

# Trends in Acute Renal Failure in Central Anatolia

## *İç Anadolu'da Akut Böbrek Yetmezliği Seyri*

### ABSTRACT

**OBJECTIVE:** Our main purpose was to evaluate the epidemiological properties and mortality rate of this study and to evaluate the etiology and factors associated with mortality in patients with ARF.

**MATERIAL and METHODS:** In this prospective observational study a total of 541 patients with ARF were assessed between January 2008 - January 2012. The etiological spectrum and predictors of mortality were evaluated in this population.

**RESULTS:** The mean age was  $64.9 \pm 15.6$  years and the majority of patients were male. The most common etiology of ARF was medical causes. Diarrheal disease and drug-induced ARF were the major medical causes. One hundred and fifty four patients needed dialysis. The most common cause of death was cardiopulmonary failure. In multivariate analysis, dialysis necessity, age, C-reactive protein, serum sodium, serum phosphorus, serum albumin, and hemoglobin were independently associated with death after adjusting for other variables.

**CONCLUSION:** ARF resulting from medical diseases was higher compared to surgical causes. Use of medication with antibiotics and non-steroid anti-inflammatory drugs was predominantly increased; however the main cause was diarrheal disease. Hypoalbuminemia, anemia, dialysis requirement and hyperphosphatemia were found to be the main predictors of mortality in patients with ARF.

**KEY WORDS:** Acute renal failure, Diarrheal disease, Hypoalbuminemia, Mortality, Central Anatolia, Turkey

### ÖZ

**AMAÇ:** Akut böbrek yetmezliği (ABY), yıllar içinde tedavisinde hayli gelişmeler olmasına rağmen hala yüksek ölüm oranlarına sahiptir. Bu yüzden sebepleri ve ölümlerle ilişkili öngörüye katkıda bulunan belirteçler ayrıntılı bir şekilde araştırılmıştır. Bu çalışmamızda, ABY nedenlerinin yıllar içerisindeki değişiklikleri ile ölüme katkıda bulunan nedenleri ortaya koymayı amaçladık.

**GEREÇ ve YÖNTEMLER:** Bu prospektif tek merkezli gözlemsel çalışma üniversitemiz nefroloji bölümünde 541 ABY'li hastayı kapsayacak şekilde Ocak 2008- Ocak 2012 arasında yapılmıştır. Takip esnasında hemogram, biyokimyasal parametreler ve ABY nedenleri ile hastalık ilişkili ölümler kaydedilmiştir.

**BULGULAR:** Çalışmamızdaki hastaların önemli bir kısmı erkek ve ortalama yaş  $64.9 \pm 15.6$  yıl olarak bulunmuştur. En sık ABY nedenleri arasında oral alım bozukluğu-ishal ile ilaç kaynaklı nedenler göze çarpmıştır. Hastalarımızın 154'ü takip esnasında diyaliz gereksinimi doğmuştur. En sık ölüm nedeni ise kalp kaynaklı ölümler ilk sırayı almaktadır. Renal biyopsi yapılan hastalar içinde patolojik tanı açısından en fazla akut interstisyel nefrit tanısı konmuştur. Çok değişkenli analizde, diyaliz gereksinimi, yaş, C-reaktif protein, serum fosfor, albumin ve hemoglobinin seviyeleri sağkalım ile bağımsız şekilde ilişkili bulunmuştur.

**SONUÇ:** Daha önceki merkez verilerimiz gözönünde bulundurulduğunda, nonsteroid anti inflamatuvar ilaç ve antibiyotik kaynaklı ABY olgularında artış saptanırken, sağkalımla ilişkili parametreler benzer şekilde hypoalbuminemi, anemi, diyaliz gereksinimi ve hiperfosfatemi olarak bulunmuştur.

**ANAHTAR SÖZCÜKLER:** Akut böbrek yetmezliği, Diareal hastalık, Hipoalbuminemi, Ölüm, İç Anadolu, Türkiye

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## INTRODUCTION

Acute renal failure is one of the most important clinical problems which is often observed in hospitalized patients and sometimes requires critical care. The mortality rate still remains high in this population despite recent advances in critical care medicine, rapid initial therapy modalities and increased number of nephrology clinics (1). Causative problems have been investigated for many years and have changed over the years. In Turkey, medical causes much more common than surgical and obstetric problems. Preventive measures could play a key role and be responsible for the changes in the causes of acute renal failure. The mortality rate has declined over time due to these measures and advances in medicine (2). The factors associated with mortality in ARF have been investigated over the years. Although many factors have been shown to be related to mortality, clues to explain the mechanism and predict morbidity or mortality have not been established. Researchers have reported that ARF is a heterogeneous clinical syndrome; in addition the factors associated with the mortality rate can vary widely. Such factors include oliguria, presence of diabetes mellitus, APACHE scoring systems, anemia, hypoalbuminemia and dialysis requirement (3-5).

