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Original Article

The Effects of Fluid Balance Disorders on Mortality in Patients Hospitalized for Acute Disease in the Internal Medicine Clinic

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Backgorund: Previous studies conducted on critical patients in intensive care units have shown that fluid balance disorder (FBD) increases mortality. The purpose of this study is to investigate the effect of FBD on mortality of patients hospitalized in internal medicine ward.

Methods: The present study was designed as an observational study and follow-up period of the patients began in the first 8 hours of admission to the emergency room who had hypervolemia findings in physical examination were included in the fluid balance FB (+) group; those who had any of the dehydration findings were included in FB (–) group, those who had both hypervolemia and dehydration findings were included in FB (mix) group, and those with normal examination findings were included in FB (N) group.

Results: A total of 303 patients, mean age of 66.4 ± 15.9 years, 54.5% male, were included in the study, which covered the period between May 1, 2019 and September 30, 2019. In-hospital, monthly and quarterly cumulative survival rates of the patients were respectively; 91.7 ± 2.7%, 89.2 ± 2.8%, 81.7 ± 3.5% in FB (N) group; 86.3 ± 5.2%, 82.2 ± 5.7%, and 57.8 ± 7.4% in FB (–) group; 70.9 ± 4.4%, 68.1 ± 4.4%, and 54.9 ± 4.7% in FB (+) group; 57.6 ± 10.2%, 56.0 ± 9.9%, 44.0 ± 9.9% in FB (mix) group. It was determined that there was an approximately 3-fold increase in both monthly and quarterly mortality risks in those who had FBD compared to those who were not (HR: 3.077 and 3.031, respectively). It was shown with the multivariate Cox regression analyses that this risk increases independently from both preliminary diagnosis, concomitant diseases, vital disorders (30-day and 90-day AHR 2.541 and 2.517, respectively), and from the biochemical disorders (30-day and 90-day AHR 2.132 and 2.124, respectively).

Conclusions: Our study is important in terms of emphasizing the value of physical examination which lost its popularity with the development of technology and many medical instruments, but still simple and cheap.

Key words: *fluid balance distribution disorders, hypovolemia, hypervolemia, acute disease, mortality*

Introduction

Disorders of water balance and sodium balance are common, but the pathophysiology is frequently misunderstood. As an example, the plasma sodium concentration is regulated by changes in water intake and excretion, not by changes in sodium balance. Hyponatremia is primarily due to the intake of water that cannot be excreted, hypernatremia is primarily due to the loss of water that has not been replaced, hypovolemia represents the loss of sodium and water, and edema is primarily due to sodium and water

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retention.[1] As it is already known, although it varies according to age and gender, approximately 2/3 of the body fluids exist in the intracellular area, 1/3 in the extracellular area; and 1/3 of the extracellular fluid (ECF) exists in the intravascular (plasma) area, and 2/3 exist in the extravascular (interstitial) area.[2] It is possible to define the increase, decrease or differences in the distribution of the fluid volume in any of these layers as fluid balance disorders (FBDs).[3-5]

Lack of ECF is defined as dehydration or hypovolemia; its excessive amount is defined as hyperhydration or hypervolemia. Both imbalances can be reflected in the clinical manifestation in hypotonic, isotonic, or hypertonic way with their own unique findings. The excess ECF, which is mostly accompanied by the sodium increase and is encoded as FB (+) by us, often referred to as "edema" in clinical practice, might manifest itself by accumulating in pretibial, periorbital, perineal, periscroteal, presacral areas, which have more tissue flexibility, and in subcutaneous interstitial area in the gravitational direction, or might present itself in peritoneal, pleural or pericardial membrane, or in intestinal, pulmonary and cerebral areas with original clinical findings. Hypovolemia, which is induced by unchanged water and sodium losses, and which is encoded by us as FB (–), is the deterioration of vital signs, weight loss in the body, decreased urine amount, decreased skin turgor tonus, drying of mucous membranes, reduced filling in peripheral veins. Loss of ECF volume might also lead to a decrease in tissue perfusion. However, it is observed clinically that ECF volume and tissue perfusion do not always change in the same direction. For example, although it is observed that tissue perfusion is decreased because of low heart debit in heart failure or vasodilation in liver cirrhosis, the volume of ECF is increased at most times. To explain this fluid distribution imbalance, "effective arterial blood volume" or "effective circulation volume" terms are used in the literature.[1,6] In the liquid distribution imbalance, which is encoded as FB (mix) by us, both edema and dehydration findings can be seen together. When we examine the literature, we found that there were many studies on FB (+) and less frequently FB (–) patients, but we did not find any studies on FB (mix).

FBD management in hospitalized patients might seem easy in theory; however, it may sometimes be very difficult in clinical practice. Many previously conducted studies showed that there is a positive relation between fluid excess and negative results, especially in critical patients. It was shown in previous studies that excessive fluid increase the durations of mechanical ventilation and intensive care unit (ICU) stays in patients with acute liver damage;[7] the need for renal replacement therapy (RRT) and the incidence of acute kidney injury (AKI) in septic patients;[8] and increased infectious complication risk in surgical patients;[9] and had a relation with mortality in all patient categories.[10] However, all of these studies were conducted with patients who were followed-up in ICUs, and when the literature was reviewed, the relationship between mortality and FBD in patients followed up and treated in internal medicine ward, requiring hospitalization for acute illnesses—but not requiring ICU—has not been investigated yet.

With this study, the purpose was to examine the effects of FBD, which can only be detected by physical examination regardless of electrolytes and without considering the osmolarity/tonicity measurements, on hospitalization time and short-term mortality in patients admitted to the internal medicine ward from the emergency department.

Methods

Design of the Study—Patient Population

The present study was a prospective and observational study conducted on patients in the internal medicine ward of our hospital. Our study was in line with the Helsinki Declaration, and was conducted after the necessary ethical board permission was obtained.

All the patients who were over the age of 18, who applied to the emergency service, and referred to the internal medicine ward because of acute medical disorders were included in the study successively. Our ward is the general internal medicine the emergency department which follows and treats non-surgical acute diseases. No exclusion criteria were used. The follow-up period began when the patient was admitted to the emergency department, and all patients who were referred to the internal medicine ward were examined by a team of at least 10 years of experienced internal medicine specialists and assistants in 8 hours. The demographic data, comorbidities, hospitalization indications, clinical findings (anamnesis, blood pressure, peak heartbeat, respiratory count per minute, skin turgor tonus, mucous membranes and tongue dryness, peripheral vein fullness, peripheral edema findings, and lung and abdomen examination results),

Glasgow Coma Scale (GCS), and the first laboratory findings were recorded in the study-specific case report and in the database.

