A Prospective Study Correlating Fluid Balance and Outcome in Critically Ill Patients

Mohammed Abdel Monem Saeed*[1], Mena Gerges Abdoh[2], Hesham Mohammed Mahmoud Elazzazi[2], Mayar Hassan Said Ahmed Elsersi[2], Sameh Ahmed Refaat Mustafa[2]
[1]Critical Care Medicine Department, Faculty of Medicine, Helwan University, Egypt
[2]Anesthesia Department, Faculty of Medicine, Ain Shams University, Egypt
***Corresponding author:** Mohammed Abdel Monem Saeed, **Mobile:** (+20)1099292999, **E-Mail:** mohammedicu1@gmail.com

ABSTRACT

Background: Fluid administration can be lifesaving as fluid accumulation after initial resuscitation and stabilization of hemodynamics can lead to avoidable adverse effects and less favorable outcomes.

Objective: The aim of the work was to evaluate whether even fluid balance in comparison to negative or even fluid status is correlated with increased morbidity and mortality rates in critically ill patients.

Patients and Methods: An observational prospective study was done on 145 patients older than eighteen years, admitted to the general intensive care (Medical & Surgical ICU) units in Helwan University Hospitals and Ain Shams University Hospitals during the period from November 2020 till May 2021.

Results: One hundred twenty-four patients (85.5%) who survived, having the median cumulative fluid balance of -110ml (IQR-2.1 – 2.2L) after four days following randomization while the median cumulative fluid balance of the 21 patients (14.5%) who didn't survive was 3800 ml (IQR 1.7-5.2L), after four days of ICU admission. Fluid balance more than 1.2 liters per day in our study had higher ICU complications: Increased risk of AKI, longer ICU and hospital stays, mechanical ventilation and fluid balance was an independent factor associated with increased mortality.

Conclusion: It could be concluded that negative fluid balance for 4 days in critically ill patients was associated with less length of stay in the general ICU, and less mechanical ventilation duration, while positive fluid balance, leads to higher mechanical ventilation duration, vasopressors requirements, and significantly associated with higher mortality.

Keywords: Fluid balance, ICU, ICU Mortality

INTRODUCTION

Appropriate fluid management in critically sick patients is one of the most difficult parts of treatment for the ICU patient care team **(1)**.

Fluid resuscitation is vital for maintaining hemodynamic stability and enhancing tissue oxygenation; nevertheless, in critically sick patients, there is a link between fluid excess and poor outcomes. Multiple studies have found that a positive cumulative fluid balance (FB) is a powerful predictive factor for death in sepsis **(2)**.

Further fluid administration, once adequate fluid resuscitation has been achieved, may increase intravascular pressure and vascular permeability, resulting in fluid leakage, tissue edoema, decreased oxygenation index, higher incidence of acute kidney injury (AKI), and increased mortality, as found in many studies **(3)**.

Fluid accumulation consequences was tudied in many researches especially in critically ill patients such as hypertension, tissue and peripheral edema, respiratory failure and increased cardiac demand **(4)**.

One day of negative balance is a predictor of survival in patients with septic shock, while positive mean daily fluid balance was a significant predictor of mortality in ICU, at the same time, a more positive fluid balance (in both resuscitation and cumulatively over 4 days) is associated with increased risk of mortality **(5)**, same results were also reported in other populations like acute renal failure **(4)**, acute lung injury**(6)**, aneurysmal subarachnoid hemorrhage (ASH)**(7)**, and surgical patients**(8)**.

Also, Payen *et al.* found that the mean ICU fluid balance, was an independent factor correlated with a high risk of ICU mortality **(4)**. An essential part of the process of care of critically ill patients is the fluid balance monitoring; balancing of the intake and output of fluid permit metabolic processes to function correctly, fluid balance plays an important role in managing critically ill patients, accurate balancing of fluid balance activities is a vital part of patients baseline information, which directs medical and nursing interventions to achieve physiological stability **(9)**.

For patients admitted to intensive care units, fluid balance should be carefully monitored and recorded (ICUS). Fluid balance is one of the crucial metrics noted in the patient's daily observation sheet, along with nursing interventions, vital signs, and medical procedures. The fluid balance is the difference between the intake and output quantities **(10)**.

Conservative fluid administration and diuretics were widely targeted to achieve earlier and more negative fluid balance once the hemodynamic status was stable, this is the current evidence proven**(11)**.