In this study we aimed to demonstrate the etiological and epidemiological features of ARF in our clinic and evaluate the factors associated with morbidity and mortality in this population.

## PATIENTS and METHOD

### Study Population

This is a prospective observational cohort study that aimed to investigate the etiological factors and predictors of mortality in patients with ARF. Five hundred and forty one patients with ARF were admitted to the Nephrology Department of the Erciyes University Medical Faculty Hospital in Turkey between January 2008 - January 2012. The patient population was from the city of Kayseri and other cities in Central Anatolia including urban and rural areas. Our hospital serves an area of nearly 3.000.000 population and is located in the Central Anatolia region of Turkey. ARF was defined as an acute decrease in renal function (rise in serum creatinine levels to  $> 2$  mg/dl despite absence or correction of prerenal causes). The diagnosis of ARF was based on medical history, physical examination, laboratory evaluations, and clinical course.

Patients with pre-existing renal disease and those less than sixteen years of age were excluded from this study. The patients were classified as oliguric (less than 400 ml urine/24 h) or non-oliguric (more than 400 ml urine/24 h). A renal biopsy was performed in selected patients who had unexplained renal failure, systemic disease such as systemic lupus erythematosus, signs suggesting glomerular, vascular, and interstitial disorders, and when duration of ARF exceeded 3 weeks.

All patients were assessed for dialysis therapy indications during the follow-up period. The indications for dialysis included the following: severe uremia (blood urea nitrogen above 100 mg/dl), hyperkalemia resistant to conservative therapy, presence of uremic encephalopathy, metabolic acidosis (serum bicarbonate under 15 mEq/L) and volume overload. Mortality was defined as death during the episode of ARF.

### Biochemical Measurements

All samples were obtained from patients and controls in the morning after 12 h of fasting for measurement of serum albumin, total serum cholesterol, triglyceride (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Total plasma cholesterol, TG and HDL cholesterol were measured by enzymatic colorimetric method with Olympus AU 600 auto analyzer using reagents from Olympus Diagnostics GmbH (Hamburg, Germany). LDL cholesterol was calculated by Friedewald's formula. Serum total calcium was measured by the cresolphthalein complexone method using Menagent Calcium 60sec kits (Menarini Diagnostics, Florence, Italy). Serum phosphorus was measured by the ammonia molybdate complex method using Menagent Phosphofix kits (Menarini Diagnostics). Tripotassium EDTA based anticoagulated blood samples were drawn to measure whole blood count at 4 C° and assessed by a Sysmex K-1000 (Block Scientific, USA) auto analyzer within 30 min of sampling. Hs-CRP was measured by using a BN2 model nephelometer (Dade-Behring, Germany). The expected values for hs-CRP in our laboratory ranged from 0 to 3 mg/l.

All patients underwent the following evaluations: urine analyses, urine indices such as the fractional excretion of sodium (FENa) and renal ultrasonography.

### Statistical Analysis

SPSS 15.0 (SPSS for Windows, 2007, Chicago) was used for the statistical analysis. Continuous variables with normal distribution were presented as mean  $\pm$  standard deviation. Median value was used when normal distribution was absent. A logistic regression analysis was performed to calculate the odds ratio and examine the predictive effect of each factor on death. Kaplan-Meier time-to-event curves were generated for patients with a serum albumin level above and below the normal value ( $<4.0$ ,  $\geq 4.0$ ); we assessed the equality of survival distributions by log-rank test. A two-tailed  $P < .05$  was considered statistically significant.

## RESULTS

Table I shows the characteristics of patients with ARF. The mean age was  $64.9 \pm 15.6$  years. The majority of patients were male. The median length of hospital stay was six days (range 2-41). Also, the median numbers of dialysis sessions were three in our cohort. The majority of acute renal failure cases were characterized by oliguria. One hundred and fifty four patients

