Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1254921

Anatolian Curr Med J. 2023;5(3):247-252

Evaluation of ultrafiltrated fluid overloaded patients: a single center study

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Cite this article as: Can Ö, Baş S, Güven Apaydın S, Manga Şahin G. Evaluation of ultrafiltrated fluid overloaded patients: a single center study. *Anatolian Curr Med J.* 2023;5(3):247-252.

Received: 22.02.2023 • **Accepted**: 05.07.2023 • **Published**: 28.07.2023

ABSTRACT

Aims: Fluid overloaded patients with heart or renal insufficiency have poor quality of life and increased morbidity and mortality. In this study, we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered.

Methods: Three groups of patients were compared: Group 1: Patients with chronic kidney disease and ejection fraction ≤ 40%; Group 2: Patients with chronic kidney disease and ejection fraction > 40%; Group 3: Patients with ejection fraction ≤ 40% but without chronic kidney disease. Patients were also evaluated regarding mortality.

Results: Group 1, 2 and 3 consisted of 14, 62 and 16 patients: respectively. There were statistically significant results for 24-hour urine volume (p=0.040), proteinuria (p=0.010), ultrafiltration volume/weight at hospitalization (p<0.001), ejection fraction (p<0.001), left ventricular hypertrophy (p=0.040), uric acid (p<0.001), hemoglobin (p<0.001), dialysis dependency after hospital discharge (p<0.001) and mortality (p<0.001) when three groups were compared. However, there was no statistically significant result for ultrafiltration volume (p=0.100). Compared to survived patients those who did not survived were significantly older (p<0.001), had lower ejection fraction (p=0.010), creatinine (p<0.001), sodium (p=0.020), ferritin (p=0.040), proteinuria (p=0.010). They also had statistically significantly higher hemoglobin (p<0.001), creatinine clearance (p<0.001), uric acid (p<0.001) levels. However, the percentage of patients using loop diuretics at hospitalization (p=0.040) was higher in the group who survived.

Conclusion: Patients with HF were more prone to hypervolemia and mortality. The ultrafiltration volume/weight at hospitalization and serum uric acid levels were also significantly higher in these patients. Patients with chronic kidney disease had significantly higher proteinuria, creatinine and lower hemoglobin levels. The rate of loop diuretic usage at hospitalization was significantly higher in the survived group.

Keywords: Dialysis, ejection fraction, heart failure, loop diuretics, left ventricular hypertrophy, mortality, ultrafiltration

INTRODUCTION

Patients followed for cardiorenal syndrome are prone to fluid overload and they have higher risk of morbidity and mortality.[1] Unfortunately, hospitalizations are inevitable for some of these patients. Ultrafiltration (UF) is applied to patients whose volume overload cannot be controlled with intravenous diuretics and water restriction. Removal of excess fluid with UF relieves symptoms of congestion, improves exercise capacity and cardiac filling pressures.[2,3] It also has favorable effects on pulmonary function and neurohormone levels.[4-6]

The current definition of cardiorenal syndrome does not add diagnostic and prognostic value to the separate evaluation of heart failure (HF) and kidney disease. It is also hard to document if the inciting event is HF or renal failure in cardiorenal syndrome.[7] So, with this study we did not define the type of this syndrome, rather we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered in a tertiary hospital.

METHODS

For this study, approval was obtained from İstanbul Haydarpaşa Numune Training and Research Hospital Ethics Committee (Date: 28.05.2019, Decision No: 771). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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One hundred forty-two patients who were ultrafiltrated in the emergency dialysis unit between January 2012 and May 2017 were evaluated retrospectively. Post-renal obstruction, pregnancy, hypervolemia after surgery, UF after switch from peritoneal dialysis to hemodialysis (HD), malignancy and cirrhosis were the exclusion criteria. Fifty patients were excluded and finally the study population consisted of 92 patients.

The decision of UF was taken by the patients' own doctors. Most of the patients were ultrafiltrated with temporary dialysis catheters. In stage 5 chronic kidney disease (CKD) patients previously created arteriovenous fistulas were used. HD was performed with high-flux membranes and heparin was used as an anticoagulant. The rate of fluid removal was adjusted considering the hemodynamic and volume status of the patients.

