational studies demonstrated a negative association between fluid balance and outcomes of ARDS,[8,9] the data were limited.

Therefore, in this study, we sought to assess general fluid management in China and the association between fluid balance and survival of ARDS patients. Our hypothesis was that the more negative the fluid balance within 7 day, the higher the survival.

METHODS

Study setting and patients

This study was a post-hoc analysis based on data from the China ARDS (CHARDS) epidemiology study (NCT02975908), which was conducted in 18 respiratory ICUs/medical ICUs (RICUs/MICUs) in China from March 2016 to February 2018. The detailed study design, patient inclusion and exclusion criteria have been published previously.[10]

Data collection and analysis

Patients' demographic characteristics, comorbidities, risk factors, organisms, laboratory examinations, organ support, and outcomes were obtained from the database. To reflect the association between fluid balance and prognosis of patients with ARDS. Patients were divided into four groups based on cumulative fluid balance of the first 7 day after ICU admission: Group I (≤0 L), Group II (>0 L, ≤3 L), Group III (>3 L, ≤5 L), and Group IV (>5 L). The primary outcome was hospital survival. Secondary outcomes were invasive positive pressure ventilation (IPPV) free days within 28 day, ICU length of stay, and hospital length of stay.

Day 1 was the day a subject met the ARDS criteria. Daily fluid balance was the difference value between fluid input and fluid output per day, and cumulative fluid balance was the sum of daily fluid balance (total fluid input minus total fluid output on a certain day of ICU admission). If a patient was discharged, transferred out of the ICU, or died, cumulative fluid balance was recorded at the time of disposition. Invisible dehydration was not routinely measured and not taken into account. New organ failure was defined as sequential organ failure assessment (SOFA) score > 3.

First, we described the fluid management of patients with ARDS in China and compared clinical characteristics and outcomes between survivors and nonsurvivors. Second, clinical characteristics and outcomes of patients subdivided by cumulative fluid balance were also analyzed. To avoid potential confounders, multivariable logistic regression analysis was performed with hospital mortality as the outcome. Then, the association between cumulative fluid and hospital mortality was analyzed by a trend test.

Statistical analysis

Statistical analysis was conducted with SPSS 26.0 for Windows software (SPSS Inc.). Statistical significance was defined as a p-value less than 0.05. Categorical variables were reported as frequency or percentage, continuous variables were reported as mean (standard deviation) or median (interquartile range). Categorical variables were compared using Chi-square or Fisher's exact test, and for continuous variables, the t test, Mann–Whitney U test, or Kruskal–Wallis test was used to assess the differences between groups. To evaluate the potential independent prognostic role of cumulative fluid balance, a multivariable logistic regression was conducted. The model was adjusted by age, acute physiology and chronic health evaluation (APACHE) II, arterial oxygen pressure/fraction of inspiration (PaO_2/FiO_2) on diagnosis, and the need for IPPV. Moreover, a Cochran–Armitage trend test of hospital mortality was

TABLE 1 Characteristics and outcomes of all patients, survivors, and nonsurvivors.

