

# Clinical outcomes of acute kidney injury developing outside the hospital in elderly

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## Abstract

**Purpose** Although various studies have improved our knowledge about the clinical features and outcomes of acute kidney injury developing in the hospital (AKI-DI) in elderly subjects, data about acute kidney injury developing outside the hospital (AKI-DO) in elderly patients (age  $\geq 65$  years) are still extremely limited. This study was performed to investigate prevalence, clinical outcomes, hospital cost and related factors of AKI-DO in elderly and very elderly patients.

**Methods** We conducted a prospective, observational study in patients (aged  $\geq 65$  years) who were admitted to our center between May 01, 2012, and May 01, 2013. Subjects with AKI-DO were divided into two groups as “elderly” (group 1, 65–75 years old) and “very elderly” (group 2,  $>75$  years old). Control group (group 3) consisted of the hospitalized patients aged 65 years and older with normal serum creatinine level. In-hospital outcomes and 6-month outcomes were recorded. Rehospitalization rate within

6 months of discharge was noted. Hospital costs and mortality rates of each group were investigated. Risk factors for AKI-DO were determined.

**Results** The incidence of AKI-DO that required hospitalization in elderly and very elderly patients was 5.8 % (136/2324) and 11 % (100/905), respectively ( $p < 0.001$ ), with an overall incidence of 7.3 % (236/3229). Chronic kidney disease (CKD) was developed in 43.4 % of group 1 and 67 % of group 2 within the 6 months of discharge ( $p < 0.001$ ). Progression to CKD was significantly lower in the control group than in groups 1 and 2 ( $p < 0.001$ ). Mortality rates for groups 1, 2 and 3 were 23.5 % ( $n = 32$ ), 31 % ( $n = 31$ ) and 4.2 % ( $n = 8$ ), respectively ( $p < 0.05$ ). Rehospitalization rate within the 6 months of discharge for the groups with AKI-DO was higher than for the control group ( $p < 0.001$ ). Hospital cost of groups 1 and 2 was significantly higher than that of the control group ( $p < 0.001$ ). Nonsteroidal anti-inflammatory drugs (NSAIDs) (OR: 6.839, 95 % CI = 4.392–10.648), angiotensin-converting enzyme inhibitors (ACEI) (OR: 7.846, 95 % CI = 5.161–11.928), angiotensin receptor blockers (ARB) (OR: 6.466, 95 % CI = 4.813–8.917), radiocontrast agents (OR: 8.850, 95 % CI = 5.857–13.372), hypertension (OR: 4.244, 95 % CI = 2.729–6.600), diabetes mellitus (OR: 2.303, 95 % CI = 1.411–3.761), heart failure (OR: 3.647, 95 % CI = 2.276–5.844) and presence of infection (OR: 3.149, 95 % CI = 1.696–5.845) were found as the risk factors for AKI-DO in elderly patients ( $p < 0.001$  for all). Patients with AKI-DO had higher 6-month mortality rate (HR 1.721, 95 % CI: 1.451–2.043,  $p < 0.001$ ). Mortality risk increased 0.519 times at 20th day.

**Conclusions** The incidence of AKI-DO requiring hospitalization is higher in very elderly patients than elderly ones, especially in male gender. Use of ACEI, ARB, NSAID and

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radiocontrast agents is the main risk factors for the development of AKI-DO in the elderly.

**Keywords** Acute kidney injury · Cost · Elderly · Gender · Outcome · Rehospitalization

## Background

Twelve percent of the total population consist of elderly individuals, and it is expected to rise to 21 % by the year 2040. This tendency causes a gradual rise in the number of rehabilitation beds, emergency and acute care beds, as seen mainly in the developed nations [1]. In this sense, the specific renal problems along with their management should be well defined in elderly people.

The increased incidence of acute kidney injury (AKI) in the elderly people is favored by certain predisposing factors such as histological and functional alterations in the aged kidneys, different pharmacokinetics of drugs, polypharmacy and associated comorbid diseases like diabetes mellitus (DM), hypertension (HT) and heart failure [2].