Grouping of the Patients

In physical examination, any of hypervolemia findings (jugular venous fullness, pulmonary edema, pleural effusion in the posterior-anterior pulmonary X-ray, pericardial effusion in echocardiography, ascides in abdominal examination or in abdominal ultrasonography, or edema positivity in palpable subcutaneous areas like pretibial, periorbital, perineal, periscroteal, and presacral areas) were included in the FB (+) group; those who had any of the dehydration findings (decreased turgor tonus of the skin, dryness in the mucous membranes and tongue, weak pulse, and low arterial blood pressure) were included in the FB (–) group; those who had both hypervolemia findings and dehydration findings were included in the FB (mix) group; and those who had normal examination findings other than these were included in the FB (N) group.

Clinical Follow-Up of the Patients

The hospital admission dates, hospitalization times, clinical discharge dates, discharge status (as is, healed, refusal of treatment, transfer to ICU and exitus), and the dates of transfer to ICU of all patients were recorded in the same way. The hospitalization (internal medicine ward ± ICU) periods as of the admission to emergency service dates, monthly and quarterly follow-ups were recorded. The in-hospital, monthly and quarterly mortality rates were checked from the national mortality notification system. The findings were recorded in case report forms.

Statistical Analyses

The data were analyzed by using IBM Statistical Package for Social Sciences (SPSS version 22 for Windows; IBM Corp., Armonk, NY, USA), and were considered significant at $\alpha < 0.05$. After confirming the about normality of the data by using skewness and kurtosis, descriptive statistics for biochemical parameters were presented by arithmetic mean (standard deviation [SD]) or percentages (and number). Comparisons among the groups were analyzed by ANOVA (continuous variables) or the χ^2 tests (categorical variables). Posthoc comparisons were corrected with the Bonferroni test. Kaplan–Meier survival charts predicted in-hospital mortality, monthly and quarterly mortality among the groups categorized by fluid balance. Univariate Cox regression analyses were carried out to assess the association for in-hospital, monthly and quarterly mortality in all variables. Then, multivariate Cox regression analyses were performed to determine the monthly and quarterly mortality with significant variables in the univariate analysis. The hazard ratio (HR) and adjusted HR (AHR) with 95% confidence interval (CI) were calculated in the regression models.

Results

A total of 303 patients between May 1, 2019 and September 30, 2019, who had a mean age of 66.4 ± 15.9 years, 165 of whom were male (54.5%), and 185 of whom were geriatric (61.0%) were included in the present study.

When the internation reasons of the patients were evaluated, it was determined that AKI ranked the first with 168 patients (55.4%); acute gastrointestinal bleeding (AGIB) ranked the second with 107 patients (35.3%); general condition disorder (GCD) ranked the third with 44 patients (14.5%). These were followed by acute liver injury (ALI) with 22 patients (7.3%), acute heart failure (AHF) with 10 patients (3.3%), sepsis with 14 patients (4.9%), and acute pancreatitis with 6 patients (2.0%). GCD is a term that we use to describe neglected patients accompanied by electrolyte imbalance—not bad enough to require ICU—we cannot include in any acute disease category.

In terms of concomitant diseases, hypertension (HT) (n = 164), chronic kidney disease (CKD) (n = 102), diabetes mellitus (DM) (n = 95) were in the top three; followed by malignancies (oncological-hematological) (n = 76), coronary artery disease (CAD) (n = 57), chronic heart failure (CHF) (n = 45), chronic obstructive pulmonary disease (COPD) (n = 34), stroke (n = 28), Alzheimer's disease (n = 20), and liver cirrhosis (n = 17) followed.

In addition to socio-demographic characteristics of all the patients according to fluid balance, pre-diagnosis at admission to hospital, concomitant diseases, physical examination findings, laboratory findings, mortality rates, and survival times are shown in Table 1.

Analysis Based on FBD

When examined in terms of fluid balance, as seen in Table 1, it was determined that 120 (39.6%) of the patients had normal fluid balance, and 183 (60.4%) were found to be FBD. A total of 45 of those with FBD were in the FB (–) group, 113 were in the FB (+)

Table 1. Baseline characteristics stratified by FB (N = 303)[a]