Data include demographic data, comorbid diseases, complete blood count, creatinine, albumin, electrolytes, uric acid (UA), C-reactive protein (CRP) and thyroid stimulating hormone (TSH), hospitalization time, cardiac ejection fraction (EF), left ventricular hypertrophy (LVH), 24-hour urine volume and proteinuria, UF volume during hospitalization, dialysis dependency after hospital discharge.

Three groups of patients were compared:

- **Group 1:** Patients with CKD (estimated glomerular filtration rate (eGFR) < 60 ml/min) and cardiac EF ≤ 40%
- **Group 2:** Patients with CKD and cardiac EF > 40%
- **Group 3:** Patients with EF ≤ 40% but without CKD

Survived and non-survived patients were also compared.

Statistical Analysis

The statistical analysis was carried out by Statistical Package for Social Sciences for Mac ver. 20.0 (SPSS Inc., Chicago, IL). Data were expressed as mean±standard deviation for normally distributed data, while median (minimum-maximum) were used for non-normally distributed data. The normality tests were conducted with both Shapiro-Wilk and Kolmogorov Smirnov tests and when both tests produced p values >0.05, the distribution was assumed normal.

Statistical comparisons of individual groups were based on independent samples t test and One-way ANOVA for continuous and normally distributed variables. When the distribution was not normal, Mann-Whitney U and Kruskal-Wallis tests were implemented. If One-way ANOVA and Kruskal-Wallis revealed any differences, the source of differences was investigated with Post-hoc tests Tukey HSD and Mann-Whitney U and the means having difference were allocated a letter a and b in **Table 1.** Relationship between two categorical variables were investigated with Chi-square test of independence. If Chi-square test revealed statistical difference, Post-hoc tests between groups were conducted with adjusted residuals analysis and statistical significance of these difference were indicated with letters k and l.

In addition, mortality related factors were investigated with ROC Curve Analysis. A value of p<0.05 was considered to be statistically significant.

Table 1. Comparison of groups regarding clinical and laboratory data

Parameters	Group 1 (n=14)	Group 2 (n=62)	Group 3 (n=16)	p
Age (year)	63.8±12	62.7±14	70.4±12.5	0.138
Male (n, %)	11 (17.2)	42 (65.6)	11 (17.2)	0.727
Hospitalization time (days)	14.5 (5-34)	11.5 (1-45)	17.0 (2-32)	0.439
Survival time (days)	100.5 (16-880)	554 (23-1331)	65 (2-1585)	0.090
24-hour urine volume (ml)	350 (0-4000)[a]	865 (0-4500)[a,b]	400 (0-1480)[b]	0.040*
Proteinuria (g/24 hour)	2.33 (0.13-15.73)[a]	2.31 (0.17-25.67)[b]	0.21 (0.08-0.64)[a,b]	0.010*
Ultrafiltration volume (kg)	10.32±5.8	9.64±4.8	12.6±5.1	0.100
Ultrafiltration volume /weight at hospitalization (%)	10[a]	10[b]	15[a,b]	<0.001*
Ejection fraction (%)	35 (20-40)[a]	60 (45-70)[a,b]	30 (25-40)[b]	<0.001*
LVH (n, %)	3 (11.1)[k]	23 (85.2)[k,l]	1 (3.7)[l]	0.040*
Sodium (mmol/l)	136 (118-143)	137 (118-144)	135.5 (101-138)	0.672
Potassium (mEq/L)	4.8±0.8	4.8±0.9	4.5±0.8	0.273
Uric acid (mg/dl)	9.3±2.4	7.5±2.5[a]	11.4±3.6[a]	<0.001*
Albumin (g/dl)	2.8±0.7	2.8±9.7	2.9±9.5	0.310
Hemoglobin (g/dl)	10.3±2.1[a]	9.0±1.8[a,b]	10.7±1.7[b]	<0.001*
CRP (mg/dl)	3.5 (2.8-8.5)	2.7 (1.26-15.59)	2.15 (1.0-6.3)	0.240
TSH (mIU/l)	1.3 (0.3-16.50)	1.3 (0.2-18.7)	1.94 (0.2-28.2)	0.500
Dialysis dependency (n, %)	10 (15.6)[k]	49 (76.6)[k,l]	5 (7.8)[l]	<0.001*
Mortality (n, %)	6 (12.2)[k]	27 (55.1)[k]	16 (32.7)	<0.001*

*: statistically significant difference at 0.05 significance level. CRP: C-reactive protein; LVH: Left ventricular hypertrophy; TSH: Thyroid stimulating hormone; a, b: Letters indicating statistical difference based on Tukey's HSD and Mann-Whitney U test; k, l: Letters indicating statistical difference based on Adjusted Residuals; Each percentage in this table represents row percentage.

