ACUTE KIDNEY INJURY AFTER HIP FRACTURE SURGERY AND ITS IMPACT ON MORTALITY

KALÇA KIRIĞI CERRAHİSİ SONRASI AKUT BÖBREK HASARI VE MORTALİTEYE ETKİSİ

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ABSTRACT

INTRODUCTION: Acute kidney injury is a serious complication after major surgery, which may lead to increased morbidity and mortality. The objective of our study was to identify the possible risk factors for renal dysfunction after hip fracture surgery and the impact of acute kidney injury on the short and long-term clinical outcomes.

MATERIAL AND METHOD: Our retrospective study was conducted between March 2012 and November 2017 on 238 patients who underwent hip fracture surgery. At admission, clinical and biochemical parameters were measured and acute kidney injury was defined according to the Acute Kidney Injury Network criteria. The impacts of acute kidney injury on short and long-term mortality were investigated.

RESULTS: Of the 238 patients, 47 (19.7%) developed acute kidney injury during hospitalization and 165 (69.3%) died after a mean follow-up period of 22.1±19.9 months. The overall mortality rate was 38.2%, 54.2%, 61.8%, 65.1%, and 68.1% at 1, 2, 3, 4 and 5-years, respectively. The baseline serum creatinine level, hemoglobin level, number of transfused erythrocytes, presence of chronic kidney disease or more than one comorbidity were independent risk factors for acute kidney injury. Patients with acute kidney injury during hospitalization had significantly higher rates of short- and long-term mortality than those without acute kidney injury. After multivariable adjustment, only chronic kidney disease emerged as an independent predictor for acute kidney injury, while congestive heart disease and longer preoperative hospitalization were the risk factors for short-term mortality.

CONCLUSION: Acute kidney injury is a frequent complication in patients undergoing hip fracture surgery and is independently associated with increased short- and long-term mortality.

Keywords: *Acute kidney injury, comorbidity, hip fracture, mortality.*

ÖZET

AMAÇ: Akut böbrek hasarı, büyük cerrahiler sonrası artmış mortalite ve morbiditeye yol açabilen önemli bir komplikasyondur. Çalışmamızda kalça kırığı cerrahisi sonrası, böbrek fonksiyon bozukluğu için olası risk faktörlerinin ve akut böbrek hasarının kısa ve uzun dönem klinik sonuçlar üzerine etkilerinin belirlenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Mart 2012-Kasım 2017 tarihleri arasında, kalça kırığı nedeniyle ameliyat edilen 238 hasta retrospektif olarak incelendi. Başvuru esnasındaki klinik ve biyokimyasal parametreler kaydedildi ve akut böbrek hasarı "Acute Kidney Injury Network" kriterlerine göre tanımlandı. Akut böbrek hasarının kısa ve uzun dönem mortalite üzerine etkileri araştırıldı.

BULGULAR: Hastanede yattıkları sürede 238 hastanın 47'sinde (%19.7) akut böbrek hasarı gelişti ve tüm takip süresince 165 (%69.3) hasta öldü. Ortalama takip süresi 22.1 ± 19.9 aydı. Mortalite oranları 1, 2, 3, 4 ve 5. yıllarda sırasıyla %38.2, %54.2, %61.8, %65.1 ve %68.1 bulundu. Bazal serum kreatinin ve hemoglobin düzeyleri, eritrosit transfüzyon sayısı, kronik böbrek hastalığı ve birden fazla komorbidite varlığı, akut böbrek hasarı için bağımsız risk faktörleriydi. Hastane yatışı sırasında akut böbrek hasarı gelişen hastalarda, gelişmeyenlere oranla, kısa ve uzun dönem mortalite oranları anlamlı derecede yüksekti. Çok değişkenli analize göre, sadece kronik böbrek hastalığı, akut böbrek hasarı için bağımsız bir risk belirleyicisi iken; konjestif kalp hastalığı ve daha uzun operasyon öncesi yatış süresi, kısa dönem mortalite için risk belirleyicisiydi.

SONUÇ: Kalça kırığı cerrahisi sonrası akut böbrek hasarı sık görülen bir komplikasyondur ve kısa ve uzun dönem mortalitede artış ile ilişkilidir.