	All $N = 527$	Survivors $N = 283$	Nonsurvivors $N = 244$	p
Age, years	55.2 ± 17.4	52.2 ± 16.9	58.8 ± 17.4	<0.001
Male, *n*%	369 (70)	187 (66.1)	182 (74.6)	0.033
APACHEII	17.2 ± 7.8	15.2 ± 7.1	19.6 ± 8.0	<0.001
SOFA	7.3 ± 3.8	6.4 ± 3.6	8.4 ± 3.9	<0.001
BMI, kg/m^2	24.2 ± 4.6	24.6 ± 4.2	23.8 ± 4.9	0.032
Smoking, *n*%	180 (34.4)	92 (32.9)	88 (36.1)	0.440
Alcoholic, *n*%	98 (18.7)	50 (17.9)	48 (19.7)	0.609
Risk factors for ARDS, *n*%				
Pneumonia, *n*%	402 (76.3)	205 (72.4)	197 (80.7)	0.026
Aspiratory, *n*%	17 (3.2)	10 (3.5)	7 (2.9)	0.667
Extra pulmonary sepsis, *n*%	38 (7.2)	20 (7.1)	18 (7.4)	0.891
Trauma, *n*%	8 (1.5)	5 (1.8)	3 (1.2)	0.731
Pancreatitis, *n*%	18 (3.4)	17 (6)	1 (0.4)	<0.001
Others, *n*%	44 (8.3)	26 (9.2)	18 (7.4)	0.454
Organism of ARDS, *n*%				
Bacteria, *n*%	59 (11.2)	23 (8.1)	36 (14.8)	0.016
Fungi, *n*%	29 (5.5)	13 (4.6)	16 (6.6)	0.324
Viruses, *n*%	82 (15.6)	39 (13.8)	43 (17.6)	0.225
Mixed infection, *n*%	49 (9.3)	25 (8.8)	24 (9.8)	0.693
Others, *n*%	198 (37.6)	108 (38.2)	90 (36.9)	0.763
Comorbidities, *n*%				
Hypertension, *n*%	176 (33.6)	94 (33.6)	82 (33.6)	0.993
Diabetes, *n*%	101 (19.3)	56 (20)	45 (18.5)	0.669
Coronary heart disease, *n*%	57 (10.9)	22 (7.9)	35 (14.3)	0.017
Chronic heart failure, *n*%	26 (5)	10 (3.6)	16 (6.6)	0.119
Chronic renal failure, *n*%	56 (10.7)	22 (7.9)	34 (14)	0.024
Chronic lung diseases, *n*%	30 (5.7)	9 (3.2)	21 (8.6)	0.008
Liver cirrhosis, *n*%	21 (4)	5 (1.8)	16 (6.6)	0.005
Connective tissue diseases, *n*%	35 (6.7)	12 (4.3)	23 (9.4)	0.019
Active neoplasm, *n*%	41 (7.8)	14 (5)	27 (11.1)	0.010
ARDS category, *n*%				
Mild, *n*%	51 (9.7)	35 (12.4)	16 (6.6)	0.024
Moderate, *n*%	250 (47.4)	149 (52.7)	101 (41.4)	0.010
Severe, *n*%	226 (42.9)	99 (35)	127 (52)	<0.001
pH on diagnosis	7.42 (7.36–7.46)	7.42 (7.36–7.47)	7.41 (7.35–7.46)	0.419
PaO_2/FiO_2 on diagnosis, mmHg	113 (80–161)	127 (87–170)	100 (70–135)	<0.001
$PaCO_2$ on diagnosis, mmHg	36.3 (31.2–42.7)	36.4 (30.9 –42)	36.4 (32–44.9)	0.271
Need for IPPV	400 (75.9)	178 (62.9)	222 (91)	<0.001

(Continues)

TABLE 1 (Continued)

	All $N = 527$	Survivors $N = 283$	Nonsurvivors $N = 244$	p
IPPV parameters				
PEEP, cmH_2O	8 (6–12)	8 (6–12)	8 (6–12)	0.646
VT, mL/kg PBW	6.8 (5.8–7.9)	6.9 (6–7.7)	6.8 (5.9–8)	0.919
Plateau pressure, cmH_2O	20 (16–26)	20 (15–23)	23 (18–28)	<0.001
Driving pressure, cmH_2O	12 (8–16)	11 (7–14)	20 (15–23)	<0.001
Airway resistance, cmH_2O/L/S	12 (8–18)	11 (7–16)	12.7(9.8–20)	0.019
Compliance, mL/cmH_2O	35 (25–44)	37 (28–53)	33 (23–40)	0.002
Adjunctive measures				
NMBAs, *n*%	107 (26.8)	43 (24.2)	66 (29.7)	<0.001
RM, *n*%	44 (11)	16 (5.7)	28 (11.5)	0.016
PPV, *n*%	85 (21.3)	34 (19.1)	51 (23)	0.006
ECMO, *n*%	61 (15.3)	21 (11.8)	40 (18)	0.001
HFOV, *n*%	3 (0.8)	0	3 (1.2)	0.099
Cumulative FB Day 7, mL	1669 (−1101 to 4351)	754 (−1769 to 3195)	3129 (419–5323)	<0.001
CRRT, *n*%	119 (22.6)	40 (14.1)	79 (32.4)	<0.001
IPPV–free days within 28 days	6 (0–22)	20 (13–28)	0 (0–0)	<0.001
ICU length of stay	11 (7–21)	13 (8–26)	10 (5–17)	<0.001
Hospital length of stay	19 (10–29)	23 (15–35)	12 (7–21)	<0.001