**Table I:** Characteristics and basement biochemical parameters of patients with acute renal failure (n: 541).

Characteristic	n (%)
Age (years)	64.9 ± 15.6
Gender	
Male	311 (57.5)
Female	230 (42.5)
Type	
Oliguria	371 (68.6)
Non-oliguria	169 (31.2)
Blood urea nitrogen (mg/dL)	75 ± 25.77
Creatinine (mg/dL)	4.8 ± 2.5
Sodium (mmol/L)	136 ± 6
Potassium (mmol/L)	4.9 ± 0.9
Calcium (mg/dL)	8.6 ± 1.5
Phosphorus (mg/dL)	4.8 ± 1.2
Uric acid (mg/dL)	9.3 ± 2.4
Albumin (g/dL)	3.5 ± 0.5
Whole blood count (mm <sup>3</sup> )	13081 ± 5284
Hemoglobin (g/dL)	11.4 ± 1.9
C-reactive protein (mg/L)	21 (3-379)
Dialysis necessity	154 (28.5)
Length of hospital stay	6 (2-41)
The number of dialysis sessions	3 (1-14)

needed dialysis. The causes of acute renal failure are presented in Table II. The most common etiology of ARF was medical causes. Diarrheal disease and drug-induced ARF were the major medical causes. The most important drug groups to cause drug-induced ARF were non-steroid anti-inflammatory drugs and b-lactams (Table III). Urinary obstruction was the most common cause of surgical-induced ARF. The prevalence of ARF resulting from obstetric problems was extremely low.

Figure 1 shows the outcomes of patients with ARF. Of the 541 patients, 453 (83.7%) completely recovered. Partial improvement was observed in 40 (7.4%) patients. On the other hand, only 8 (1.5%) patients progressed to ESRD whereas 40 (7.4%) patients died. The most common cause of death was cardiopulmonary failure (see Table IV). Renal biopsy was performed in only 35 (6.4%) patients. The diagnoses of patients undergoing renal biopsy are presented in Table V. Acute interstitial nephritis, all cases of which were caused by drugs, was the most common diagnosis in those patients undergoing renal biopsy. Table VI

**Table II:** Causes of acute renal failure (n: 541).

Etiology	n (%)
Medical	422 (78.0)
Acute diarrheal disease	190 (35.1)
Drug-induced	80 (14.8)
Congestive heart failure	52 (9.6)
Contrast media nephropathy	38 (7.0)
Sepsis	29 (5.4)
Gastrointestinal bleeding	15 (2.8)
Glomerulonephritis	12 (2.2)
Others	6 (1.1)
Surgical	113 (20.9)
Urinary obstruction	83 (15.3)
Postoperative	25 (4.6)
Crush injury	8 (1.5)
Obstetric	6 (1.1)
HELLP syndrome	3 (0.6)
Postpartum acute renal failure	2 (0.4)
Septic abortion	1 (0.2)

**HELLP:** Hemolysis elevated liver enzymes low platelets

**Table III:** Susceptible agents responsible for drug-induced acute renal failure.

Drugs	n (%)
NSAIDs	30 (37.5)
B-lactams	24 (30.0)
Diuretics	10 (12.5)
Aminoglycosides	8 (10)
Others	8 (10)

**NSAIDs:** Non-steroidal anti-inflammatory drugs

shows univariate and multiple logistic regression analysis for predictors considered to be related with death. In multivariate analysis, dialysis necessity, age, C-reactive protein, serum phosphorus, serum albumin, and hemoglobin were significantly and independently associated with death after adjusting for other variables.

Figure 2 shows the relationship between low albumin levels with survival. The mean albumin level among patients who died was ≥4 g/dl as compared with <4 g/dl in survivors (log rank, p= 0.035). The dashed lines and uninterrupted lines show the

survival of patients with normal albumin level and survival of patients with low albumin level respectively.

### DISCUSSION

In a study of cases with acute renal failure who were evaluated at our institution in the 1980s and 1990s, the causes of ARF in 1980s were as follows: medical reasons in 52.6% of patients, surgical reasons in 28.4%, and obstetric reasons in 19.0% whereas the causes of ARF in the 1990s were medical reasons in 61.3% of patients, surgical reasons in 23.8%, and obstetric reasons in 14.9% (2). In this study performed in the 2000s, similar changes in etiologic trend were observed in ARF. While the number of ARF cases due to surgical causes

decreased, those resulting from medical diseases increased. However, the most noticeable change was the decrease in the development of ARF caused by obstetric disorders. The most important reasons for this change are probably the disappearance of septic abortion and improvements in antenatal care. In the 1970s, obstetric reasons were the most common cause of ARF in Turkey, accounting for 78% of all cases of ARF (6). The most common cause of ARF due to medical diseases was still acute diarrheal disease, which is rare in developed countries, but frequent in developing countries (7). The risk may be related with poor sanitation, low socioeconomic conditions, and delay in the correction of fluid and electrolyte loss. On the other hand, the aging of the population also seems to be to contribute to this condition because the mean age was significantly higher in patients with acute diarrheal disease than in those without acute diarrheal disease ( $69 \pm 13$  vs.  $62 \pm 16$  years, respectively, data not shown). As is known, older individuals are more susceptible to dehydration. An important observation in the medical causes of ARF was the decrease in the incidence of drug-induced ARF. The incidence decreased by approximately 50%. This reduction may be a result of the more rational use of drugs, especially antibiotics such as aminoglycosides and rifampicin. The most important drug groups to cause drug-induced ARF were non-steroid anti-inflammatory drugs and b-lactams.