Anahtar Kelimeler: *Akut böbrek hasarı, komorbidite, kalça kırığı, mortalite*

INTRODUCTION

Hip fractures constitute a leading cause of hospital admissions and length of stay among the elderly patients. They are associated with functional impairments and major disabilities and result in high rates of hospitalization and mortality (1). The estimated mortality rate associated with hip fractures is 5-10% within one month and 12-37% at one year, depending on both the pre- and post-fracture health status. The excess mortality following hip fracture is sustained for several years and comorbidities

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such as cardiovascular disease, chronic obstructive pulmonary disease, dementia, malnutrition, infection, and thromboembolism increase the hip fracture-related mortality rate (2-5).

Acute kidney injury (AKI) is a common morbidity in hospitalized patients and is a frequent complication after hip fracture surgery. Electrolyte imbalance and chronic kidney disease (CKD) are related to in-hospital mortality, and preoperative renal dysfunction is associated with long-term mortality in patients with a hip fracture (4,6,7). However, few studies have examined the impact of AKI on long-term mortality in elderly patients after hip fractures.

The aim of this study was to identify the patients with renal injury after total hip fracture surgery and to detect the possible risk factors. In addition, we investigated the potential role of AKI as a predictor of short- and long-term mortality following hip fracture surgery.

MATERIAL AND METHODS

Our single-center, retrospective study included a cohort of 238 patients (86 males, 152 females) who underwent hip fracture surgery. Approval of the local medical ethics committee was obtained prior to the study. The inclusion criteria were to be of age ≥55 years, have first time experience with hip fracture, and to have undergone hip fracture surgery between March 2012 and November 2017. Patients with a previously diagnosed end-stage renal disease on renal replacement therapy, a history of hip disease or fracture or patients with a follow-up period of less than one year were excluded.

Demographic and biochemical data, including age, gender, height, weight, blood pressure, smoking habit and alcohol use was retrieved from the patient files. Hemoglobin, leukocyte, platelet levels and biochemical parameters such as albumin, sodium, potassium, urea, and creatinine levels at admission were defined as baseline, daily and discharge blood values. The American Society of Anesthesiologists (ASA) score, operative time, type of anesthesia, intensive care stays, the number of transfused erythrocytes and the length of pre- and postoperative stay were assessed. Data on comorbidities such as diabetes, CKD, hypertension, heart failure, and history of a coronary artery disease (CAD) or cerebrovascular accident (CVA) were also obtained from the records.

Baseline and follow-up creatinine levels were monitored and AKI was defined according to the Acute Kidney Injury Network (AKIN) classification based on the changes in the serum creatinine level (8). AKI was defined as an absolute increase in the serum creatinine level of more than or equal to 0.3 mg/dL, or a percentage increase in serum creatinine of more than or equal to 50% within the first 48 hours. The urine output criterion for AKI was not used in the present study. The absolute changes in serum creatinine were calculated according to the peak and baseline creatinine levels.

Chronic kidney disease was diagnosed in patients with an estimated glomerular filtration rate (eGFR) of<60 mL/min per 1.73 m2 for a period of more than three months, based on the guidelines of the National Kidney Foundation (9). The glomerular filtration rate (GFR) was calculated based on the demographic and biochemical variables using the Modification of Diet in Renal Disease (MDRD) formula:

186 x serum creatinine-1.154 x age-0.203(x1.212 if African-American), x 0.742 if female(10).

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as numbers and percentages. The patients were categorized according to the presence of AKI and mortality. Categorical variables were compared using the x2 or Fisher exact test, when appropriate. Continuous variables were first analyzed for normality by examining the histograms and normal Q-Q plots, and were then compared using Student's t-test or the Mann-Whitney U test, when appropriate. Thus, factors associated with AKI and mortality were investigated. The odds ratios (ORs) for AKI were determined by crude and multivariate logistic regression analyses. To assess the impact of AKI on mortality, we used crude and multivariate binomial logistic regression analyses. Survival curves were plotted using the Kaplan-Meier method and were analyzed using the log-rank tests. All tests were performed using the SPSS for Windows v.17.0 software (SPSS Inc, Chicago, IL, USA). P values of <0.05 were deemed to indicate statistical significance.