RESULTS

Comparison of three groups regarding clinical and laboratory data is shown in **Table 1**. Group 1, 2 and 3 consisted of 14, 62 and 16 patients; respectively. There were statistically significant results for 24-hour urine volume (p=0.040), proteinuria (p=0.010), UF volume/weight at hospitalization (p<0.001), EF (p<0.001), LVH (p=0.040), UA (p<0.001), hemoglobin (p<0.001), dialysis dependency after hospital discharge (p<0.001) and mortality (p<0.001) when three groups were compared. However, there was no statistically significant result for age (p=0.138), gender (p=0.727), hospitalization time (p=0.439), survival time (p=0.090), total UF volume during hospitalization (p=0.100), sodium (p=0.672), potassium (p=0.273), albumin (p=0.310), CRP (p=0.240) and TSH (p=0.500). Statistically significant results between groups are shown with letters in **Table 1.**

Comparison of the survived and non-survived groups is shown in **Table 2.** Compared to survived patients those who did not survived were significantly older (p<0.001), had lower EF (p=0.010) and rate of loop diuretic usage at hospitalization (p=0.040), creatinine (p<0.001), sodium (p=0.020), ferritin (p=0.040), 24-hour proteinuria (p=0.010). On the other hand, results for hemoglobin (p<0.001), creatinine clearance (p<0.001), UA (p<0.001) were significantly higher for patients who did not survive. However, there were no statistically significant results for gender (p=0.070), hospitalization time (p=0.410), UF volume (p=0.700), UF volume/weight at hospitalization (p=0.990), dialysis dependency after hospital discharge (p=0.610).

ROC curve was drawn to determine the effect level and cut-off value of age, hemoglobin, creatinine clearance and uric acid variables in non-survived group (**Figure 1**) (**Table 3**). The area under the curve in the ROC curve drawn for the age variable of non-survived group is 0.833. The area under the ROC curve was statistically significant (p=0.001). The cut-off value for age was found to be 63.5 years. The sensitivity of this value is 82.4%, and the specificity is 80%. The area under the curve in the ROC curve drawn for the hemoglobin variable of non-survived group is 0.745. The area under the ROC curve was statistically significant (p=0.018). The cut-off value for hemoglobin was found to be 8.81 g/dl. The sensitivity of this value is 76.5%, and the specificity is 67%. The area under the curve in the ROC curve drawn for the creatinine clearance variable of non-survived group is 0.739. The area under the ROC curve was statistically significant (p=0.021). The cut-off value for creatinine clearance was found to be 7.82 ml/min. The sensitivity of this value is 70.6%, and the specificity is 54%. The area under the curve in the ROC curve drawn for the UA variable of non-survived group is 0.789. The area under the ROC curve was statistically significant (p=0.011). The cut-off value for UA was found to be 8.00 mg/dl. The sensitivity of this value is 70.6%, and the specificity is 73.3%.

Table 2. Comparison of survived and non-survived group

Parameter	Survived group (n=43)	Non-survived group (n=49)	p
Age (years)	57.39±13.53	70.18±10.97	<0.001*
Male (n,%)	30 (46.9)	34 (53.1)	0.070
Patients' groups (n,%) • CKD & EF ≤40% • CKD & EF >40% • EF ≤40 no CKD	 8 (57.1) 35 (56.5) 0 (0)	 6 (42.9) 27 (43.5) 16 (100)	 <0.001*
Hospitalization time (days)	14.5±10.8	16.2±9.4	0.410
Ejection fraction (%)	54.4±13.0	46.3±12.7	0.010*
Ultrafiltration volume (kg)	10.5±5.3	10.1±5.0	0.700
Ultrafiltration volume /weight at hospitalization (%)	11.8±5.3	11.7±5.0	0.990
Proteinuria (g/24 hour)	5.94±4.79	2.62±4.97	0.010*
Hemoglobin (g/dl)	8.8±1.8	10.2±1.9	<0.001*
Creatinine (mg/dl)	6.6±2.7	4.42±2.8	<0.001*
Creatinine clearance (ml/min)	7.9±4.1	14.7±9.4	<0.001*
Sodium (mmol/L)	136.7±5.0	133.6±7.3	0.020*
Ferritin (uq/l)	404.6±496.6	227.4±277.0	0.040*
Uric acid (mg/dl)	7.2±2.6	9.6±3.0	<0.001*
Loop diuretic usage (n, %) (At hospitalization)	27 (64.3)	15 (35.7)	0.040*
Dialysis dependency (n, %)	29 (45.3)	35 (55.7)	0.610