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CRRT, continuous renal replacement therapy; EMCO, extracorporeal membrane oxygenation; FB, fluid balance; FiO_2, fraction of inspiration; HFOV, high–frequency oscillatory ventilation; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; NMBAs, neuromuscular blockades; PaO2, arterial oxygen pressure; PaCO2, partial pressure of carbon dioxide; PBW, predicted body weight; PEEP, positive end expiratory pressure; PPV, prone position ventilation; RM, lung recruitment manoeuvre; SOFA, sequential organ failure assessment; VT, tidal volume.

made, using fluid balance as the single stratification variable.

RESULTS

Fluid management in China

In total, 527 ARDS patients were included in our study, including survivors ($n = 283$) and nonsurvivors ($n = 244$). The median age was 55.2 years, the median APACHEII score was 17, and the median SOFA was 7. The most common risk factor for ARDS was pneumonia (76.3%). Most of the patients had moderate or severe ARDS (47.4%; 42.9%). The average PaO_2/FiO_2 on diagnosis was 113 (80–161) mmHg. The mean cumulative fluid balance was 1669 (−1101 to 4351) mL in the first 7 day after ICU admission. Survivors had lower cumulative fluid balance than non-survivors in the first 7 day after ICU admission [754 (−1769 to 3195) mL vs. 3129 (419 to 5323) mL, $p < 0.001$]. Compared with nonsurvivors, survivors had longer ICU length of stay and hospital length of stay, respectively (13 [8–26] vs. 10 [5–17], $p < 0.001$; 23 [15–35] vs. 12 [7–21], $p < 0.001$) (Table 1 and Figure 1).

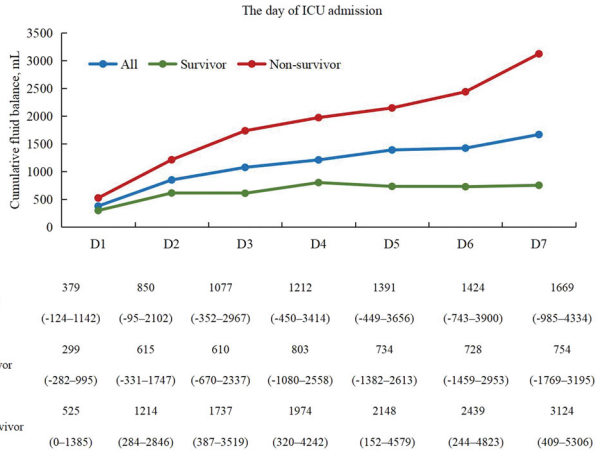

FIGURE 1 Median cumulative fluid balance in the first 7 days of ICU admission. ICU, intensive care unit.

TABLE 2 Characteristics of patients subdivided by cumulative fluid balance.