RESULTS

The mean age of the patients was 78.9±8.6 (range: 55-96) years. There were 72 (30.3%) patients with diabetes, 70 (29.4 %) with CKD, 160 (67.2%) with hypertension, 69 (29.0%) with a congestive heart disease (CHD), 47 (19.7%) had a history of CAD and 23 (9.7%) had a history of CVA. The mean length of follow-up was 22.1±19.9 months.

The Incidence And Predictors Of AKI

In total, 47 patients (19.7%) developed AKI during hospitalization according to the AKIN criteria: 31 patients were classified as AKIN Stage 1, nine as Stage 2 and seven as Stage 3. One patient progressed to AKI requiring dialysis. The comparisons of the demographic, laboratory, and clinical characteristics of the patients with and without acute renal failure are shown in **Table 1.**

The preoperative serum urea and creatinine levels were higher, and the hemoglobin level was lower in patients with AKI. The preoperative serum sodium level was lower in patients who had AKI, however, that association had a borderline statistical significance. Postoperative serum albumin level was lower (2.9±0.4 vs. 3.1±0.4, p=0.039) and postoperative first day potassium level was higher (5.0±0.8 vs. 4.7±0.6, p=0.027) in patients who had

AKI. The number of transfused erythrocytes was higher in patients with AKI. Patients with AKI had a higher prevalence of CKD and more than one comorbidities. Multivariate logistic regression analysis revealed that CKD (OR: 0.187, 95% CI: 0.037-0.950, p=0.043) was significantly associated with the occurrence of AKI.

Table 1 Baseline characteristics and clinical outcomes of the patients

	AKI (n=47) Mean±SD	Non-AKI (n=191) Mean±SD	p*
Age (years)	80.1±7.4	78.6±8.8	0.219
Gender (male), n (%)	18 (38.3)	68 (35.6)	0.737
BMI (kg/m2)	26.5±4.6	25.8±4.5	0.422
Hypertension, n (%)	35 (76.1)	125 (66.1)	0.220
Diabetes, n (%)	19 (41.3)	53 (28.0)	0.108
CAD, n (%)	12 (25.5)	35 (18.5)	0.309
CHD, n (%)	19 (41.3)	50 (26.6)	0.070
CKD, n (%)	27 (57.4)	43 (22.5)	**<0.001**
CVA, n (%)	6 (13.0)	17 (9.0)	0.414
Comorbidities >1, n (%)	34 (72.3)	105 (55.0)	**0.033**
Systolic BP (mmHg)	126.4±14.5	122.2±14.8	0.083
Diastolic BP (mmHg)	73.3±9.7	73.0±9.3	0.836
Hemoglobin (g/dL)	11.2±1.6	11.9±2.0	**0.026**
Leukocyte (103/mm3)	10.8±4.4	11.2±4.4	0.663
Urea (mg/dL)	67.5±37.6	56.7±28.5	**0.032**
Creatinine (mg/dL)			
Baseline	1.5±0.9	1.1±0.6	**0.013**
Peak	2.4±1.5	0.9±0.5	**<0.001**
eGFR (mL/min/1.73 m2)	59.1±37.5	70.9±31.7	0.028
Albumin (g/L)	3.7±0.4	3.9±0.4	0.302
Sodium (mmol/L)	137.5±4.6	138.8±4.0	0.052
Potassium (mmol/L)	4.7±0.8	4.7±0.7	0.939
ASA score	2.7±0.7	2.7±0.6	0.516
Surgery type (replacement), n (%)	22 (46.8)	97 (50.8)	0.745
Type of anesthesia (general), n (%)	6 (12.8)	17 (8.9)	0.414
Duration of anesthesia (minutes)	89.6±36.5	97.5±33.6	0.157
Need for intensive care, n (%)	18 (38.3)	104 (54.5)	0.052
Number of transfused RBCs(units)	1.1±1.0	0.8±0.9	**0.035**
Pre-op length of stay (days)	6.4±3.3	7.0±4.6	0.401
Post-op length of stay (days)	7.7±9.9	5.9±4.3	0.218
Overall length of stay (days)	14.1±10.5	12.9±6.5	0.445
First-month mortality, n (%)	10 (21.3)	15 (7.9)	**0.014**
First-year mortality, n (%)	25 (53.2)	66 (34.6)	**0.029**
Long-term mortality, n (%)	39 (83.0)	126 (66.0)	**0.023**