Acute kidney injury, even mild or moderate, can result in increased morbidity and mortality [3]. Elderly adults are more susceptible to AKI, but it is more important to understand whether AKI is associated with more or less severe consequences in elderly population. Although various studies have expanded our knowledge about clinical features and outcomes of acute kidney injury developing in the hospital (AKI-DI) in the elderly subjects [4], data about acute kidney injury developing outside the hospital (AKI-DO) in the elderly (age  $\geq$  65 years old) and very elderly patients (age  $\geq$  75 years old) are extremely limited. Although the incidence of AKI-DO was 3.5 times more than AKI-DI [5] and increased mortality was reported [6], the studies carried out are still not enough.

The aim of this study is to investigate the incidence, clinical presentations, risk factors, associated factors, mortality, hospital cost and outcomes of AKI-DO in elderly and very elderly patients.

## Patients and methods

A prospective, observational case–control study was designed, and patients aged 65 years and older who admitted to our center between May 01, 2012, and May 01, 2013, were included in the study. Data collection and analysis of the study were approved by the Human Research Ethics Committee (2012/104, 22.04.2012). Written informed consent was obtained from patients for their participation in the study.

## Subjects of the study

Patients were eligible for enrollment if they were aged  $\geq$  65 years and were diagnosed AKI-DO that needed hospitalization. As average life expectancy is 74 years in our country (<http://www.tuik.gov.tr/PreHaberBultenleri.do?id=8428>), patients were divided into two groups as “elderly” (group 1, 65–75 years) and “very elderly” (group 2, >75 years). Patients aged 65 years old and older who were hospitalized with normal serum creatinine level were included in the control group (group 3). The criteria for diagnosis of AKI were increase in serum creatinine level by 0.3 mg/dl within 48 h or increase in serum creatinine level to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or urine volume less than 0.5 ml/kg/h for 6 h [7]. Patients were followed up for 6 months after discharge from the hospital. Return of serum creatinine level back to normal range (serum creatinine: 0.6–1.1 mg/dl) was accepted as complete recovery.

## Data collection

Vital signs, plasma glucose, urea, serum creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, serum albumin, thyroid-stimulating hormone (TSH), liver enzymes, C-reactive protein (CRP) levels, analysis of arterial blood gases, urinalysis and albumin/creatinine ratio in spot urine sample were measured at admission for all subjects.

Serum urea, creatinine, sodium, fasting blood glucose, albumin were assessed by “Olympus AU 640, Japan.” Serum potassium, magnesium, chloride, calcium, phosphorus were measured by “Roche Cobas Integra 800 Chemistry Analyzer, Switzerland.”

Urinalysis was evaluated by “Urisys 2400/UF100, Japan.” Albumin/creatinine ratio in spot urine was assessed by “Roche Cobas Integra 800 Chemistry Analyzer, Switzerland.”

Estimated glomerular filtration rate (eGFR) was calculated for each participant by “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) formula which can be shown as  $CKD-EPI = eGFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$  [if female]  $\times 1.159$  [if black] [8].

## Exclusion criterias

Patients younger than 65 years of age, patients with chronic kidney disease (CKD) (eGFR < 60 ml/min, persistent proteinuria [ $>1$  g/day], persistent glomerular hematuria or persistently high serum creatinine level), patients with renal anatomic abnormalities including polycystic kidney disease, atrophic kidney(s) (vertical length <9 cm), bilateral

renal artery stenosis, renal artery stenosis of solitary kidney, transplanted kidney and patients with AKI-DI were all excluded from the study.