*: statistically significant difference at 0.05 significance level; Each percentage in this table represents row percentage

Table 3: ROC Curve Analysis Results

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	Area Under Curve (95% Confidence Interval)	p
Age	63.5	82.4	80	0.833 (0.671-0.952)	0.001 *
Hemoglobin	8.81	76.5	67	0.745 (0.564-0.888)	0.018 *
Creatinine clearance	7.82	70.6	54	0.739 (0.559-0.886)	0.021 *
Uric acid	8.00	70.6	73.3	0.789 (0.641-0.938)	0.011 *

*: statistically significant difference at 0.05 significance level

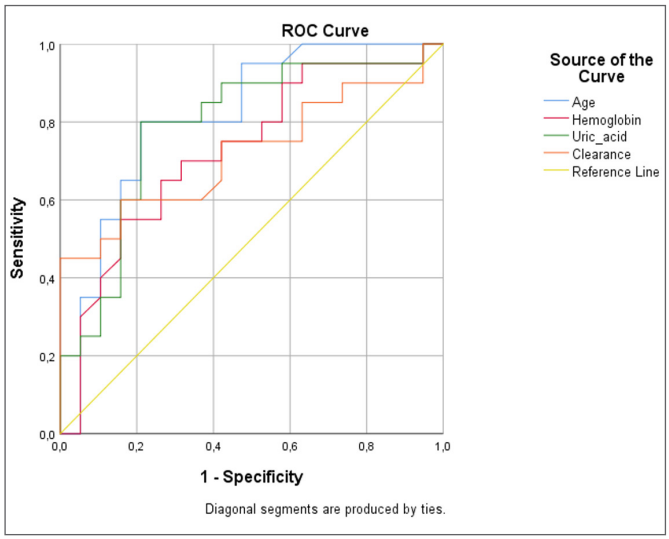

Figure 1: ROC Curve of age, hemoglobin, creatinine clearance, and uric acid variables in non-survived group

DISCUSSION

In this study, we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered. One of the main findings of this study was serum UA. The patients in group 3 had significantly higher UA levels than patients in group 2. The non-survived patients also had significantly higher levels of UA levels than survived group. The non-survived group included patients with significantly lower EF and all group in group 3 were in the non-survived group. The National Health and Nutrition Examination Survey also demonstrated hyperuricemia in nearly half of the patients with HF.[8] In HF, anaerobic metabolism in tissues due to low oxygen availability increases the levels of serum lactic acid which in turn intensifies the reabsorption of UA in the kidney leading to an increase in serum UA levels.[9] Diets low in sodium and reduction in renal UA excretion with declining GFR are also causes of hyperuricemia in patients with HF.[10,11] Serum UA also rises in response to the institution of diuretics.[10] It is also demonstrated that there is an inverse relation between EF and serum UA.[12] A recent meta-analysis by Huang et al.[13] showed that hyperuricemia was associated with an increased risk of incident HF. They showed that for every 1 mg/dl increase of serum UA, the risk of all-cause mortality and the composite endpoint in HF increased by 4 % and 28%: respectively.[13]

In this study, the EF was significantly lower in non-survived group compared to survived group and all patients in group 3 died. Regarding EF, a metaanalysis by Jørgensen et al.[14] showed a significantly lower risk of mortality in HF patients with improved EF, compared to patients with persistently reduced EF, with an estimated risk ratio of 0.34.