Our study targeted to assess whether positive fluid balance in comparison with negative or even fluid balance is associated with increased morbidity and mortality rates in critically ill patients.

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PATIENTS AND METHODS

This prospective observational study was performed on 145 Patients older than 18 years admitted to the general intensive care units at Helwan University Hospitals and Ain Shams University Hospitals during the period from November 2020 till May 2021.

Patients representing sample size were divided into three main groups as following:

Group A: Patients with positive fluid balance. They were classified into two subgroups: **A1** Patients with positive cumulative fluid balance >2000 ml after 4 days from ICU admission, and **A2** Patients with positive cumulative fluid balance <2000 ml after 4 days from ICU admission

Group B: Patients with restricted fluid intake and negative fluid balance. They were classified into two subgroups: **B1** Patients with negative cumulative fluid balance >2000 ml after 4 days from ICU admission, and **B2** Patients with negative cumulative fluid balance <2000 ml after 4 days from ICU admission.

Group C: Patients with even fluid balance (zero balance) after 4 days from ICU admission.

Inclusion criteria include patients older than 18 years admitted to ICU, while exclusion criteria include age <18 years, admission <4 days, planned cardiac surgery, pregnancy, brain death on admission, patients with more than one ICU stay and chronic kidney disease patients.

All patients were subjected to: Full Clinical examination including detailed history taking with special stress on age, sex, nephrotoxic drug intake and presence of other systemic diseases specially DM and HTN. Routine investigations that include: Complete blood picture (CBC), serum creatinine, BUN, serum electrolytes, ABG, fluid intake, fluid output, urine output (UO) and cumulative fluid balance after 4 days from ICU admission had been recorded; fluid balance was calculated as fluid intake minus fluid output.

Data had been collected on demographics, comorbidity conditions, APACHE II, SOFA score and SAPSII scores, AKI according to the creatinine-based Kidney Disease Improving Global Outcome criteria (KDIGO), the need of renal replacement therapy. Vasopressors use, ICU mortality, hospital lengths of stay, mechanical ventilation and mechanical ventilation duration had been also registered.

The primary endpoint was hospital mortality. Secondary endpoints include length of stay in ICU and maximum sequential organ failure assessment (SOFA) and simplified acute physiology score (SAPS) II during the ICU stay. A rise of more than 1.5 times above baseline serum creatinine was considered as AKI according to the creatinine-based Kidney Disease Improving Global Outcome criteria (KDIGO).

APACHE II, SOFA score and SAPSII scores Calculated by using Combination ICU Mortality Calculator APACHE II, SAPS II, and SOFA scores to predict hospital mortality. This calculator is designed for researchers who are calculating a number of different ICU mortality scores on a single patient. By combining data entry into one form, a researcher will not be required to enter the same variable (such as heart rate or serum sodium) multiple times on multiple online calculators.

Ethical consent:

An approval of the study was obtained from Helwan University and Ain Shams University Academic and Ethical Committees. Written informed consent of all the subjects was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical analysis was performed using SPSS version 25 software (IBM, 2017). Results were presented by tables and graphs. Results were expressed as the mean, Standard deviation, median and range for Continuous variables, number and percentage for categorical variables. We used Kolmogorov-Smirnov and Levene tests to determine the distribution characteristics of variables and variance homogeneity. Chi-square test was used to test differences for categorical variables. Independent samples Mann-Whitney U test was used, as appropriate, to test differences for continuous variables between two groups. One-way ANOVA was used to test differences when more than two independent groups were present and variances were equal, while Kruskal-Wallis test was used when equal variances were not present. Binary logistic regression analysis of mortality and associated factors was done and reported as odds ratios and 95% confidence interval. The sensitivity, specificity, and accuracy of fluid balance as predictor of mortality in critically ill patients. Receiver operating characteristic (ROC) curves were plotted for the optimal cut-off values of fluid balance as predictor of mortality in critically ill patients. The optimal cut-off values were defined as the values that allow discrimination between respiratory allergies patients from control with highest sensitivity and specificity. A P-value of < 0.05 was accepted as statistically significant.

RESULTS

Table (1) shows that there was statistically significant difference between study groups in length of stay at ICU and mechanical ventilation. Group C had less length of stay at ICU and less mechanical ventilation than other groups.