	Group I ≤0 L *N* = 168	Group II 0–3 L *N* = 155	Group III 3–5 L *N* = 104	Group IV >5 L *N* = 100	*p*
Age, years	54.9 ± 17.4	56.6 ± 16.9	54.7 ± 17.4	54.1 ± 18.4	0.844
Male, *n*%	108 (64.3)	116 (74.8)	74 (71.2)	71 (71)	0.216
APACHEII	16.7 ± 7.5	17.1 ± 8.3	16.7 ± 7.5	18.7 ± 7.8	0.260
Pneumonia	16.5 ± 7.5	16.7 ± 8.3	15.9 ± 7	18.1 ± 7.9	0.414
SOFA	7.2 ± 4	7.1 ± 3.6	7.6 ± 3.5	7.8 ± 4.2	0.394
Pneumonia	7 ± 3.8	6.8 ± 3.4	7 ± 3.4	7.5 ± 4.3	0.823
BMI	24.6 ± 4.8	23.9 ± 4.2	24 ± 3.2	24.4 ± 5.8	0.866
Smoking, *n*%	51 (30.4)	52 (33.5)	37 (36.6)	40 (40)	0.410
Alcoholic, *n*%	27 (16.2)	36 (23.2)	19 (18.8)	16 (16)	0.352
Risk factors for ARDS, *n*%					
Pneumonia, *n*%	125 (74.9)	121 (78.1)	80 (76.9)	76 (76.3)	0.890
Aspiratory, *n*%	4 (2.4)	7 (4.5)	2 (1.9)	4 (4.0)	0.580
Extra pulmonary sepsis, *n*%	12 (7.1)	11 (7.1)	8 (7.7)	7 (7.0)	0.997
Trauma, *n*%	4 (2.4)	0	2 (1.9)	2 (2.0)	0.125
Pancreatitis, *n*%	6 (3.6)	4 (2.6)	5 (4.8)	3 (3.0)	0.800
Others, *n*%	15 (8.9)	10 (6.5)	6 (5.8)	5 (5.0)	0.592
Organism of ARDS, *n*%					
Bacteria, *n*%	18 (10.7)	20 (12.9)	10 (9.6)	11 (11.0)	0.859
Fungi, *n*%	10 (6.0)	8 (5.2)	6 (5.8)	5 (5.0)	0.983
Viruses, *n*%	28 (16.7)	25 (16.1)	15 (14.4)	14 (14.0)	0.923
Mixed infection, *n*%	18 (10.7)	16 (10.3)	8 (7.7)	7 (7.0)	0.674
Others, *n*%	57 (33.9)	54 (34.8)	43 (41.3)	44 (44.0)	0.280
Comorbidities, *n*%					
Hypertension, *n*%	60 (35.7)	49 (31.6)	38 (37.6)	29 (29)	0.514
Diabetes, *n*%	37 (22)	25 (16.2)	22 (21.8)	17 (17)	0.481
Coronary heart disease, *n*%	17 (10.1)	20 (12.9)	13 (12.9)	7 (7)	0.437
Chronic heart failure, *n*%	6 (3.6)	11(7.1)	7 (7)	2 (2)	0.178
Chronic renal failure, *n*%	13 (7.7)	16 (10.4)	12 (11.9)	15 (15)	0.303
Chronic lung diseases, *n*%	5 (3)	10 (6.5)	10 (9.9)	5 (5.1)	0.120
Liver cirrhosis, *n*%	3 (1.8)	6 (3.9)	6 (5.9)	6 (6.1)	0.216
Connective tissue diseases, *n*%	7 (4.2)	11 (7.1)	8 (7.9)	9 (9)	0.414
Active neoplasm, *n*%	7 (4.2)	14 (9)	5 (5)	15 (15)	0.008
ARDS category, *n*%					
Mild, *n*%	21 (12.5)	12 (7.7)	9 (8.7)	9 (9.0)	0.499
Moderate, *n*%	89 (53)	75 (48.4)	38 (36.5)	48 (48.0)	0.069
Severe, *n*%	58 (34.5)[III]	68 (43.9)	57 (54.8)[I]	43 (43.0)	0.012
pH on diagnosis	7.41 (7.35–7.46)	7.43 (7.36–7.47)	7.41 (7.36–7.46)	7.43 (7.38–7.47)	0.390

(Continues)

TABLE 2 (Continued)