### Etiologic factors

Use of nephrotoxic agents like intravenous contrast agents, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), aminoglycoside, spironolactone, loop diuretics was recorded. Factors which may cause prerenal AKI like diarrhea, vomiting, decrease in oral intake, gastrointestinal bleeding were noted. Respiratory, urinary and gastrointestinal system infections were recorded. Comorbid diseases like DM, HT, cirrhosis, chronic obstructive pulmonary disease, Alzheimer's disease, neoplastic diseases, congestive heart failure, stroke, and eventually total number of comorbidities were recorded. The reasons for admission to the hospital were analyzed. Postrenal causes such as benign prostatic hypertrophy and prostatic adenocarcinoma, pelvic malignancies which may result in urethral obstruction, retroperitoneal fibrosis were investigated. Renal biopsy was performed for the patients whose etiology of prolonged AKI could not be determined.

### Clinical outcomes of AKI-DO

Clinical outcomes of AKI-DO like complete recovery, progression to CKD and in-hospital mortality and 6-month mortality rates were recorded. Clinical outcomes and mortality reasons of each group were compared with each other. Need for hemodialysis (HD), intensive care unit (ICU) and mechanic ventilator (MV), and length of hospital stay, hospital cost, mortality rates of groups were compared with each other. Rehospitalization rate of each group was calculated.

### Related factors of AKI-DO

Associations of AKI-DO and age, sex, serum potassium level, presence of infection, need for HD, need for ICU, duration of hospitalization, clinical outcomes (mortality, progression to CKD, recovery), hospital cost, number of comorbidities, use of NSAID, ACEI, ARB, radiocontrast agents were investigated.

### Risk factors for AKI-DO

Age, sex, number of comorbidities, presence of infection, HT, DM, heart failure, use of NSAID, ACEI, ARB and radiocontrast agents were investigated whether they were risk factors for AKI-DO. In addition to this, risk of AKI-DO due to specific drug combinations was investigated.

Risk of AKI-DO in the presence of specific comorbid disease was investigated. Mortality risk analysis was performed for patients with AKI-DO by using serum creatinine values.

Invoices regarding laboratory tests, imaging procedures, surgical interventions, histopathologic investigations, medications, feeding, consultations, medical equipment, and all supportive care performed during the hospital stay were evaluated in order to determine total hospital cost.

### Statistical analysis

MedCalc packet program was used for statistical analysis. Shapiro–Wilk test was used to identify whether variables were normal distribution. Mean  $\pm$  standard deviation was used for descriptive statistics for non-normal distribution variables. The mean comparisons of binary groups were done with Student's *t* test. Spearman correlation was used to test correlation between two continuous variables. Chi-square statistics were used to compare two categorical variables. Logistic regression and odds ratios were used for risk analysis.

### Results

The study included 3229 patients, aged  $\geq 65$  years. Group 1 consisted of 136 participants [male/female (M/F): 78/58], whereas group 2 consisted of 100 participants (M/F: 58/42), and group 3 (control group) included 190 subjects (M/F: 112/78).

### Incidence of AKI-DO

The incidence of AKI-DO in group 1 and group 2 was 5.8 % (136/2324) and 11 % (100/905), respectively ( $p < 0.001$ ), whereas the overall incidence of AKI-DO was 7.3 % (236/3229) in elderly patients. Incidence of AKI-DO was 4.2 % for males and 3 % for females ( $p < 0.05$ ). Clinical and laboratory parameters of the groups are shown in Table 1.

### Etiology of AKI-DO

Clinical features of the groups at admission are listed in Table 2. Frequency of prerenal, renal and postrenal causes for AKI-DO was 63, 27 and 10 % in group 1 and 63, 29 and 8 % in group 2, respectively. Prerenal factors were the most common cause of AKI-DO in both groups ( $p < 0.05$ ). Inadequate oral intake was the most common prerenal factor in both groups. Use of NSAID, ACEI, ARB, radiocontrast agents, loop diuretics, spironolactone and other nephrotoxic agents was 14.7 and 14, 37.5 and 35, 11.8 and 10,