Variable	FB (N) (n = 120)	FB (–) (n = 45)	FB (+) (n = 113)	FB (mix) (n = 25)	*p*
Demographics and preliminary diagnosis					
Age, years	59.0 ± 17.6	72.6 ± 12.6	70.3 ± 12.5	72.6 ± 12.1	< 0.001
Gender (female)	48 (40.0)	16 (35.6)	66 (58.4)	8 (32.0)	0.005
Acute kidney injury	45 (37.5)	27 (60.0)	79 (69.9)	17 (68.0)	< 0.001
Acute liver injury	3 (2.5)	1 (2.2)	14 (12.4)	4 (16.0)	0.005
Acute heart failure	0 (0.0)	0 (0.0)	8 (7.1)	2 (8.0)	0.006
Acute gastrointestinal bleeding	66 (55.0)	16 (35.6)	21 (18.6)	4 (16.0)	< 0.001
Acute pancreatitis	6 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.025
Sepsis	3 (2.6)	0 (0.0)	9 (8.5)	2 (8.7)	0.064
General condition disorder	7 (5.8)	8 (17.8)	23 (20.4)	6 (24.0)	0.006
Coexisting disease					
Diabetes mellitus	28 (23.3)	12 (26.7)	52 (46.0)	3 (12.0)	< 0.001
Hypertension	55 (45.8)	22 (48.9)	72 (63.7)	15 (60.0)	0.038
Chronic kidney disease	30 (25.0)	19 (42.2)	46 (40.7)	7 (28.0)	0.039
Cirrhosis	4 (3.3)	0 (0.0)	12 (10.6)	1 (4.0)	0.025
Atrial fibrillation	9 (7.5)	5 (11.1)	13 (11.5)	4 (16.0)	0.548
Coronary artery disease	15 (12.5)	4 (8.9)	31 (27.4)	7 (28.0)	0.005
Myocardial infarction history	3 (2.5)	0 (0.0)	0 (0.0)	1 (4.0)	0.189
Chronic heart failure	7 (5.8)	4 (8.9)	30 (26.5)	4 (16.0)	< 0.001
Coronary artery by-pass graft	4 (3.3)	2 (4.4)	9 (8.0)	0 (0.0)	0.243
Chronic obstructive pulmonary disease	8 (6.7)	3 (6.7)	20 (17.7)	3 (12.0)	0.042
Stroke	9 (7.5)	7 (15.6)	7 (6.2)	5 (20.0)	0.096
Alzheimer's disease	7 (5.8)	6 (13.3)	3 (2.7)	4 (16.0)	0.029
Oncological malignancy	22 (18.3)	18 (40.0)	28 (24.8)	8 (32.0)	0.031
Findings at emergency room admission					
Body temperature, °C	36.7 ± 0.5	36.6 ± 0.5	36.8 ± 0.7	36.7 ± 0.8	0.275
Pulse rate, bpm	88.5 ± 16.5	87.0 ± 15.5	90.0 ± 18.5	91.3 ± 20.1	0.558
Systolic blood pressure, mm Hg	115.5 ± 23.6	109.9 ± 19.8	123.8 ± 27.2	120.5 ± 27.8	0.008
Diastolic blood pressure, mm Hg	70.5 ± 13.2	68.7 ± 10.8	72.1 ± 14.6	73.4 ± 16.5	0.422
Respiratory rate, c/min, mean	14.8 ± 4.2	15.6 ± 4.1	16.9 ± 5.6	17.2 ± 3.9	0.011
Oxygen saturation, %	95.6 ± 2.6	95.9 ± 1.9	93.8 ± 4.1	95.4 ± 3.5	0.014
Glasgow Coma Scale	14.9 ± 0.6	14.8 ± 0.8	14.8 ± 0.8	14.2 ± 2.0	0.012
Creatinine, mg/dL	2.0 ± 1.9	3.2 ± 2.6	3.2 ± 2.5	2.8 ± 2.0	< 0.001
Urea, mg/dL	96.2 ± 69.5	139.4 ± 84.2	136.5 ± 77.4	132.3 ± 76.6	< 0.001
Albumin, mg/dL	35.1 ± 6.0	31.1 ± 7.0	31.0 ± 6.4	28.2 ± 6.8	< 0.001
Sodium, mEq/L	136.4 ± 6.1	134.9 ± 6.4	132.7 ± 7.1	137.2 ± 11.3	< 0.001
Potassium, mEq/L	4.4 ± 0.8	4.7 ± 1.1	4.8 ± 1.0	4.5 ± 1.0	0.008
Chlorine, mEq/L	102.7 ± 6.5	102.4 ± 7.6	100.5 ± 7.5	103.1 ± 10.3	0.102
Correted calcium, mg/dL	9.1 ± 0.9	9.5 ± 1.6	9.2 ± 1.1	9.8 ± 2.3	0.051
Leukocyte, 10^3/uL	9.9 ± 5.1	10.9 ± 6.7	10.3 ± 8.6	15.8 ± 14.8	0.008
Hemoglobin, g/dL	9.8 ± 2.7	9.7 ± 2.7	9.4 ± 2.0	9.9 ± 3.1	0.618

Table 1. Baseline characteristics stratified by FB (N = 303)[a] (continued)

Variable	FB (N) (n = 120)	FB (–) (n = 45)	FB (+) (n = 113)	FB (mix) (n = 25)	*p*
Platelet Count, 1,000/mm^2	249.3 ± 120.0	244.8 ± 124.9	245.7 ± 144.5	261.6 ± 138.3	0.953
Neutrophil/lymphocyte ratio, %	6.7 ± 9.1	10.5 ± 12.0	9.4 ± 8.0	15.1 ± 16.0	0.001
Mortality rates					
Non-survivors (in-hospital)	10 (8.3)	6 (13.3)	32 (28.3)	10 (40.0)	< 0.001
Non-survivors (monthly)	13 (10.8)	8 (17.8)	36 (31.9)	11 (44.0)	< 0.001
Non-survivors (quarterly)	22 (18.3)	19 (42.2)	51 (45.1)	14 (56.0)	< 0.001
Hospitalization time, days	7.8 ± 8.0	9.0 ± 9.8	14.9 ± 11.9	13.2 ± 9.7	< 0.001
Monthly survival time, days	28.3 ± 5.7	28.1 ± 5.4	25.1 ± 8.8	22.6 ± 10.1	< 0.001
Quarterly survival time, days	79.6 ± 24.8	68.4 ± 28.7	61.0 ± 35.0	51.4 ± 37.5	< 0.001

[a]Values are expressed as the mean ± SD or percentage (%). FB (N): normal fluid balance, FB (–): negative fluid balance, FB (+): positive fluid balance, FB (mix): mix fluid balance.
SD: standard deviation.

group, and 25 of them were included in the FB (mix) group. The patients who had FBD were older (FBD and non-FBD, mean age was 71.2 ± 12.5 years and 59.0 ± 17.7 years, respectively); those who were FB (+) were mostly women (FB [N], [–], [+] and [mix] were 40%, 36%, 58.4%, and 32% were female, respectively).

According to prediagnosis at admission of the applicants, FBD in AKI, 1.8 times; in ALI, 4.2 times; 3.5 times in GCD, and significantly more in AHF; 2.5 times more in AGIB, and significantly less in acute pancreatitis. It was also determined that AKI and GCD patients could be presented with three types of disorders, liver cirrhosis. In terms of chronic diseases, it was observed that there were significantly more intensive FBDs in patients with DM, HT, CKD, liver cirrhosis, CAD, CHF, COPD, Alzheimer's disease, and malignancy. It was also determined that DM, liver cirrhosis, CHF, and COPD patients presented with more FB (+) findings; CKD patients presented with both FB (–) and FB (+) findings; HT and CAD patients presented mostly with hypervolemia ± dehydration findings; Alzheimer's and malignancy patients were found to be presented with signs of dehydration ± hypervolemia.

In terms of physical examination findings, it was determined that SBP in FB (–), oxygen saturation in FB (+), and GCS in FB (mix) were significantly low, and respiration rate was found to be significantly faster in FB (mix). In terms of biochemical disorders, urea was high in all three FBDs, creatinine was higher at significant levels only in FB (–) and FB (+). In addition, sodium was low, and potassium was high in FB (N) compared to FB (+). Albumin level was significantly lower in FB (mix) compared to others; the number of leukocytes and even neutrophil/lymphocyte ratio was significantly higher. In addition to these, a comparative review of the mortality rates and survival times between the groups is given in Table 1.