*Significant p values are written in bold
AKI: acute kidney injury, ASA: American Society of Anesthesiologists, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CHD: congestive heart disease, CKD: chronic kidney disease, CVA: cerebrovascular accident, eGFR: estimated glomerular filtration rate, RBC: red blood cell.

Acute kidney injury significantly affected the short- and long-term outcomes. Patients with AKI had higher rates of mortality at the first month (21.3% vs. 7.9% respectively, p=0.014), at the first year (53.2%vs.34.6% respectively, p=0.029) and in the long-term (83.0% vs. 66.0% respectively, p=0.023).

Table 2 Characteristics of the patients according to overall survival status

	Survivors (n=73) Mean±SD	Non-survivors (n=165) Mean±SD	p*
Age (years)	76.3±9.3	80.0±8.0	**0.002**
Gender (male), n (%)	29(39.2)	57 (34.8)	0.561
BMI (kg/m2)	27.1±4.6	25.6±4.5	**0.044**
Hypertension, n (%)	50(68.5)	110 (67.9)	1.000
Diabetes, n (%)	21(28.8)	51 (31.5)	0.760
CAD, n (%)	18(24.7)	29 (17.8)	0.223
CHD, n (%)	16(22.2)	53 (32.7)	0.121
CKD, n (%)	15(20.3)	55 (33.5)	**0.046**
CVA, n (%)	3(4.2)	20 (12.3)	0.060
Comorbidities >1, n (%)	41(55.4)	98 (59.8)	0.571
Systolic BP (mmHg)	121.2±12.3	123.8±15.7	0.184
Diastolic BP (mmHg)	72.1±9.9	73.4±9.1	0.343
Hemoglobin (g/dL)	12.6±1.8	11.4±1.8	**<0.001**
Leukocyte (103/mm3)	11.2±4.7	11.0±4.3	0.730
Urea (mg/dL)	52.5±27.0	61.7±31.9	**0.023**
Creatinine (mg/dL) Baseline Peak	 1.1±0.5 1.1±1.0	 1.2±0.7 1.3±0.9	 **0.049** 0.173
eGFR (mL/min/1.73 m2)	74.6±33.6	65.9±32.7	0.059
Albumin (g/L)	4.0±0.4	3.8±0.5	**0.034**
Sodium (mmol/L)	139.2±3.1	138.3±4.5	0.083
Potassium (mmol/L)	4.6±0.7	4.7±0.7	0.247
ASA score	2.5±0.6	2.8±0.6	**0.001**
Surgery type (replacement), n (%)	74(50.3)	45 (49.5)	1.000
Type of anesthesia (general), n (%)	5(6.8)	18 (11.0)	0.354
Duration of anesthesia (minutes)	104.7±33.1	92.0±34.2	**0.008**
Need for intensive care, n (%)	28(37.8)	94 (57.3)	**0.008**
Number of transfused RBCs (units)	0.6±0.8	0.9±1.0	**0.040**
Pre-op length of stay (days)	6.8±5.0	6.9±4.1	0.858
Post-op length of stay (days)	5.7±3.4	6.5±6.7	0.334
Overall length of stay (days)	12.5±6.3	13.4±7.9	0.379
AKI, n (%)	8 (11.0)	39 (23.6)	**0.023**

*Significant p values are written in bold.
All given laboratory parameters are baseline values.
ASA: American Society of Anesthesiologists, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CHD: congestive heart disease, CKD: chronic kidney disease, CVA: cerebrovascular accident, eGFR: estimated glomerular filtration rate, RBC: red blood cell.