**Table 1** Clinical and laboratory parameters of elderly and very elderly on admission

Parameters	Group 1 (n = 136)	Group 2 (n = 100)	Group 3 (n = 190)
Age (years)	69.6 ± 3.2 <sup>b,c</sup>	81.2 ± 4.2 <sup>a,c</sup>	75.5 ± 7.5 <sup>a,b</sup>
Systolic blood pressure (mmHg)	138.22 ± 45.3	139.32 ± 47.1	127.45 ± 6.5
Diastolic blood pressure (mmHg)	87.34 ± 28.4	88.12 ± 28.8	76.79 ± 4.6
Fasting blood glucose (mg/dl)	100.4 ± 21.2	98.6 ± 18.4	97.3 ± 12.2
ALT (U/l)	32.2 ± 8.9	29.7 ± 6.1	29.3 ± 5.7
ALP (U/l)	110.4 ± 11.5	115.6 ± 9.2	113.3 ± 8.8
Serum creatinine (mg/dl)	5.91 ± 2.2 <sup>b,c</sup>	6.68 ± 1.4 <sup>a,c</sup>	0.54 ± 0.2 <sup>a,b</sup>
eGFR (ml/min/1.73 m <sup>2</sup> )	8.89 ± 0.81 <sup>b</sup>	7.06 ± 0.73 <sup>a</sup>	99.35 ± 3.45 <sup>a,b</sup>
Hemoglobin (gr/dl)	11.44 ± 3.7	10.59 ± 4.2	11.56 ± 3.8
Potassium (mEq/l)	5.46 ± 1.4	5.62 ± 1.4	4.71 ± 0.5
Sodium (mEq/l)	134.43 ± 14.8	135.26 ± 8.4	133.54 ± 2.3
CRP (mg/l)	12.4 ± 6.1 <sup>b,c</sup>	23.1 ± 7.9 <sup>a,c</sup>	2.1 ± 0.5 <sup>a,b</sup>
Arterial blood pH	7.29 ± 0.3 <sup>c</sup>	7.30 ± 0.3 <sup>c</sup>	7.37 ± 0.3 <sup>a,b</sup>

ALT alanine aminotransferase; ALP alkaline phosphatase; CRP C-reactive protein; eGFR estimated glomerular filtration rate

<sup>a</sup> Shows the statistically significant difference when a parameter in group 1 is compared with the same parameter in another group

<sup>b</sup> Shows the statistically significant difference when a parameter in group 2 is compared with the same parameter in another group

<sup>c</sup> Shows the statistically significant difference when a parameter in group 3 is compared with the same parameter in another group

**Table 2** Clinic features of groups

Features	Group 1 (n = 136)	Group 2 (n = 100)	Group 3 (n = 190)
Need for ICU (%/n)	20.4/17 <sup>b,c</sup>	63/63 <sup>a,c</sup>	5.7/9 <sup>a,b</sup>
Need for HD (%/n)	27.7/38 <sup>b,c</sup>	39/39 <sup>a,c</sup>	6.3/12 <sup>a,b</sup>
Need for MV (%/n)	7.4/10	10/10 <sup>c</sup>	5.3/10 <sup>b</sup>
LHS (day)	6.8 ± 2.9 <sup>b,c</sup>	10.6 ± 4.7 <sup>a,c</sup>	4.7 ± 1.8 <sup>a,b</sup>
Mortality (%/n)	14/19 <sup>b,c</sup>	20/20 <sup>a,c</sup>	4.2/8 <sup>a,b</sup>
Cost (USD)	1383.3 ± 529.6 <sup>b,c</sup>	2.167 ± 1.213 <sup>a,c</sup>	120.7 ± 90.3 <sup>a,b</sup>
Number of comorbidities	2.5 ± 0.8 <sup>b,c</sup>	2.8 ± 0.6 <sup>a,c</sup>	1.3 ± 0.6 <sup>a,b</sup>
CKD (%)	43.4 <sup>b,c</sup>	67 <sup>a,c</sup>	5.3 <sup>a,b</sup>

ICU intensive care unit; HD hemodialysis; MV mechanic ventilator; LHS length of hospital stay; CKD chronic kidney disease; USD United States dollar

<sup>a</sup> Shows the statistically significant difference when a parameter in group 1 is compared with the same parameter in another group

<sup>b</sup> Shows the statistically significant difference when a parameter in group 2 is compared with the same parameter in another group

<sup>c</sup> Shows the statistically significant difference when a parameter in group 3 is compared with the same parameter in another group

11.8 and 15, 2 and 3, 4.4 and 3, 5.2 and 5.4 % for groups 1 and 2, respectively. Administration of nephrotoxic drugs was similar for two groups ( $p > 0.05$ ).