Analysis According to Surveys

In-hospital mortality rate of all patients was 19.1% (n = 58), one-month mortality rate was 22.4% (n = 68), and quarterly mortality rate was 35% (n = 106).

The patients were grouped as survivors and non-survivors after 90 days follow-ups, and the data are presented in Table 2. In this context, non-survivors were older (63.5 ± 17.1 and 71.6 ± 11.7; $p < 0.001$); presentation with more GCDs (8.6% and 25.5%; $p < 0.001$), presentation with less AGIB (41.6% and 23.6%; $p = 0.002$), CKD (29.4% and 41.5%; $p = 0.034$), Alzheimer's disease (4.1% and 11.3%; $p = 0.015$), and malignancy (17.3% and 39.6%; $p < 0.001$) were more frequent. The blood pressure scores, GCS, and albumin levels were lower, and respiratory count per minute, urea, corrected Ca, leukocyte, neutrophil/lymphocyte ratio, and lactate levels were found to be higher in patients who proceeded as quarterly mortal during hospital admission.

In addition, it was observed that presentation with FB (N) was in favor of survivors (49.7% and 20.8%); FBDs were in favor of non-survivors (FB

Table 2. Baseline characteristics stratified by mortality at 90 days (N = 303)[a]

Variable	Survivors (n = 197)	Non-survivors (n = 106)	*p*
Demographics and preliminary diagnosis			
Age, years	63.5 ± 17.1	71.6 ± 11.7	< 0.001
Gender (female)	107 (45.5)	31 (45.6)	0.993
Acute kidney ınjury	101 (51.3)	67 (63.2)	0.046
Acute liver ınjury	10 (5.1)	12 (11.3)	0.046
Acute heart failure	7 (3.6)	3 (2.8)	0.851
Acute gastrointestinal bleeding	82 (41.6)	25 (23.6)	0.002
Acute pancreatitis	6 (3.0)	0 (0.0)	0.215
Sepsis	8 (4.3)	6 (5.9)	0.117
General condition disorder	17 (8.6)	27 (25.5)	< 0.001
Coexisting disease			
Diabetes mellitus	61 (31.0)	34 (32.1)	0.924
Hypertension	99 (50.3)	65 (61.3)	0.064
Chronic kidney disease	58 (29.4)	44 (41.5)	0.034
Cirrhosis	10 (5.1)	7 (6.6)	0.191
Atrial fibrillation	22 (11.2)	9 (8.5)	0.984
Coronary artery disease	37 (18.8)	20 (18.9)	0.942
Myocardial infarction history	3 (1.5)	1 (0.9)	0.640
Chronic heart failure	28 (14.2)	17 (16.0)	0.727
Coronary artery by-pass graft	9 (4.6)	6 (5.7)	0.386
Chronic obstructive pulmonary disease	18 (9.1)	16 (15.1)	0.783
Stroke	18 (9.1)	10 (9.4)	0.542
Alzheimer's disease	8 (4.1)	12 (11.3)	0.015
Oncological malignancy	34 (17.3)	42 (39.6)	< 0.001
Findings at emergency room admission			
Body temperature, °C	36.8 ± 0.6	36.7 ± 0.6	0.994
Pulse rate, bpm	88.0 ± 16.4	91.9 ± 20.3	0.196
Systolic blood pressure, mm Hg	120.9 ± 24.7	113.1 ± 25.9	0.021
Diastolic blood pressure, mm Hg	72.7 ± 13.6	68.2 ± 13.4	0.037
Respiratory rate, c/min, mean	14.7 ± 3.9	17.7 ± 6.1	< 0.001
Oxygen concentration of arterial blood, %	95.2 ± 3.3	94.2 ± 3.3	0.081
Glasgow Coma Scale	14.9 ± 0.8	14.6 ± 0.9	0.042
Creatinine, mg/dL	2.5 ± 2.2	3.0 ± 2.7	0.057
Urea, mg/dL	107.8 ± 77.3	144.5 ± 75.5	0.014
Total bilirubin,mol/L	0.8 ± 1.2	2.0 ± 4.5	0.011
Albumin, mg/dL	34.1 ± 6.4	29.2 ± 6.5	< 0.001
Sodium, mEq/L	135.4 ± 6.7	133.9 ± 8.6	0.113
Potassium, mEq/L	4.6 ± 0.9	4.7 ± 1.0	0.247
Chlorine, mEq/L	102.6 ± 7.3	100.6 ± 7.7	0.026
Correted calcium, mg/dL	9.2 ± 0.9	9.5 ± 1.9	0.022
Leukocyte, 10^3/uL	9.4 ± 6.5	13.0 ± 11.4	< 0.001

Table 2. Baseline characteristics stratified by mortality at 90 days (N = 303)[a] (continued)

Variable	Survivors (n = 197)	Non-survivors (n = 106)	*p*
Hemoglobin, g/dL	9.9 ± 2.4	9.2 ± 2.3	0.012
Platelet count, 1,000/mm^2	250.9 ± 120.0	243.4 ± 163.0	0.853
Neutrophil/lymphocyte ratio, %	7.3 ± 9.2	12.2 ± 12.3	< 0.001
Lactate, mmol/L	2.1 ± 1.3	2.6 ± 1.7	< 0.001
Fluid balance			
FB (N)	98 (49.7)	22 (20.8)	< 0.001
FB (–)	26 (13.2)	19 (17.9)	
FB (+)	62 (31.5)	51 (48.1)	
FB (mix)	11 (5.6)	14 (13.2)	

[a]Values are expressed as the mean ± SD or percentage (%). FB (N): normal fluid balance, FB (–): negative fluid balance, FB (+): positive fluid balance, FB (mix): mix fluid balance.
SD: standard deviation.

[–]: 13.2%, 17.9%; FB [+]: 31.5%, 48.1%; FB [mix]: 5.6%, 13.2%) (Table 2).

FBD and Mortality Rates

Hospital mortality of the patients with FB (N) at hospital admission, one-month mortality and quarterly mortality rates were 8.3% (n = 10), 10.8%, and 18.3% (n = 22); and in patients with FBD, these mortality rates were 26.2% (n = 48), 30.1% (n = 55), and 45.9% (n = 84), respectively. When FBD patients were examined separately, FB (–) patients in-hospital, one month and quarterly mortality rates were 13.3% (n = 6), 17.8% and 42.2% (n = 19); FB (+) patients had mortality rates as 28.3% (n = 32%), 31.9% (n = 36), and 45.1% (n = 51); the mortality rates of those with FB (mix) were 40% (n = 10), 44% (n = 11), and 56% (n = 14), respectively (Fig. 1).