	Group I ≤0 L *N* = 168	Group II 0–3 L *N* = 155	Group III 3–5 L *N* = 104	Group IV >5 L *N* = 100	*p*
PaO2/FiO2 on diagnosis, mmHg	127 (90.3–181)[III, IV]	113 (82–161)	102 (73.5–144.7)[I]	110 (71–152)[I]	0.002
$PaCO_2$ on diagnosis, mmHg	36 (30–42.6)	37 (32–44)	37.4 (32–43.3)	34.9 (30.5–41.1)	0.281
Need for IPPV	109 (64.9)[II, III, IV]	122 (78.7)[I]	80 (76.9)[I]	89 (89)[I]	<0.001
PEEP, cmH_2O	10 (6–12)	8 (5–10)	8 (6–10)	8 (5–10)	0.199
VT, mL/kg PBW	6.8 (5.9–7.9)	6.8 (6–8)	6.6 (5.6–7.7)	7.1 (6.1–8)	0.431
Plateau pressure, cmH_2O	20 (15–24)	20 (15–25)	22 (16.3–27)	20 (18–25.8)	0.682
Driving pressure, cmH_2O	12 (8–15)	12 (8–15)	14 (6.5–17)	13 (8–18)	0.484
Airway resistance, cmH_2O/L/S	13.9 (8.9–20.3)	11 (7.2–16)	12 (8–17.4)	12 (09.6–16.6)	0.425
Compliance, mL/cmH_2O	34 (24.8–51.6)	33.5 (24.5–43.8)	35 (22–43)	36 (26.3–41.5)	0.859
NMBAs, *n*%	30 (27.5)	27 (22.3)	26 (32.5)	24 (27)	0.458
RM, *n*%	14 (12.8)	10 (8.2)	11 (13.8)	9 (10.1)	0.563
PPV, *n*%	24 (22.0)	29 (23.8)	18 (22.5)	14 (15.7)	0.533
ECMO, *n*%	19 (17.4)	14 (11.5)	13 (16.3)	15 (16.9)	0.575
HFOV, *n*%	0	1 (0.8)	2 (2.5)	0	0.170
Cumulative FB Day 7	−2042 (−3976 to −826)	1465 (754–2235)	3894 (3408−4501)	7520 (5968–9832)	<0.001

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CRRT, continuous renal replacement therapy; EMCO, extracorporeal membrane oxygenation; FB, fluid balance; FiO2, fraction of inspiration; HFOV, high–frequency oscillatory ventilation; ICU, intensive care unit; IPPV, invasive positive pressure ventilation; NMBAs, neuromuscular blockades; PaO2, arterial oxygen pressure; PaCO2, partial pressure of carbon dioxide; PBW, predicted body weight; PEEP, positive end expiratory pressure; PPV, prone position ventilation; RM, lung recruitment manoeuvre; SOFA, sequential organ failure assessment; VT, tidal volume.

Characteristics of patients subdivided by cumulative fluid balance

There were no significant differences in age, APACHEII, SOFA, risk factors for ARDS, or comorbidities on diagnosis between groups. The cumulative fluid balances in the first 7 day after ICU were −2042 (−3976 to −826) mL in Group I, 1465 (754 to 2235) mL in Group II, 3894 (3408 to 4501) mL in Group III, and 7520 (5968 to 9832) mL in Group IV. The PaO_2/FiO_2 was lower with more cumulative fluid balance in Group III and Group IV (102 mmHg and 110 mmHg in Group III and Group IV vs. 127 mmHg Group I, $p = 0.002$). The need for IPPV was highest in Group IV (89% vs. 64.9%, 78.7%, and 76.9%, $p < 0.001$). Besides, the parameters of IPPV and the need of adjunctive measures were similar between groups (Table 2).

Complications and outcomes

Patients in Group IV had higher rate of continuous renal replacement therapy (CRRT) (31% in Group IV vs. 22.6% in Group I, 14.8% in Group II and 26% in Group III, $p = 0.018$) and cardiovascular failure (57% in Group IV vs. 28.6% in Group I, 31% in Group II and 36.5% in Group III, $p < 0.001$). There was significantly lower ICU mortality (26.8% in Group I vs. 43.9% in Group II, 51% in Group III, and 66% in Group IV, $p < 0.001$) and hospital mortality (28.6% in Group I vs. 44.5% in Group II, 53.8% in Group III, and 71% in Group IV, $p < 0.001$) in patients with a lower cumulative fluid balance on Day 7 of ICU admission. Moreover, a more positive cumulative balance was associated with fewer ventilator-free days within 28 day (19 in Group I vs. 8 in Group II, 0 in Group III, and 0 in Group IV, $p < 0.001$) (Table 3).

After adjusting for age, APACHE II, PaO_2/FiO_2 on diagnosis, and the need for IPPV, a higher cumulative fluid balance at day 7 was associated with higher hospital mortality (Group II OR 1.803 [1.082−3.004], $p = 0.024$; Group III OR 2.786 [1.555−4.992], $p = 0.001$; Group IV OR 5.495 [2.993−10.088], $p < 0.001$] (Figure 2 and Table 4). Hospital mortality increased linearly with the increase of cumulative fluid balance in the first 7 day of ICU admission (from 28.6% to 71%, $p < 0.001$) (Figure 3).