In this study there was also significantly lower level of proteinuria in group 3 and the survived group had significantly higher level of proteinuria compared to non-survived group. A study by Albright et al.[15] demonstrated that there can be modest proteinuria in patients with HF and successful treatment of HF reverse the proteinuria. Intrinsic renal disease should be thought in these patients when the proteinuria exceeds 1 g/day, and the proteinuria does not reverse with successful HF therapy. When the intrinsic renal disease in group 1 and 2 was considered, the significantly higher proteinuria was expected in these groups compared to group 3.

There were also statistically significant results in favor of survived group regarding CKD characteristics. Because more patients with CKD rather than HF are in the survived group, the results were more related to characteristics of CKD patients. First of all, the serum creatinine level was higher, and the creatinine clearance was lower in the survived group. In the survived group, the mean hemoglobin level was also lower. Again, when three groups were compared, the hemoglobin level was statistically lower in patients in group 2 compared to group 1 and 3. As a complication of CKD, the prevalence of anemia increases as the stage of CKD increases[16] and lower hemoglobin levels in patients with CKD is expected. Again, the statistically higher ferritin levels in survived group can be because of iron replacement for anemia management during CKD follow up.

For CKD patients, the prevalence of LVH increases as the renal function of patients decreases and rises to 90% after the initiation of dialysis.[17] Systolic hypertension, elevated pulse pressure with fluid overload and increased arterial stiffness play role in LVH development in patients with advanced CKD.[18] In our study the number of patients with LVH was also statistically higher in group 2 and the hemoglobin level was also lower in these patients. Despite significantly higher level of ferritin in the survived patients; the hemoglobin level was significantly lower, that one can think the need of erythropoietin in these patients. The lower hemoglobin level also points out the higher percentage of patients with LVH in the survived group.[19]

UF may be associated with worsening renal function in patients with HF.[20-22] A study by Dev et al.[23] evaluated 70 ultrafiltrated patients with diagnosis of diuretic resistant acute decompensated HF. The percentage of dialysis dependent patients was 10% after UF. In another study, 11 diuretic resistant HF patients with a mean baseline eGFR of 38 ml/min were evaluated. The percentage of dialysis dependent patients was 45% after UF.[24] In our study, the percentage of dialysis dependent

patients in group 3 was %31. There was, however, no statistically significant result for dialysis dependency after hospital discharge when the survived and non-survived groups were compared.

Another finding of this study was the data regarding UF volume. Despite the total UF volume during hospitalization did not differ between 3 groups; the UF/weight at hospitalization was significantly higher in group 3. Again, the 24-urine volume was lower in group 1 and 3 which is most commonly encountered in patients with right sided HF because of increased central and renal vein pressures. These data can demonstrate that patients with HF are more prone to hypervolemia. The fluid retention in these patients makes the diuretic usage necessary. There should be vigorous volume control with diuretics during their follow-up. Unfortunately, the percentage of patients using diuretics were significantly lower in the non-survived group.

Hypervolemia may be a marker for poor prognosis. In a study, a relationship was found between fluid overload and length of stay in the intensive care unit in patients undergoing surgery.[25] In a different study, Stein et al.[26] similarly found a significant relationship between fluid overload and length of stay in the intensive care unit in patients undergoing cardiac surgery. Hypervolemia may worsen the prognosis in patients by causing myocyte damage and malignant ventricular tachyarrhythmia.[27] In our study, we found that the mortality rate was lower in patients with high creatinine levels compared to patients in group 3. The reason for this may be that patients with high creatinine are taken to ultrafiltration in a shorter time, preventing complications that may occur as a result of hypervolemia.

Study Limitations

The limitations of our study included retrospective nature and small number of patients. There was also not a specific UF protocol and UF was done based on the decision of patients' own doctors. However, UF volume was evaluated for the first time which is the main strength of our study.

CONCLUSION

Patients with HF were more prone to hypervolemia and mortality. The ultrafiltration volume/weight at hospitalization and serum uric acid levels were also significantly higher in these patients. Patients with chronic kidney disease had significantly higher proteinuria, creatinine and lower hemoglobin levels. The rate of loop diuretic usage at hospitalization was significantly higher in the survived group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Haydarpaşa Numune Training and Research Hospital Ethic Committee (Date: 28.05.2019, Decision No: 771).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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