As seen in the figure, in-hospital, 30-daily, and quarterly mortality rates in FB (–), FB (+), and FB (mix) patients had a statistically increasing trend, respectively. The highest mortality rates were in patients presented with FB (mix).

FBD and Survival Analysis

Hospitalization time was 7.8 ± 8.0 days (95% CI: 2–22%) in FB (N) group, 9.0 ± 9.8 days (95% CI: 2–28%) in FB [–] group), 14.9 ± 11.9 days (95% CI: 2–41%) in FB (+) group, and 13.2 ± 9.7 days (95% CI: 2–30%) in FB (mix) group (Table 1).

Mean survival time of monthly in FB (N) group at hospital admission was 28.3 ± 5.7 days (95% CI: 27.2–29.3%); in FB (–) group, 28.1 ± 5.4 days (95% CI: 26.5–29.7%); in FB (+) group, 25.1 ± 8.8 days (95% CI: 23.5–26.7%); and in FB (mix) group, 22.6 ± 10.1 days (95% CI: 18.5–26.7%) (Table 1).

Mean survival time of quarterly in FB (N) group, 79.6 ± 24.8 days (95% CI: 75.1–84.2%); in FB (–), 68.4 ± 28.7 days (95% CI: 60.2–76.7%); in FB (+), 61.0 ± 35.0 days (95% CI: 54.6–67.4%); and in FB (mix) group, 51.4 ± 37.5 days (95% CI: 36.9–65.8%) (Table 1).

As shown in the figure in Kaplan–Meier charts, intra-group hospital mortality rates did not differ (log rank: 0.177, breslow: 0.235), and both monthly and quarterly mortality rates differed significantly between the groups (both log ranks < 0.001).

The cumulative in-hospital survival rate was 91.7 ± 2.7% in FB (N) group; in FBD patients, it was 73.8 ± 4.2%; and monthly cumulative survival rates in FB (N) group and FBD were 89.2 ± 2.8% and 69.9 ± 3.4%, respectively; the quarterly cumulative survival rates were 81.7 ± 3.5% and 54.1 ± 3.7%, respectively.

When the patients with FBD were examined separately, the in-hospital, one-month and quarterly cumulative survival rates of the patients were 86.3 ± 5.2%, 82.2 ± 5.7%, and 57.8 ± 7.4% in FB (–) group in order; FB (+) 70.9 ± 4.4%, 68.1 ± 4.4%, and 54.9 ± 4.7% , respectively; FB (mix) was 57.6 ± 10.2%, 56.0 ± 9.9%, and 44.0 ± 9.9%, respectively.

Relation Between FBD and Mortality

In univariate Cox regression analyses, no relations were detected between fluid balance and in-hospital mortality (HR: 1.33, 95% CI: 0.98–1.79, *p* =

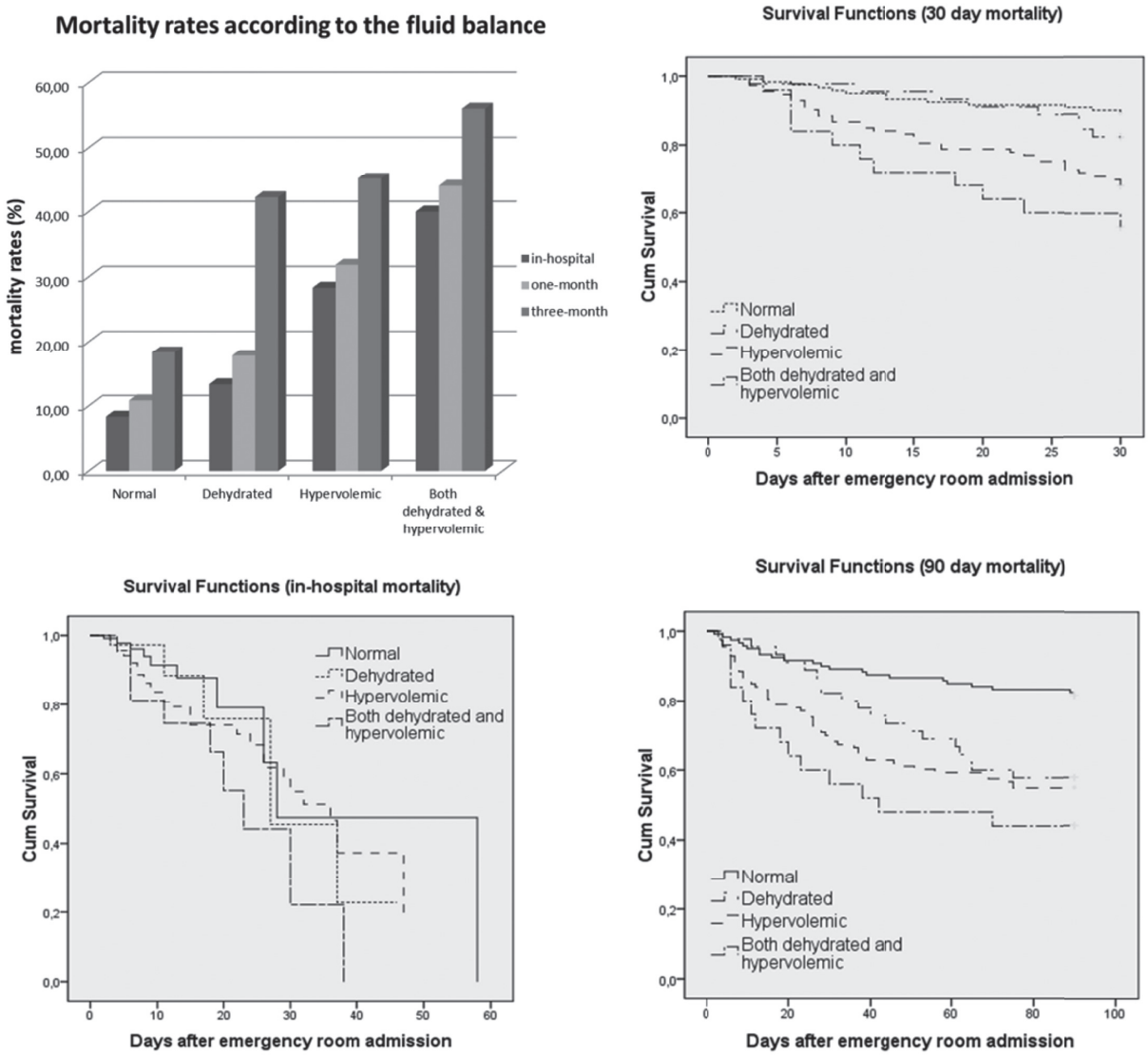

Fig. 1. The graph of mortality rates and the Kaplan–Meier charts according to in-hospital mortality, 30-day mortality and 90-day mortality of patients with fluid balance disorders.