Predictors Of First-Month Mortality

In our cohort, 25 patients (10.5%) died within the first month. The preoperative serum creatinine, postoperative first day white blood cell and potassium levels were significantly higher (p=0.012, p=0.004 and p=0.037, respectively), whereas the preoperative serum albumin and postoperative hemoglobin levels were significantly lower (p=0.040 and p=0.038 respectively) in patients who died during the first month. Patients who died during the first month had a significantly longer preoperative hospitalization period and higher need for intensive care (p=0.021 and p=0.003 respectively). The rate of mortality at the first month was higher in patients who were operated under general anesthesia and who had more erythrocyte transfusion (p=0.021 and p=0.029 respectively). In addition, the patients who died during the first month had a higher prevalence of CHD, CKD and AKI (p=0.038, p=0.018 and p=0.014, respectively). However, according to multivariate analysis, only the presence of CHD (OR: 0.056, 95% CI: 0.005-0.644, p=0.021) and longer preoperative hospitalization period (OR: 1.266, 95% CI: 1.027-1.464, p=0.024) were associated with first month mortality.

Predictors Of First-Year Mortality

During the study period, 91 patients died within the first year. The mean age was higher in the non-surviving patients (p=0.007). The preoperative serum urea, creatinine and potassium levels were significantly higher (p=0.049, p=0.034 and p=0.044, respectively), whereas the preoperative serum sodium and postoperative hemoglobin levels were significantly lower (p=0.009 and p=0.008 respectively) in the patients who died within the first year. The need for intensive care and the prevalence of CKD and AKI were higher among the patients who died within the first year (p=0.016, p=0.019 and p=0.029, respectively). Multivariate logistic regression analysis revealed that age (OR: 1.063, 95% CI: 1.009-1.120, p=0.023), preoperative sodium (OR: 0.892, 95% CI: 0.800-0.995, p=0.041) and postoperative hemoglobin (OR: 0.724, 95% CI: 0.545-0.962, p=0.026) levels were significantly associated with first-year mortality.

Predictors Of Long-Term Mortality

The characteristics of the patients according to clinical outcomes are shown in **Table 2.** Compared to the survivors, the body mass index (BMI), duration of anesthesia, baseline serum hemoglobin and albumin levels were lower, while the mean age, ASA score, the number of transfused erythrocytes and baseline serum urea and creatinine levels were higher among the non-survivors. In addition, the prevalence of CKD, AKI and the need for intensive care were significantly higher in the non-surviving patients. **Figure 1** shows the Kaplan-Meier survival probabilities for all-cause mortality based on AKI. Patients who developed AKI during hospitalization had significantly increased long-term mortality compared to those without AKI (log-rank test, p=0.031). During the study period, 165 patients died. The median time of death after discharge was nine months and 49 patients died within the first three months. Overall, the 1-year, 2-year, 3-year, 4-year and 5-year all-cause death rates were 38.2%, 54.2%, 61.8%, 65.1%, and 68.1%, respectively.

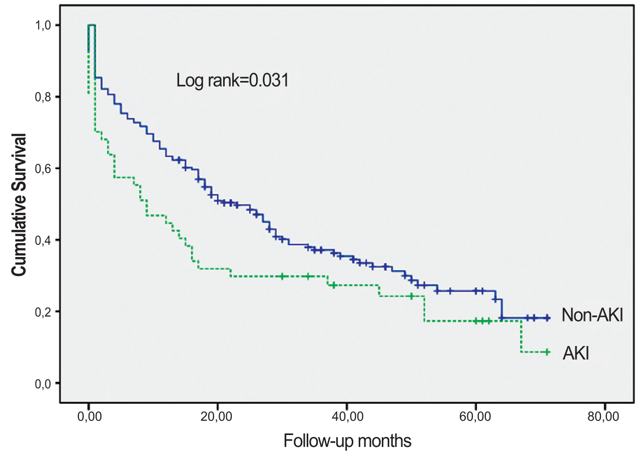

Figure 1 The effects of acute kidney injury after hip fracture surgery on long-term mortality

DISCUSSION

Studies show that AKI is associated with the duration of hospitalization, progression to chronic kidney disease, functional status in daily activities, and mortality risk in various populations (7,11,12). The short-term effects of AKI on the clinical outcomes in patients with hip fractures have been demonstrated in several studies, while the long-term impacts of AKI on survival have not been described well in this population.