Table (1): Baseline characteristics on studied patients.

Variables	Group A (n=60)	Group B (n=49)	Group C (n=36)	Test of sig.	P
Age (years):				**F**	
Mean ± SD	57.7 ± 17.3	51.7 ± 15.2	52.6 ± 16.2	2.2	0.1
Sex:				χ^2	
Males	30 (50.0%)	29 (59.2%)	15 (41.7%)	1.8	0.7
Females	30 (50.0%)	20 (40.8%)	21 (58.3%)		
Admission category:				χ^2	
**Elective surgical*	5 (8.3%)	3 (6.1%)	1 (2.8%)	4.3	0.3
**Emergency surgical*	7 (11.7%)	10 (20.4%)	3 (8.3%)		
**Medical*	48 (80.0%)	36 (73.5%)	32 (88.9%)		
Length of stay at ICU (days):					
Median	8.0	6.0	5.0	**KW**	**<0.001**
IQ-Range	6.0 – 15.0	4.0 – 12.0	5.0 – 7.0	16.0	**HS**
Mechanical ventilation:					
Yes	32 (53.3%)	20 (40.8%)	7 (19.9%)	χ^2	**0.005**
No	28 (46.7%)	29 (59.2%)	29 (80.6%)	10.8	**S**
Renal dialysis:				χ^2	
Yes	4 (6.7%)	0 (0.0%)	1 (2.8%)	3.7	0.1
No	56 (93.3%)	49 (100%)	35 (97.2%)		
Vasopressors:				χ^2	
Yes	4 (6.7%)	4 (8.2%)	0 (0.0%)	2.9	0.2
No	56 (93.3%)	45 (91.8%)	35 (100%)		
Comorbidities:				χ^2	
*Cardiovascular disease	32 (53.3%)	23 (46.9%)	14 (38.9%)	4.1	0.1
*Diabetes mellitus	25 (41.7%)	21 (42.9%)	18 (50.0%)	2.3	0.3
*Respiratory disease	12 (20.0%)	9 (18.4%)	7 (19.4%)	1.7	0.6
*Sepsis	8 (13.3%)	6 (12.2%)	4 (11.1%)	1.4	0.6
*Neurovascular disease	34 (56.7%)	12 (24.5%)	9 (25.0%)	2.5	0.3
*Renal disease	23 (38.3%)	21 (42.9%)	18 (50.0%)	1.6	0.6

Table (2) shows that there was no statistically significant difference between study groups in ICU values of different scores on admission.

Table (2): ICU values of studied patients on admission.

At admission	Group A (n=60)	Group B (n=49)	Group C (n=36)	Test of sig.	P
SAPS II points:				**KW**	
Median	29.5	26.0	22.0	11.8	**0.3**
IQ-Range	19.0 – 43.5	15.5 – 33.5	13.8 – 27.5		**NS**
SAPS II (%):				**KW**	
Median	10.2	7.2	4.7	11.8	**0.3**
IQ-Range	3.4 – 31.6	2.2 – 14.7	1.7 - 8.4		**NS**
SOFA points:				**KW**	
Median	4.0	3.0	2.0	12.7	**0.2**
IQ-Range	3.0 – 5.0	2.0 – 4.0	0.0 – 4.0		**NS**
SOFA (%):				χ^2	
<10%	49 (81.7%)	44 (89.8%)	36 (100%)	7.8	**0.2**
15% - 20%	11 (18.3%)	5 (10.2%)	0 (0.0%)		**NS**
APACHE II points:				**KW**	
Median	11.0	9.0	9.0	6.7	**0.3**
IQ-Range	6.0 – 19.0	5.5 – 12.0	3.0 – 11.8		**NS**
APACHE II (%):				**KW**	
Median	12.9	9.9	9.9	6.8	**0.3**
IQ-Range	6.7 – 32.2	6.3 – 14.6	4.4 – 14.2		**NS**
KDIGO:				χ^2	
No	58 (96.7%)	45 (91.8%)	35 (97.2%)	8.2	0.8
KDIGO 1	0 (0.0%)	4 (8.2%)	1 (2.8%)		NS
KIDGO 2	2 (3.3%)	0 (0.0%)	0 (0.0%)		

Table (3) shows that there was statistically significant difference between study groups in ICU values after 4 days. Group A had high SAPS II, SOFA, APACHE II and KDIGO than other groups.