ARF during hospitalization is related with high mortality rate in hospital. In critically ill patients in intensive care who develop ARF requiring dialysis, the in-hospital mortality rate

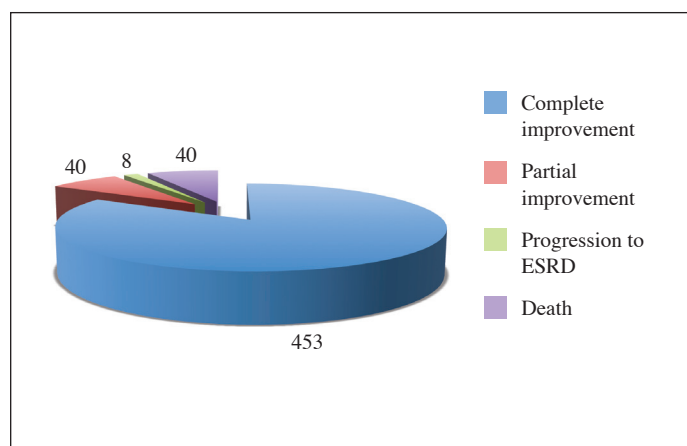


Figure 1: The outcomes of patients with acute renal failure.

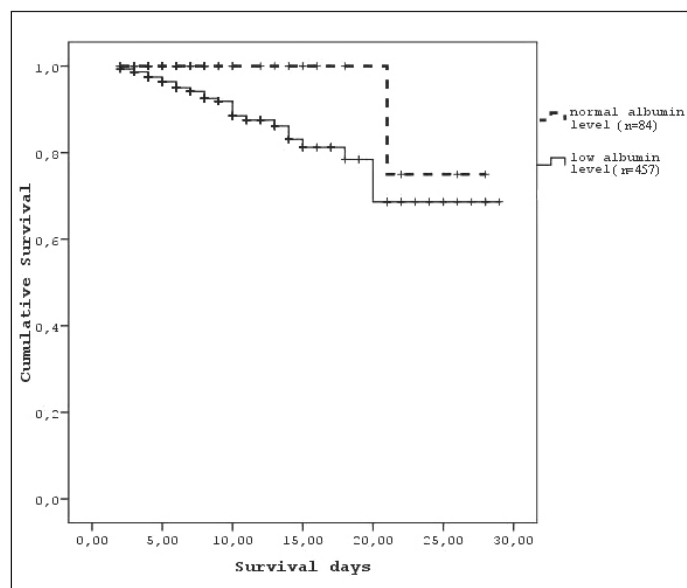


Figure 2: Kaplan-Meier cumulative (Cum) survival plot for serum albumin. Symbols are: (-) event times in patients with albumin  $\geq 4$  g/dl; (---) albumin  $< 4$  g/dl

Table IV: Causes of death (n:40).

Cause	n (%)
Cardiorespiratory failure	28 (70.0)
Sepsis	4 (10.0)
Myocardial infarction	4 (10.0)
Pulmonary embolism	3 (7.5)
Gastrointestinal bleeding	1 (2.5)

Table V: The diagnosis of 35 patients undergoing renal biopsy.

The diagnosis	n (%)
Acute interstitial nephritis	20 (58)
APSGN	4 (12)
Crescentic glomerulonephritis	3 (9)
Lupus nephritis (class IV)	1 (3)
Acute tubular necrosis	3 (9)
Non-diagnostic	3 (9)