0.062), monthly mortality risk increased in FBD (HR: 3.077, 95% CI: 1.68–5.63, $p < 0.001$), and quarterly mortality risk increased (HR: 3.031, 95% CI: 1.89–4.85, $p < 0.001$). Similarly, significant relations were detected in the univariate analyses among the age, AGIB, GCD, malignancy, systolic and diastolic blood pressure, respiratory rates, GCS, urea, total bilirubin, albumin, corrected Ca, uric acid, C-reactive protein, leukocyte, neutrophil/lymphocyte ratio, lactate levels, and both 30-daily and 90-daily mortality rates and AKI, Alzheimer's disease, pulse rate, hemoglobin levels, and only quarterly mortality rates (Table 3).

As seen in Model 1, it was observed that the monthly mortality relation with FBD, detected in univariate regression analyses, continued independent of socio-clinical features—age, AGIB, GCD, malignancy, blood pressures, respiratory rate, GCS (AHR: 2.541, 95% CI: 1.25–5.18, $p = 0.010$); and as seen in Model 2, independent of laboratory findings—urea, total bilirubin, albumin, corrected Ca, uric acid, C-reactive protein, leukocyte, neutrophil/lymphocyte ratio, and lactate levels (AHR: 2.132, 95% CI: 1.03–4.40, $p = 0.041$) (Table 4).

The quarterly mortality relation with FBD, detected in univariate regression analyses, continued independent of socio-clinical features—age, AKI,

Table 3. Univariate analysis for monthly and quarterly mortality after emergency room admission in all subjects (N = 303)

Variable	Monthly mortality			Quarterly mortality		
	p	HR	95% CI	*p*	HR	95% CI
Demographics and preliminary diagnosis						
Age, years	0.001	1.030	(1.01–1.05)	0.000	1.030	(1.02–1.04)
Gender (female)	0.945	1.017	(0.63–1.64)	0.994	0.999	(0.68–1.46)
Acute kidney ınjury	0.202	1.375	(0.84–2.24)	0.050	1.485	(1.00–2.20)
Acute liver ınjury	0.130	1.769	(0.85–3.70)	0.045	1.851	(1.01–3.38)
Acute heart failure	0.839	0.864	(0.21–3.53)	0.755	0.833	(0.26–2.63)
Acute gastrointestinal bleeding	0.020	0.515	(0.29–0.90)	0.002	0.494	(0.32–0.77)
Acute pancreatitis	0.408	0.048	(0.00–63.4)	0.281	0.048	(0.00–11.98)
Sepsis	0.559	1.257	(0.58–2.71)	0.451	1.373	(0.60–3.13)
General condition disorder	0.001	2.530	(1.48–4.34)	0.000	2.664	(1.72–4.13)
Coexisting disease						
Diabetes mellitus	0.938	0.980	(0.59–1.64)	0.857	1.038	(0.69–1.56)
Hypertension	0.228	1.349	(0.83–2.19)	0.066	1.444	(0.98–2.13)
Chronic kidney disease	0.537	1.168	(0.71–1.91)	0.053	1.465	(1.00–2.16)
Cirrhosis	0.249	1.638	(0.71–3.79)	0.559	1.257	(0.58–2.71)
Atrial fibrillation	0.910	1.046	(0.48–2.29)	0.556	0.815	(0.41–1.61)
Coronary artery disease	0.844	1.062	(0.58–1.94)	0.875	1.040	(0.64–1.69)
Myocardial infarction history	0.897	1.139	(0.16–8.20)	0.731	0.708	(0.10–5.07)
Chronic heart failure	0.651	1.161	(0.61–2.21)	0.595	1.151	(0.69–1.93)
Chronic obstructive pulmonary disease	0.733	0.873	(0.40–1.91)	0.218	1.397	(0.82–2.38)
Stroke	0.598	0.783	(0.31–1.95)	0.982	1.008	(0.53–1.93)
Alzheimers disease	0.344	1.499	(0.65–3.47)	0.018	2.071	(1.14–3.78)
Oncological malignancy	0.002	2.171	(1.34–3.53)	0.000	2.363	(1.60–3.49)
Findings at emergency room admission						
Pulserate, bpm	0.148	1.010	(1.00–1.02)	0.049	1.011	(1.00–1.02)
Systolic blood pressure, mmHg	0.020	0.987	(0.98–1.00)	0.008	0.988	(0.98–1.00)
Diastolic blood pressure, mmHg	0.037	0.981	(0.96–1.00)	0.007	0.980	(0.97–0.99)
Respiratory rate, min	0.000	1.112	(1.07–1.16)	0.000	1.102	(1.07–1.14)
Glasgow Coma Scale	0.027	0.838	(0.72–0.98)	0.030	0.861	(0.75–0.99)
Creatinine, mgdL	0.420	1.041	(0.94–1.15)	0.056	1.076	(1.00–1.16)
Urea, mgdL	0.007	1.004	(1.00–1.01)	0.000	1.004	(1.00–1.01)
Total bilirubin	0.000	1.094	(1.05–1.14)	0.000	1.095	(1.05–1.14)
Albumin, mgdL	0.000	0.906	(0.87–0.94)	0.000	0.910	(0.88–0.94)
Sodium, mEqL	0.117	0.973	(0.94–1.01)	0.074	0.975	(0.95–1.00)
Potassium, mEqL	0.195	1.167	(0.92–1.48)	0.197	1.135	(0.94–1.37)
Correted calcium, mg/dL	0.001	1.230	(1.09–1.39)	0.005	1.185	(1.05–1.33)
Uricacid	0.000	1.156	(1.08–1.23)	0.000	1.132	(1.07–1.20)
C-reactive protein, mgL	0.003	1.004	(1.00–1.01)	0.000	1.004	(1.00–1.01)
Leukocyte, 10^3uL	0.003	1.029	(1.01–1.05)	0.000	1.034	(1.02–1.05)