Table (3): ICU values of studied patients after 4 days.

After 4 days	Group A (n=60)	Group B (n=49)	Group C (n=36)	Test of sig.	P
SAPS II points:					
Median	27.0	24.0	17.5	**KW** 17.4	**<0.001 HS**
IQ-Range	18.0 – 40.0	15.5 – 29.5	13.0 – 21.0		
SAPS II (%):					
Median	8.1	5.8	2.8	**KW** 18.2	**<0.001 HS**
IQ-Range	2.9 – 30.6	2.3 – 10.2	1.5 – 4.2		
SOFA points:					
Median	3.0	3.0	2.0	**KW** 11.7	**0.003 S**
IQ-Range	1.0 – 6.0	1.0 – 4.0	0.0 – 3.0		
SOFA (%):					
<10%	46 (76.8%)	47 (95.9%)	36 (100%)	χ^2 17.2	**0.009 S**
15% - 20%	7 (11.6%)	2 (4.1%)	0 (0.0%)		
40% - 50%	7 (11.6%)	0 (0.0%)	0 (0.0%)		
KDIGO:					
No	50 (83.3%)	47 (95.9%)	33 (91.7%)	χ^2 8.8	**0.04 S**
KDIGO 1	4 (6.7%)	2 (4.1%)	3 (8.3%)		
KDIGO 2	6 (10.0%)	0 (0.0%)	0 (0.0%)		

Table (4) shows that there was high statistically significant difference between study groups in mortality rates. Group A had higher mortality rate than other groups.

Table (4): Mortality rates in study groups.

Mortality	Group A (n=60)	Group B (n=49)	Group C (n=36)	χ^2	P
Yes	18 (30.0%)	3 (6.1%)	0 (0.0%)	20.5	**<0.001 HS**
No	42 (70.0%)	46 (93.9%)	36 (100%)		

Table (5) shows that there was no statistically significant difference between study groups in ICU scores values at admission.

Table (5): Subgroup analysis of ICU values of studied patients on admission.

At admission	Subgroups					Test of sig.	P
	A1(n=32)	A2(n=28)	B1(n=23)	B2 (n=26)	C (n=36)		
SAPS II points:							
Median	24.0	30.0	33.0	20.5	22.0	**KW**	**0.1**
IQ-Range	17.0–47.0	23.0–41.8	24.0–37.0	13.8–29.0	13.8–27.5	19.1	**NS**
SAPS II (%):							
Median	5.8	10.6	14.0	4.0	4.7	**KW**	**0.1**
IQ-Range	2.6 – 39.3	5.2 – 28.1	5.8 – 19.6	1.7 – 9.7	1.7 - 8.4	19.1	**NS**
SOFA points:							
Median	5.0	4.0	4.0	2.5	2.0	**KW**	**0.1**
IQ-Range	2.3 – 7.8	3.0 – 5.0	3.0 – 5.0	1.8 – 4.0	0.0 – 4.0	21.8	**NS**
SOFA (%):							
<10%	21(65.6%)	28(100%)	20(87.0%)	24(92.3%)	36 (100%)	χ^2	**0.1**
15%-20%	11(34.4%)	0(0.0%)	3(13.0%)	2(7.7%)	0 (0.0%)	26.1	**NS**
APACHE II points:							
Median	12.0	9.5	11.0	7.0	9.0	**KW**	**0.1**
IQ-Range	7.0 – 20.0	6.0 – 13.5	9.0 – 16.0	4.0 – 9.4	3.0 – 11.8	17.7	**NS**
APACHE II (%):							
Median	14.6	10.6	12.9	7.6	9.9	**KW**	**0.1**
IQ-Range	7.9 – 35.5	6.7 – 17.6	9.9 – 23.5	5.1 – 10.3	4.4 – 14.2	17.7	**NS**
KDIGO:							
No	30(93.8%)	28(100%)	20(87.0%)	25(96.2%)	35(97.2%)	χ^2	0.08
KDIGO 1	0 (0.0%)	0 (0.0%)	3(13.0%)	1(3.8%)	1(2.8%)	15.6	NS
KDIGO 2	2(6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		

Table (6) shows that there was statistically significant difference between study groups in ICU values after 4 days. Group A1 and A2 had high SAPS II, SOFA, KDIGO , mortality rate, length of stay at ICU, mechanical ventilation and renal dialysis other than groups B1, B2 and C.