In our cohort, AKI occurred in 19.7% of the patients according to the AKIN criteria.

Among AKI patients, most were classified as AKI Stage 1 (66.0%) and one patient progressed to AKI requiring dialysis. The reported incidence of AKI in elderly patients who underwent hip fracture surgery ranged from 15.3-24.4% (13-15). Elderly patients are particularly susceptible to developing AKI. Postoperative AKI is often multifactorial and may be caused by pre, peri, and postoperative factors. Baseline renal function, age, comorbidities, dehydration, nephrotoxic drugs, anemia, electrolyte imbalance and malnutrition are documented risk factors for AKI (5,13,16-19). In our study, the baseline serum levels of urea, creatinine, hemoglobin; postoperative serum levels of albumin, potassium; the number of transfused erythrocytes and the presence of CKD and comorbidities of more than one were significantly associated with an increased risk of AKI, whereas after multivariable adjustment, only CKD remained as an independent predictor, similar to outcomes from previous studies (6,11).

Studies have identified age, dementia, malnutrition, comorbidities, anemia, electrolyte imbalance, infection, prolonged hospital stay and duration of anesthesia as the predictors of mortality following hip fractures (5,6,12,14,19-23). In our study, the baseline serum levels of creatinine, albumin, the postoperative levels of white blood cell, potassium, hemoglobin, the number of transfused erythrocytes, longer preoperative hospitalization period, the need for intensive care and the presence of CHD, CKD, AKI and general anesthesia were significantly associated with the first-month mortality. After multivariable adjustment, only CHD and a longer preoperative hospitalization period remained as independent predictors (11,12,24). Our first month mortality rate (10.5%) was consistent with those from other studies (3,5). We also found out that the first-year mortality was associated with the baseline serum levels of urea, creatinine, potassium, sodium, postoperative level of hemoglobin, age, the need for intensive care and the presence of CKD and AKI. However, multivariate analysis revealed that age, preoperative sodium and postoperative hemoglobin levels were significantly associated with first-year mortality, similar to previous studies (4,7,25).

Acute kidney injury not only results in increased short-term survival but also adversely affects the long-term survival (2,12,26). We confirmed that AKI after hip fracture surgery was associated with increased long-term mortality. Excess mortality inpatients following hip fracture was documented and the increased mortality risk might persist for several years after the event (12,26). Mortality is usually highest during the first year after hip fracture (26,27), as confirmed by our study. In our cohort, the rate of all-cause mortality was 38.2%, 54.2%, 61.8%, 65.1%, and 68.1% at 1st, 2nd, 3rd,4th and 5th year, respectively. Our study suggests that age, ASA score, BMI, duration of anesthesia, the number of transfused erythrocytes and baseline serum urea, creatinine, hemoglobin and albumin levels were important predictors of long-term mortality, similar to previous studies (2-5,22,26). In addition, we confirmed that the prevalence of CKD, AKI and the need for intensive care were significantly higher in the non-surviving patients.

This study had several limitations. First, as an observational, retrospective study, there was an inherent design limitation. Second, AKI was defined according to increments in the serum creatinine level only, but not in urine output. Third, we do not know the causes of death of the participating patients. Finally, the contribution of each nephrotoxic medication to the development of AKI was not studied because the patients' daily medications and intraoperative drugs given could not be grouped due to high heterogeneity. As a matter of fact, polypharmacy was very common among our patients including angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs that are known to be associated with nephrotoxic effects. However, it was not possible to determine the individual contribution of these medications due to the multiplicity of combinations.

CONCLUSION

In summary, AKI is a mostly transient but frequently encountered complication after hip fracture surgery,and is associated with increased length of hospital stay, treatment costs, mortality and morbidity. Our findings suggest that baseline renal function is an independent predictor for the development of AKI. It may be prudent to request a nephrology consultation at the time of admission for patients at high risk of AKI. The early diagnosis and prevention of AKI might be very important to improve survival in these patients because hip fractures in the elderly are associated with a marked increase in mortality. However, prospective studies should evaluate the relationship between AKI and clinical outcomes and the benefit of early diagnosis and preventive management of AKI in patients with hip fractures.

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