Table 3. Univariate analysis for monthly and quarterly mortality after emergency room admission in all subjects (N = 303) (continued)

Variable	Monthly mortality			Quarterly mortality		
	p	HR	95% CI	*p*	HR	95% CI
Hemoglobin, g/dL	0.099	0.922	(0.84–1.02)	0.015	0.909	(0.84–0.98)
Platelet count, 1,000/mm^2	0.886	1.000	(1.00–1.00)	0.620	1.000	(1.00–1.00)
Neutrophil/lymphocyte ratio, %	0.001	1.028	(1.01–1.04)	0.000	1.028	(1.01–1.04)
Lactate, mmolL	0.000	1.267	(1.13–1.42)	0.001	1.192	(1.08–1.32)
Fluid balance disorder	0.000	3.077	(1.68–5.63)	0.000	3.031	(1.89–4.85)

CI: confidential interval; HR: hazard ratio.

Table 4. Multivariate analysis for monthly and quarterly mortality after emergency room admission (N = 303)[a]

Variable	*p*	AHR	95% CI	*p*	AHR	95% CI
	Model 1 (monthly mortality)			Model 3 (quarterly mortality)		
Fluid balance disorder	0.010	2.541	(1.25–5.18)	0.001	2.517	(1.44–4.38)
Age, years	0.141	1.016	(0.99–1.04)	0.020	1.021	(1.00–1.04)
Acute kidney ınjury				0.878	0.958	(0.56–1.65)
Acute gastrointestinal bleeding	0.498	0.800	(0.42–1.53)	0.242	0.687	(0.37–1.29)
General condition disorder	0.147	1.695	(0.83–3.46)	0.055	1.780	(0.99–3.20)
Alzheimers disease				0.335	1.448	(0.68–3.07)
Malignancy	0.024	1.871	(1.08–3.23)	0.001	2.128	(1.38–3.28)
Pulse rate, bpm				0.192	1.008	(1.00–1.02)
Systolic blood pressure, mmHg	0.202	0.990	(0.98–1.01)	0.127	0.990	(0.98–1.00)
Diastolic blood pressure, mmHg	0.551	1.008	(0.98–1.03)	0.757	1.003	(0.98–1.02)
Respiratory rate/min	0.001	1.078	(1.03–1.13)	0.000	1.076	(1.03–1.12)
Glasgow Coma Scale	0.861	1.021	(0.81–1.28)	0.286	1.121	(0.91–1.38)
Variable	Model 2 (monthly mortality)			Model 4 (quarterly mortality)		
Fluid balance disorder	0.041	2.132	(1.03–4.40)	0.014	2.124	(1.17–3.86)
Urea, mgdL	0.130	1.003	(1.00–1.01)	0.013	1.004	(1.00–1.01)
Total bilirubin	0.348	1.042	(0.96–1.14)	0.244	1.039	(0.97–1.11)
Albumin, mg/dL	0.004	0.934	(1.09–1.20)	0.009	0.951	(0.92–0.99)
Corrected calcium	0.233	1.102	(0.94–1.29)	0.119	1.120	(0.97–1.29)
Uric acid	0.427	1.036	(0.95–1.13)	0.185	1.055	(0.97–1.14)
C-reactive protein, mgL	0.420	1.001	(1.00–1.00)	0.582	0.999	(1.00–1.00)
Hemoglobin, g/dL				0.186	1.014	(0.99–1.03)
Leukocyte, 10^{3}uL	0.804	1.003	(0.98–1.03)	0.073	0.910	(0.82–1.01)
Neutrophil/lymphocyte ratio, %	0.212	1.017	(0.99–1.04)	0.406	1.010	(0.99–1.03)
Lactate, mmolL	0.026	1.169	(1.02–1.34)	0.176	1.085	(0.96–1.22)

[a]Cox proportional hazard analysis for 30-day mortality (Model 1 and Model 2); for 90-day mortality (Model 3 and Model 4).
AHR: adjusted hazard ratio; CI: confidential interval.

AGIB, GCD, Alzheimer's disease, malignancy, pulse rate, blood pressures, respiratory count per minute, and GCS—as seen in Model 3 (AHR: 2.517, 95% CI: 1.44–4.38, $p = 0.001$); and independent of laboratory findings—urea, total bilirubin, albumin, corrected Ca, uric acid, C-reactive protein, hemoglobin, leukocyte,

neutrophil/lymphocyte ratio, and lactate levels—as seen in Model 4 (AHR: 2.124, 95% CI: 1.17–3.86, p = 0.014) (Table 4).

Discussion

It was determined that FBDs, who were referred from emergency department and who were followed-up by internal medicine ward were found to have increases approximately three times in both monthly and quarterly mortality risks that was detected only with physical examination findings during the hospital application (HR: 3.077 and 3.031, respectively). It was determined in multivariate Cox regression analyses that this increase in the risk were independent from both preliminary diagnosis, coexisting diseases and vital disorders (2.541 and 2.517, 30-daily and 90-daily AHR, respectively), and from biochemical disorders that affect mortality (2.132 and 2.124, 30-daily and 90-daily AHR, respectively).

It was seen that the studies in the literature were mostly on fluid balance and mortality in critical patients who were followed at ICU or on patients with/without dialysis treatment due to kidney failure. The present study of ours is important because it is the first one in internal medicine ward to examine the effect of FBD on mortality in patients who were referred with different indications and who were followed-up in non-intubated state.

There are many studies in the literature especially on hypervolemic patients. For example, Acheampong and Vincent conducted a study involving septic patients whose fluid balances were monitored for 7 days at ICU, persistence FB (+) was shown to be associated with high mortality rates.[11] In our study, we did not include the fluid balance changes throughout the internation of the patients. The data were based on FBDs at the time of the first application. Even this is valuable in that it shows the increase in short-term mortality.

In addition, our study contributes to the literature in that the patients were grouped as FB (–), FB (+), and especially FB (mix) and were analyzed comparatively. For example, a retrospective study which was conducted on 18,084 critically-ill patients by Balakumar et al., it was found that both positive and negative fluid balance was associated with 1-year mortality risk.[12] However, we did not find any studies in the literature in which ECF increased, and effective arterial volume decreased, and therefore, tissue perfusion occurred, and FB (mix), which we described as FBD, was also evaluated. However, in our study, the mortality rates of the patients who were admitted with FB (mix), which is relatively more difficult for clinicians, were relatively high for applicants with other FBD, as shown in the Kaplan–Meier charts in Fig. 1.