Table (6): Subgroup analysis of ICU values of studied patients after 4 days.

After 4 days	Subgroups					Test of sig.	P
	A1(n=32)	A2(n=28)	B1(n=23)	B2(n=26)	C (n=36)		
SAPS II points: *Median* *IQ-Range*	32.0 14.5–56.5	25.0 18.0–33.8	26.0 24.0–37.0	16.0 15.0–24.0	22.0 13.8–27.5	**KW** 25.2	**<0.001** **HS**
SAPS II (%): *Median* *IQ-Range*	12.8 1.9 – 60.7	6.5 2.9 – 18.1	7.2 5.8 – 19.6	2.5 2.0 – 5.8	4.7 1.7 - 8.4	**KW** 25.7	**<0.001** **HS**
SOFA points: *Median* *IQ-Range*	4.0 1.0 – 8.0	3.0 2.0 – 4.0	3.0 1.0 – 5.0	2.0 1.0 – 3.0	2.0 0.0 – 4.0	**KW** 16.8	**0.003** **S**
SOFA(%): *<10%* *15%-20%* *40%-50%*	20(62.5%) 5 (15.6%) 7 (21.9%)	26(92.9%) 2 (7.1%) 0 (0.0%)	21(91.3%) 0 (0.0%) 2 (8.7%)	26(100%) 0 (0.0%) 0 (0.0%)	36(100%) 0 (0.0%) 0 (0.0%)	χ^2 32.0	**<0.001** **HS**
KDIGO: *No* *KDIGO 1* *KDIGO 2*	22(68.8%) 4(12.5%) 6(18.7%)	28(100%) 0 (0.0%) 0 (0.0%)	21(91.3%) 0 (0.0%) 2(8.7%)	26(100%) 0 (0.0%) 0 (0.0%)	35(97.2%) 1(2.8%) 0 (0.0%)	χ^2 26.3	**<0.001** **HS**
Length of stay at ICU: *Median* *IQ-Range*	8.0 6.0 – 15.0	9.0 6.0 – 16.0	8.0 4.0 – 10.0	6.0 4.0 – 16.0	5.0 5.0 – 7.0	**KW** 16.7	**0.003** **S**
Mechanical ventilation: *Yes* *No*	13(40.6%) 19(59.4%)	19(67.9%) 9(32.1%)	11(47.8%) 12(52.2%)	9(34.6%) 17(65.4%)	7 (19.9%) 29(80.6%)	χ^2 16.2	**0.003** **S**
Renal dialysis: *Yes* *No*	4(12.5%) 28(87.5%)	0(0.0%) 28(100%)	0(0.0%) 23(100%)	0(0.0%) 26(100%)	1(2.8%) 35(97.2%)	χ^2 10.7	**0.03** **S**
Vasopressors: *Yes* *No*	2(6.3%) 30(93.7%)	2(7.1%) 26(92.9%)	1(4.3%) 22(95.7%)	3(11.5%) 23(88.5%)	0 (0.0%) 35 (100%)	χ^2 4.2	0.4
Mortality: *Yes* *No*	11(34.4%) 21(65.6%)	7(25.0%) 21(75.0%)	2(8.7%) 21(91.3%)	1(3.8%) 25(96.2%)	0 (0.0%) 35 (100%)	χ^2 21.8	**<0.001** **HS**

Table (7) shows that there were statistically significant differences between survivors and non-survivors in all clinical aspects.

Table (7): Comparison between survivors and non-survivors in clinical aspects.