TABLE 3 Complications and outcomes of patients subdivided by cumulative fluid balance.

	All $n = 527$	Group I ≤0 L $N = 168$	Group II 0–3 L $N = 155$	Group III 3–5 L $N = 104$	Group IV >5 L $N = 100$	p
Hospital-acquired infection, *n%*						
Hospital acquired pneumonia, *n%*	117 (22.3)	36 (21.6)	30 (19.6)	29 (27.9)	22 (22)	0.463
Catheter related blood stream infection, *n%*	23 (4.4)	7 (4.2)	5 (3.3)	7 (6.7)	4 (4.0)	0.607
Urinary tract infection, *n%*	11 (2.1)	6 (3.6)	2 (1.3)	2 (1.9)	1 (1.0)	0.432
Intra-abdominal infection, *n%*	10 (1.9)	4 (2.4)	3 (2.0)	2 (1.9)	1 (1.0)	0.864
Organ failure, *n%*						
Kidney, *n%*	130 (24.7)	44 (26.2)	27 (17.5)	31 (29.8)	28 (28)	0.090
CRRT, *n%*	119 (22.6)	38 (22.6)	23 (14.8)^{IV}	27 (26)	31 (31)^{II}	0.018
Cardiovascular, *n%*	191 (36.2)	48 (28.6)^{IV}	48 (31)^{IV}	38 (36.5)^{IV}	57 (57)$^{I, II, III}$	<0.001
Liver, *n%*	57 (10.8)	19 (11.3)	16 (10.4)	10 (9.6)	12 (12)	0.946
Coagulation, *n%*	64 (12.2)	20 (11.9)	16 (10.4)	11 (10.6)	17 (17)	0.408
Central nervous system, *n%*	38 (7.3)	11 (6.6)	9 (5.9)4	6 (5.8)	12 (12)	0.229
IPPV-free days within 28 days	6 (0–22)	19 (0–28)$^{II, III, IV}$	8 (0–21)$^{I, IV}$	0 (0–21)^{I}	0 (0–9)$^{I, II}$	<0.001
ICU length of stay	11 (7–21)	12 (7–21)	11 (6–21)	11 (7–21)	10 (6–19)	0.769
ICU mortality, *n%*	232 (44)	45 (26.8)$^{II, III, IV}$	68 (43.9)$^{I, IV}$	53 (51)^{I}	66 (66)$^{I, II}$	<0.001
Hospital length of stay	19 (10–29)	20 (12–32)	18 (9–28)	17 (10–30)	16 (7–28)	0.072
Hospital mortality, *n%*	244 (46.3)	48 (28.6)$^{II, III, IV}$	69 (44.5)$^{I, IV}$	56 (53.8)^{I}	71 (71)^{I}	<0.001
Withdrawal of life sustaining care	92 (17.5)	17 (10.1)$^{III, IV}$	27 (17.4)	26 (25)^{I}	22 (22)^{I}	0.008
Patients except withdrawal						
ICU mortality, *n%*	140 (32.2)	28 (18.5)$^{III, IV}$	41 (32)^{IV}	27 (34.6)$^{I, IV}$	44 (56.4)$^{I, II, III}$	<0.001
Hospital mortality, *n%*	152 (33.4)	31 (20.5)$^{III, IV}$	42 (32.8)	30 (38.5)^{I}	49 (50)^{I}	<0.001

Abbreviations: CRRT, continuous renal replacement therapy; ICU, intensive care unit; IPPV, invasive positive pressure ventilation.

DISCUSSION

In this study, we described the fluid management of ARDS patients in China. Survivors had lower cumulative fluid balance than non-survivors in the first 7 day after ICU admission. Moreover, we found that lower cumulative fluid balance in the first 7 day after ICU admission was associated with lower hospital mortality. With the increase of cumulative fluid balance, hospital mortality increased gradually. Additionally, higher cumulative fluid balance was associated with fewer ventilator-free days within 28 day.