APSGN: Acute poststreptococcal glomerulonephritis

**Table VI:** Univariate and Multiple Logistic Regression Analysis for predictors considered to be related with death.

Variables	Univariate analysis		p value
	Odds ratio	95% CI	
Gender	0.90	0.47-1.71	0.741
Etiology	2.06	0.79-5.39	0.140
Dialysis necessity	3.82	1.98-7.37	<b>&lt;0.001</b>
Presence of infection	2.86	1.46-5.58	<b>0.002</b>
Age	1.06	1.03-1.09	<b>&lt;0.001</b>
C-reactive protein	1.01	1.00-1.01	<b>0.002</b>
Blood urea nitrogen	1.01	1.00-1.02	<b>0.042</b>
Creatinine	0.87	0.74-1.02	0.093
Sodium	1.05	0.91-1.21	0.219
Potassium	0.78	0.54-1.13	0.189
Phosphorus	1.50	1.17-1.90	<b>0.001</b>
Uric acid	1.04	0.90-1.19	0.611
Albumin	0.13	0.07-0.23	<b>&lt;0.001</b>
Whole blood count	1.03	0.99-1.08	0.173
Hemoglobin	0.78	0.65-0.92	<b>0.004</b>
Variables	Multiple analysis		p value
	Odds ratio	95% CI	
Dialysis necessity	2.99	1.22-7.31	<b>0.017</b>
Age	1.05	1.01-1.09	<b>0.007</b>
C-reactive protein	1.01	1.00-1.01	<b>0.042</b>
Phosphorus	1.39	1.03-1.88	<b>0.034</b>
Albumin	0.25	0.11-0.54	<b>&lt;0.001</b>
Hemoglobin	0.76	0.60-0.94	<b>0.013</b>

**CI:** confidential interval

ranges from approximately 40% to 62% (8-10). In-hospital mortality rates are lower in patients with ARF in the general hospital population and range from approximately 15% to 40% (11-14). In our cohort, the in-hospital mortality rate was 7.4%. At our institution this rate was 33.6% in the 1980s whereas it was 31% in the 1990s (2), so in-hospital mortality rates have declined over time. A similar decrease in the in-hospital mortality rates in patients with ARF has been reported in other series (12,13). This declining trend of mortality rates may be a result of improvements in patient care, intensive care, and dialysis.

Many factors are associated with mortality in acute renal failure (15,16). Albumin level is one of the indicators of nutritional status that has been demonstrated as a mortality

predictor in patients undergoing dialysis (17). Additionally, serum albumin level and the association with mortality in patients with cardiovascular disease and cancer have been well established (18). Furthermore studies have focused on the role of albumin in patients with acute renal failure. Chertow et al. reported that hypoalbuminemia is one of the predictors of mortality in patients with acute tubular necrosis (3). Another study performed by Obiola et al. found similar findings; they demonstrated that serum albumin level was related with a high risk of death in patients with acute renal failure (19). In patients with end stage renal disease, serum albumin that is regulated with dietary protein intake reflects visceral protein malnutrition. However, studies on experimental models demonstrated that renal failure does not affect the albumin synthesis and the albumin pool. Hypoalbuminemia is also related with plasma

volume expansion and albuminuria (20,21). Acute renal failure is one of the conditions that induce protein catabolism due to uremic toxins, inflammatory mediators, metabolic acidosis, and hormonal imbalance (22). In addition, decreased serum albumin is associated with inflammatory conditions because it is one of the negative acute phase reactive proteins (23). Additionally, inflammation and its association with acute renal failure have been well denoted (24,25). Recently in one meta-analysis, it was reported that hypoalbuminemia is a significant predictor of both acute kidney injury and mortality due to ARF (26). In keeping with these studies our study demonstrated that serum albumin level is closely related with mortality in patients with ARF so further studies are warranted to determine measures aimed to treat hypoalbuminemia.

Anemia is very common in patients with ARF. There are many causes of anemia in these patients, such as increased erythrocyte destruction and loss, decreased erythrocyte production due to blunted erythropoietin production and the inhibitory effects of inflammatory cytokines and uremic toxins (27,28). It has been observed that low initial hemoglobin levels in patients with ARF are related with increased risk of death (29). Similarly, in this study, low hemoglobin level was a predictor considered to be related with death in multiple logistic regression analysis. However, interpretation of the impact of anemia on outcome in ARF patients may have been limited by the observational design of this study.

Dialysis necessity and hyperphosphatemia were found to be independent risk factors for death in this study. This might be a reflection of the seriousness of the disease. Similarly, in many studies, it has been observed that mortality rates were significantly higher in patients with ARF requiring dialysis compared to those with ARF that did not require dialysis (11,12).

In conclusion, the present study demonstrates that trends in acute renal failure did not change compared to the 1990's in the Central Anatolian region of Turkey. Diarrheal disease and drug-induced ARF are still the main medical reasons. Additionally, hypoalbuminemia, hyperphosphatemia and dialysis necessity are the main predictors of mortality in these patients. Finally, future studies should evaluate preventive measures and therapy modalities in ARF.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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