Variables	Survivors (n=124)	Non-survivors (n=21)	Test of sig.	P
Age (years): *Median* *IQ-Range*	 53.0 45.0 – 65.0	 70.0 57.5 – 73.5	 **MW** 3.9	 **<0.001** **HS**
Cumulative fluid balance after 4 days (L): *Median* *IQ-Range*	 -0.11 -2.1 – 2.2	 3.8 1.7 – 5.2	 **MW** 3.9	 **<0.001** **HS**
Length of stay at ICU (days): *Median* *IQ-Range*	 6.0 4.0 – 10.0	 13.0 9.0 – 16.0	 **MW** 4.0	 **<0.001** **HS**
Mechanical ventilation: *Yes (n=59)* *No (n=86)*	 45 (76.3%) 79 (91.9%)	 14 (8.7%) 7 (8.1%)	 χ^2 6.9	 **0.009** **S**
Renal dialysis: *Yes (n=5)* *No (n=140)*	 1 (20.0%) 123 (87.9%)	 4 (80.0%) 17 (12.1%)	χ^2 17.9	 **<0.001** **HS**
Vasopressors: *Yes (n=8)* *No (n=137)*	 2 (25.0%) 122 (89.1%)	 6 (75.0%) 15 (10.9%)	χ^2 25.0	 **<0.001** **HS**
Admission SAPS II: *Median* *IQ-Range*	 23.5 16.0 – 30.0	 39.0 35.5 – 51.0	 **MW** 5.2	 **<0.001** **HS**
Admission SOFA: *Median* *IQ-Range*	 3.0 2.0 – 4.0	 5.0 5.0 – 8.0	 **MW** 4.7	 **<0.001** **HS**
APACHE II: *Median* *IQ-Range*	 9.0 5.0 – 12.0	 16.0 12.0 – 23.0	 **MW** 4.3	 **<0.001** **HS**
Admission KDIGO: *No (n=138)* *KDIGO 1 (n=5)* *KDIGO 2 (n=2)*	 119 (86.2%) 5 (100%) 0 (0.0)	 19 (13.8%) 0 (0.0%) 2 (100%)	 χ^2 12.7	 **0.002** **S**

Table (8) shows that positive fluid balance, mechanical ventilation, vasopressors and high admission SAPS II, SOFA, APACHE II and KDIGO were significantly associated with high mortality.

Table (8): Binary logistic regression analysis of mortality and associated factors.

Variables	OR (95%CI)	P
Age	0.99 (0.63 – 5.4)	0.9
Positive fluid balance	2.6 (1.4 – 3.7)	**0.005 (S)**
Length of stay at ICU	1.0 (0.78 – 4.3)	0.5
Mechanical ventilation	1.7 (1.2 – 2.6)	**0.01 (S)**
Renal dialysis	1.0 (0.53 – 2.7)	0.5
Vasopressors	1.2 (1.1 – 2.0)	**0.03 (S)**
Admission SAPS II	1.8 (1.3 – 2.3)	**0.02 (S)**
Admission SOFA	1.6 (1.2 – 2.1_	**0.03 (S)**
APACHE II	2.0 (1.5 – 3.1)	**0.007 (S)**
Admission KDIGO	2.4 (1.7 – 3.5)	**0.006 (S)**

Table (9): Fluid balance as predictor of mortality in critically ill patients.

Cutoff point	AUC (95% CI)	Sensitivity	Specificity	P
>1.2 L	0.77 (0.65 – 0.88)	85.7%	67.7%	**<0.001** **HS**

This table shows that fluid balance above 1.2 L is a significant predictor of mortality, in critically ill patients, with 85.7% sensitivity and 67.7% specificity.