To date, the survival outcomes of conservative and liberal fluid strategies for ARDS patients are uncertain. Although the FACTT study supported the use of the conservative fluid strategy, it failed to show the survival benefit of the conservative fluid strategy.[6] Other randomized controlled trials (RCTs) with few participants also did not show a significant survival benefit of the conservative fluid strategy.[11–15] Furthermore, the pooled results of a systematic review and meta-analysis including ARDS patients from five RCTs showed no effect of fluid balance strategy on mortality.[16] However, several observational studies have shown a negative association between positive fluid balance and survival outcomes.[8,9] Apart from the limited studies, the largest challenge to establishing a unified conclusion on the fluid management of ARDS is the complex heterogeneity of the disease. The heterogeneity of ARDS includes risk factors, timing of onset, severity of hypoxia, genotypes, biomarkers, and inflammatory reactions.[17] Even with a well-designed RCT, the results may not be generalizable to real-world ARDS populations. In our study, we found significantly lower hospital mortality in patients with lower cumulative fluid balance.

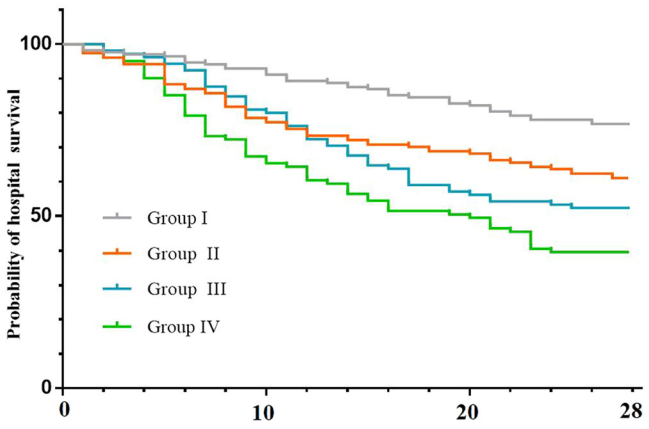

FIGURE 2 Probability of hospital survival in patients with ARDS. Patients were divided in 4 groups based on cumulative fluid balance on the first 7 days of ICU admission: Group I (≤0 L); Group II (0–3 L); Group III (3–5 L) and Group IV (≥5 L). Survival curve showed a higher likelihood of survival in Group I compared with Group II to IV.

TABLE 4 Multivariable logistic regression results to determine the potential independent prognostic role of cumulative fluid balance.

	OR (95% CI)	*p*
Age	1.020 (1.008–1.032)	0.001
APACHE II	1.037 (1.003–1.071)	0.032
PaO_2/FiO_2 on diagnosis	0.996 (0.992–0.999)	0.016
Need for IPPV	2.642 (1.498–4.661)	0.001
Group II	1.803 (1.082–3.004)	0.024
Group III	2.786 (1.555–4.992)	0.001
Group IV	5.495 (2.993–10.088)	<0.001

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FiO_2, fraction of inspiration; IPPV, invasive positive pressure ventilation; PaO_2, arterial oxygen pressure.

Several potential reasons may result in this phenomenon. First, the fundamental pathophysiological hallmark of ARDS is increased permeability of the alveolar-capillary barrier, leading to non-cardiogenic pulmonary edema. The increase of fluid balance can lead to increased pulmonary edema.[18] Pulmonary edema reduces lung compliance and exacerbates hypoxemia, which has adverse effects on the prognosis of ARDS.[19] A lower cumulative fluid balance could alleviate pulmonary edema and improve pulmonary function, which would explain the higher number of ventilator-free days in Group I. Second, the FACTT study reported that the conservative fluid strategy shortened the duration of mechanical ventilation and intensive care, which may reduce the occurrence of ventilator-induced

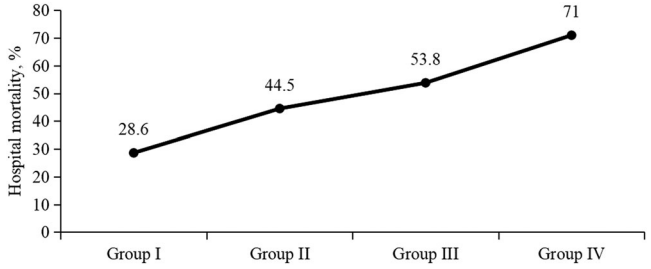

FIGURE 3 The Cochran-Armitage trend test between different groups of hospital mortality in patients with ARDS. Patients were divided in 4 groups based on cumulative fluid balance on the first 7 days of ICU admission: Group I (≤0 L); Group II (0–3 L); Group III (3–5 L) and Group IV (≥5 L). The hospital mortality was 28.6%, 44.5%, 53.8% and 71%, respectively. The results of hospital mortality showed a linear trend ($p < 0.001$).

lung injury, ventilator-associated pneumonia, and other hospital-related complications. Additionally, patients with more positive cumulative fluid balance (Group III and Group IV) had lower PaO_2/FiO_2, and these patients may be more fragile to excessive fluid.