Although monthly and quarterly surveys were shorter than others, longer hospitalization times of the patients with FB (mix) were considered to be one of the indicators of how difficult it is to manage these patients (Table 1). Although these patients were not hypotensive or did not have desaturation during application, the fact that they had tachypnea and had low GCS is one of the signs that their clinical condition is complex and bad. The fact that the neutrophil/lymphocyte ratio,[13] which was used in many previous studies and which was associated with inflammation, was significantly higher in those who had FB (mix) in our study suggests that inflammation may be responsible for this confusion. In addition, low albumin levels, which are both the indicators of negative acute phase and malnutrition, are noteworthy, and it is considered to have a major role in abnormal distribution of fluid balance.

In capillary hemodynamics, the hydrostatic pressure increase, the reduction in oncotic pressure, the changes in the capillary permeability, and the lymphatic drainage problems cause edema. It is known that the pathophysiology of FBD has renal water and sodium retention at the end point. In a study that was conducted by Wang et al. on ICU patients, the first 3 day FB (+) was an independent risk factor for AKI incidence, and even the severity of AKI increased, and was associated with an increase in the risk of mortality for 28 days after AKI.[14] It is known that ECF is basically regulated by the secretion of natriuretic peptides of the atrial and ventricles responding to the changes in the activity of renin-angiotensin-aldosterone and sympathetic nervous systems that support sodium retention and the changes in pressure supporting the excretion of sodium.[4] Loss of ECF volume might cause a decrease in tissue perfusion. However, it is observed that ECF volume and tissue perfusion do not always change in the same way. For example, it is seen in CHF that the volume of ECF is mostly increased due to low heart flow or vasodilation in liver cirrhosis despite the decreased tissue perfusion.[1,6] In both diseases, it was shown that sodium retention hormones play roles in increasing the extracellular volume, unable to normalize tissue perfusion due to

the underlying disease.[15] In our study, it was observed that the patients with CHF and liver cirrhosis admitted with FB (+) at the highest rate, and with FB (mix) as the second frequency. It was observed by us that those with Alzheimer's disease and malignancies, in which malnutrition was at the forefront, presented with FB (–) and FB (mix); and those who had HT and KAH, in which the atherosclerotic process was at the forefront, presented with FB (mix) and FB (+).

In addition, it was also determined that chronic diseases were more mortal among those with CKD, Alzheimer's disease and malignancies; however, no significant mortality differences were detected in patients diagnosed with cardiac pathology. It was expected that cardiac pathology rates were high in mortal patients; however, it was considered that non-specific or hidden cardiac symptoms could make it easier to omit the diagnoses. All in all, in our study, the diagnosed diseases were recorded, and no extra examination was performed to diagnose the symptom-free patients.

Another important point in our study was that although there were no differences between pre-diagnosis and mortality increase, mortality rates in those with GCDs were significantly higher. We would like to emphasize that particular emphasis must be made on this patient group who do not have pathological examination or laboratory disorder in the hospital application and who cannot be included in any category of the prediagnosis, but whose general condition is impaired. On the other hand, the decrease in mortality with AGIB was an already expected situation after the discovery of proton pomp inhibitors.

In our study, we did not include fluid treatments that were given to the patients during the hospitalization process or the effects of the medical treatment received by them on FB. However, in several previous studies, liquid management strategies were compared at ICU. In a study conducted by The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, which compared fluid management of 1,000 ALI patients at ICU, although no significant differences were detected in the primary results of 60-day mortality rates, it was observed that the conservative strategy of fluid management improved the pulmonary functions and reduced mechanical ventilation and intensive care times without increasing non-pulmonary organ insufficiency.[7] Similarly, in a randomized and controlled study in which liberal and restrictive fluid treatments were compared by Grams et al., the relation between the use of fluid balance and diuretic after AKI after renal injury with 60-day mortality was evaluated, it was found that after AKI, the liquid balance was associated with mortality both in corrected and in raw analyses, and it was also determined that higher furosemide doses had a protective effect on mortality; however, if the fluid balance is adjusted after AKI, it had no significant effect.[16] In another study conducted by Barmparas et al., which examined post-operative fluid balance in surgical ICU, although no significant difference was detected in mortality rates between FB (–) and FB (+), it was determined that having early FB (–) status was associated with approximately 70% decrease in mortality risk.[9] Again, on patients who were followed-up due to ALI at ICU in a prospective and multicentric and observational study that was conducted by Vaara et al. with patients receiving RRT, those who were FB (+) at the beginning of the treatment were associated with quarterly mortality even after the improvements with treatment.[17]

In addition to the strong points of our study, there were important limitations. Firstly, the method of our study was constructed on FB, which was shown by only examination findings at hospital application. Identification of clinical findings by physical examination may be considered subjective, but since only one specialist clinician of 10 years experienced is preferred, personal differences are avoided. The use of instruments such as central venous catheter (invasive way and require specific abilities) or ultrasonography (gives precious information such evaluation of inferior vena cava diameter and, more important, collapsibility with breathing) or bioimpedance analyzer (an accurate, non-invasive technique for quantitatively estimating body water compartments) is a fact that FB be seen as more objective. Although the fact that we did not use the tools, is seen as a limitation; in our opinion, the basis of the examination findings of an experienced specialist clinician, showing the importance of physical examination, is an important approach. Secondly, we did not include FB changes during hospitalization, and the treatment differences, which are considered to have absolute effects on FB or mortality, for the purpose of not to complicate the calculations. We showed that even the fluid imbalance in the initial hospital application without any intervention had an effect on mortality. Thidly, as a single-central study, our study may not be generalized for other populations. However, we had a patient pop-

ulation coming from various socio-cultural environments admitted to our hospital in a wide indication. As there is no other study on this subject in Turkey.

As a conclusion, our study is important since there are no clinical studies especially about fluid balance distribution disorders—as we say FB (mix), and it contributes to the literature if supperted by more extensive studies subsequently.

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Conflicts of Interest Statement

The authors state that they have no conflict of interest.

Data Availability

The dataset used to support the findings of this study are available from the corresponding author upon request.

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