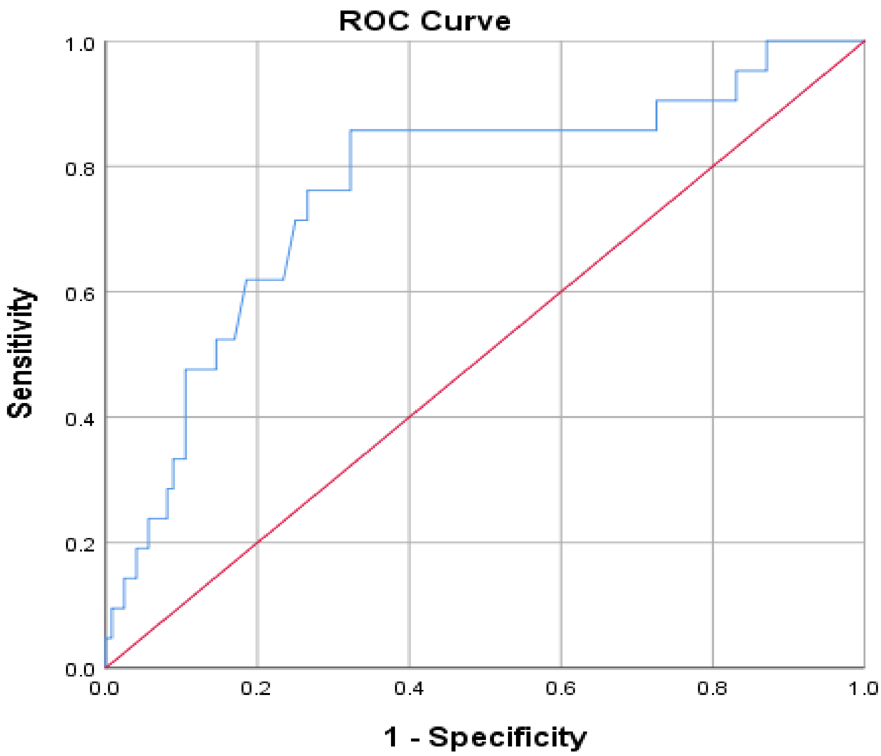

Figure (1): Receiver Operating Characteristics curve of fluid balance as predictor of mortality in critically ill patients.

DISCUSSION

The present study demonstrates that mean fluid balance in the first 4 days is significantly associated with mortality outcome. More positive fluid balance is associated with significantly increased risk of mortality; One hundred and forty-five patients more than 18 years, with ICU admission of more than 4 days were screened between November 2020 to May 2021. Twenty one of the patients (14.5%) were died and the demographic and clinical profiles between survivors and non-survivors are shown in Table 13. Non-survivors were characterized by severe morbidity in comparison to survivors where SOFA and APACHE II scores were higher; **Taccone *et al.*** [(12)] also has reported that higher SAPS II, ALI and ARDS scores, a greater need for mechanical ventilation and sepsis were associated with higher mortality in critically ill patients.

In our study the median cumulative fluid balance of the 124 patients who survive was -110 ml (IQR -2.1-2.2 L) after the fourth day following randomization while the median cumulative fluid balance of the 21 patients who did not survive was 3800 ml (IQR 1.7-5.2 L) after the fourth day in ICU, also our results runs in favor of **Almeida *et al.*** [(13)] who found that the mean fluid balance was significantly higher in non-survivors than in survivors [1675 (471–2921) vs. 887 (104–1557) ml/24 h, P = 0.017].

We used the area under the curve and the intersection of the sensitivity and specificity curves to define the accumulated fluid balance value (1200 ml/24 h) for the univariate model; **Almeida *et al.***[(13)] show accumulated fluid balance value (1100 ml/24 h).

Cronhjort *et al.* [(14)] showed that the median cumulative fluid balance of the 841 patients was 2480 ml (IQR47-5045) after the third day following randomization, the median cumulative fluid balance of the 129 patients who were excluded due to death or discharge was 1500 ml (IQR 285-3453), including the day of last fluid data registration (median second day for those who had died and second day for those who had been discharged). The difference between the results of **Cronhjort *et al.*** [(14)] study and our results is that our study involved patients with different medical and surgical causes of admission while the other study involved only septic shock patients; the 145 included patients were evenly distributed between the four fluid balance groups. We found several baseline differences between the groups. The group with the highest fluid balance had a higher mortality rate; the two lower fluid balance groups as compared with the two higher fluid balance groups show lower mortality rate. We observed lower mortality rate at inclusion in patients with a fluid balance in the middle range (0–1100 ml after 4 days at ICU) as compared to patients with a negative or more positive fluid balance (P = 0.001).

Cronhjort *et al.* [(14)] showed that more positive fluid balance was associated with a lower percentage of days alive and increase days of mechanical ventilation and vasopressors/inotropic support; many observational studies showed a negative impact of positive fluid balance especially in postoperative patients. **Brandstrup *et al.*** [(15)] declared that targeting negative fluid balance was accompanied with little problems in the postoperative course. Two randomized controlled trials compared negative and positive fluid balance in abdominal surgeries and revealed much less postoperative complications like, cardiopulmonary, hemorrhagic, thromboembolic, kidney, wound infection or tissue healing, and shorter length of stay.

In our study we found critically ill patients with fluid balance more than 1.2 liters per day had higher ICU complications: increased risk of AKI, longer ICU and hospital stays, and mechanical ventilation, and fluid balance was independently associated with mortality.

The difference in relation of positive fluid balance and mortality between the two studies may be due to the difference between study groups in both studies as in our study we collected data from surgical and medical patients in ICU.