In our study, 57% of patients in Group IV developed cardiovascular failure. Patients in Group IV had lower PaO_2/FiO_2, which indicated more serious disease, though the APACHE II score and SOFA score were similar among different groups. For these patients, positive fluid balance was necessary for resuscitation or maintaining hemodynamics stability. However, excess fluid balance stressed the circulatory system, which resulted in cardiovascular failure.[20] In a word, cardiovascular failure is not only a result but also the course of the disease.

The milestone study to investigate the effect of fluid restriction on ARDS was the FACTT study,[6] which was an RCT that enrolled 1000 patients with ARDS. The major difference between our study and the FACTT study was the severity of illness; FACTT patients all required invasive mechanical ventilation, whereas the need for IPPV in our study was 75.9%. Furthermore, the 7 day cumulative fluid balance in the FACTT study (−136 mL) was higher compared with the fluid balance in Group I of our study (−2042 mL). Perhaps the survival benefit increases as the cumulative fluid balance decreases.

Our study had several advantages. Importantly, all data came from the database of the CHARDS study, which reflects real-world ARDS patients. To the best of our knowledge, this was the first study to report the fluid management of ARDS patients in China, which may be a valuable addition to the literature and provide evidence for fluid management. In addition, all patients were subdivided into four groups in accordance with their fluid balance in the first seven consecutive days to further explore the hospital survival of patients in different combinations.

Lower hospital mortality was found in patients with lower cumulative fluid balance. Several limitations of our study should be mentioned. First, although the hospitals included in our study were general hospitals, the ICUs involved were MICUs or RICUs and intrapulmonary factors accounted for the majority of causes of ARDS. Besides, despite this was a multicenter study including 527 patients with ARDS, the number of patients was still limited, so possible selection bias and report bias were inevitable, which limited the general applicability of our study in China and even in the world. Second, we only investigated the relationship between fluid balance and prognosis of patients with ARDS, which limited the possibility to determine a cause-effect relationship between fluid balance and outcome. Third, we adjusted for as many potential confounders as possible but could not exclude all confounders. Although we adjusted for age, APACHE II score, PaO_2/FiO_2 on diagnosis, and the need for IPPV, it was possible that an unappreciated and undocumented confounder was a predictor of mortality and drove increased fluid administration. What's more, the specific measures of negative fluid balance, such as protocolized diuretic use, hyperoncotic albumin solutions, or minimization of fluid input, were not clear. A prospective randomized study of liberal versus conservative fluid management of patients in ARDS is required to definitively prove whether positive fluid balance is a "biomarker" for severity of illness or the administration of excess fluids causes mortality.

CONCLUSION

Lower fluid balance in patients with ARDS was found to have an association with lower hospital mortality. However, owing to the heterogeneity of ARDS and the limitation of retrospective study, a large-scale and well-designed RCT is needed in the future.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study or to the data acquisition, analysis or interpretation; reviewed and approved the final manuscript; and significantly contributed to this study. Drs. Chen Wang and Qingyuan Zhan took full responsibility for the integrity of the submission and publication and was involved in the study design. Drs. Qingyuan Zhan, Xu Huang, Dawei Wu, Daoxin Wang and Ziying Chen participated in the design of the study and coordination. Drs Ziying Chen, Xu Huang, Haining Lu and Wang Deng involved in data collection, had full access to all of the data in the study, took responsibility for the integrity of the data and were responsible for data verification. Dr. Ziying Chen took the responsibility for statistical analysis and drafted the manuscript. Drs. Xu Huang and Linna Huang provided crucial revision for important intellectual content. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The ethics committee of China-Japan Friendship Hospital approved this study (2015-77). All participating patients or their next of kin provided written informed consent. All methods were carried out in accordance with the Declaration of Helsinki.

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