Another study done by **Upadya *et al.*** [16] revealed that eighty seven critically ill patients , with restricted fluid therapy were two times more likely to be weaned successfully from ventilation than those with liberal fluid therapy; acute lung injury patients, **Wiedemann *et al.*** [6] brought a large randomized controlled trial comparing fluid therapy protocols , the restrictive group had much more good lung function leading to less duration on mechanical ventilation and time of ICU stay in comparison to positive balance group (mean cumulative fluid balance of 6992 ml).

Our research revealed that there is strong correlation between 96 hour cumulative fluid balance with length of mechanical ventilation and ICU stay in survivors; on the other side liberal fluid strategy was accompanied with more days on mechanical ventilation and ICU stay, **Wiedemann *et al.*** [6] showed no difference in 60- day mortality between those with restrictive or liberal group.

Our study didn't show the difference in 60 day mortality as one of our study limitations as we follow patients only in the ICU so we recommend to study post ICU effect of positive fluid balance in another study; in our study we reached to the conclusion that cumulative fluid balances over the first 96 hours of ICU admission were independently associated with death rate; the higher fluid retention in the non-survivor group may have contributed to the worsening of respiratory function and may justify the higher incidence of invasive mechanical ventilation in this group compared with the survivor group.

Compared with survivors, non-survivors presented a higher need for vasopressor agents [2 (25%) vs. 6 (75%), P < 0.001] and renal replacement therapy [1 (20%) vs. 4 (80%), P < 0.001], and non-survivors had a higher incidence of acute renal failure P < 0.002]. The need for invasive mechanical ventilation was also higher among non survivors P < 0.009], and non survivors presented an increased length of ICU stay [13 (9–16) vs. 6 (4–10) days, P = 0.001].

Almeida *et al.*[13] showed the similar result of our study as compared to survivors, non-survivors presented a higher need for vasopressor agents [34 (35.1%) vs. 19 (76%), P < 0.001] and renal replacement therapy [5 (20%) vs. 1 (1%), P < 0.001], and non-survivors had a higher incidence of acute renal failure [33 (34%) vs. 18 (72%), P < 0.001]. The need for invasive mechanical ventilation was also higher among non survivors [14 (56%) vs. 5 (5.2%), P < 0.001], and non survivors presented an increased length of ICU stay [8 (4–13) vs. 5 (4–7) days, P = 0.015]. The study done by **Alsous *et al.*** [17] revealed that septic shock treated with restricted fluid strategy of more than five hundred milliliters of negative balance for almost a day was three times more likely to be alive; also another recent research on one hundred seventy three sepsis patients , **Acheampong and Vincent** [1] showed that a positive fluid balance was independently associated with mortality; **Wiedemann *et al.*** [6] involved patients with acute lung injury, and **Alsous *et al.*** [17] **and Acheampong *et al.*** [1] involved those with sepsis.

Another brick added to the mosaic of findings on the impact of fluid balance in critically ill patients; patients with severe sepsis have generalized capillary leakage leading to sequestration of fluid in the interstitium, so positive fluid balance may be a marker of inflammatory disease. A randomized controlled trial comparing liberal, and restricted fluid balance in critically ill patient with severe sepsis revealed that fluid balance directly results in higher morbidity or mortality. AKI patients were more prone to have higher fluid balance, so that AKI patients had higher fluid balance in comparison to non AKI patients, confirmed by other researches. Positive fluid balance in AKI is associated with poorer outcome. We showed similar finding, 96-hour fluid balance was independently associated with mortality.

Also, **Payen *et al.*** [4] found that one thousand one hundred and twenty patients with AKI, mean fluid balance was an independent risk factor for 60-day mortality. A positive fluid balance more than 10% of body weight was accompanied with the high rate of 60-day mortality amongst the 618 AKI patients.

Bouchard *et al.* [15] found in a post-hoc analysis of 306 patients with AKI demonstrated higher odds ratio for 60-day mortality in the liberal fluid management when compared to the restricted group.

Our study has several limitations. First, the study involved a small number of patients. A larger multicenter trial would provide a more conclusive data. Second, body weight of patients was not measured. Finally, study of post ICU effect of fluid balance was not screened and we did not mention the type of fluid given in the study.

CONCLUSION

In the view of this study, we could conclude that Zero fluid balance and negative fluid balance independently associated with decrease in mortality and morbidity rates in critically ill patients after 4 days from admission in ICU , negative fluid balance was also associated with less length of stay in ICU and less mechanical ventilation duration.

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