The most common reasons for admission to the hospital were as follows: infection/fever 40 versus 43 %, dyspnea 22 versus 11 %, oliguria 12 versus 17 %, vomiting/diarrhea 12 versus 13 %, others 14 versus 16 %, for group 1 and 2, respectively. Fever/focal infection was the most common

reason for admission in both groups. No significant difference was obtained between the admission reasons of two groups ( $p > 0.05$ ), other than dyspnea ( $p < 0.05$ ).

Males were exposed to radiocontrast agents more common than women (18.6 vs. 9.2 %,  $p < 0.05$ ), and use of NSAID (17.3 vs. 11.4 %,  $p < 0.05$ ), ACEI (41 vs. 29 %,  $p < 0.05$ ), ARB (13.1 vs. 8 %,  $p < 0.05$ ) was also more common in males. Other etiologic factors were similar in both groups.

## Comorbidities

In this study, majority of the patients with AKI-DO had  $\geq 2$  comorbid diseases. Among AKI-DO patients, 81.3 % had  $\geq 2$  comorbid diseases, whereas 18.7 % had  $< 2$  comorbid diseases ( $p < 0.001$ ). When groups were analyzed separately 73.5 versus 92 % of subjects had  $\geq 2$  comorbid diseases and 26.5 versus 8 % had  $< 2$  comorbid diseases for groups 1 and 2, respectively ( $p < 0.05$  for all). Only 25.8 % of control group had  $\geq 2$  comorbid diseases, whereas 74.2 % had  $< 2$  comorbid diseases ( $p < 0.05$ ). In control group, the number of the subjects with  $\geq 2$  comorbid diseases was significantly lower in comparison with groups 1 and 2 ( $p < 0.001$ ). A total of 85.2 % of males and 72 % of females had  $\geq 2$  comorbid diseases ( $p < 0.05$ ).

## Clinical outcomes of AKI-DO

The length of hospital stay, need for MV support, number of comorbidities were found to be higher in very elderly patients than in elderly subjects ( $p < 0.05$ ) (Table 2).

Need for ICU was 33.8 % for all patients with AKI-DO. Need for ICU in control group was significantly lower than in groups 1 and 2 ( $p < 0.05$ ) (Table 2). Need for HD was 32.6 % for all patients with AKI-DO, whereas it was significantly lower in control group than in groups 1 and 2 ( $p < 0.05$ ) (Table 2).

Rehospitalization rate of AKI-DO within 6 months after discharge was 15.6 % for all patients with AKI-DO. Rehospitalization was needed for 15 % of group 1 patients and 17 % of group 2 patients ( $p > 0.05$ ), whereas 8.4 % of patients in control group needed rehospitalization within this period. Need for rehospitalization during 6 months after discharge in groups 1 and 2 were higher than in control group ( $p < 0.001$ ).

Chronic kidney disease was developed in 53.3 % of the patients with AKI-DO during 6 months after discharge. Chronic kidney disease was developed 43.4 % of group 1 and 67 % of group 2 ( $p < 0.001$ ), whereas CKD developed in 5.3 % of control group. Development of CKD was lower in control group than in groups 1 and 2 ( $p < 0.001$ ) (Table 2).

Mortality rates of the patients with AKI-DO for the 6 months following their discharge were 26.6 %. Mortality rate of group 1 was 23.5 %, whereas it was 31 % for group 2 ( $p < 0.05$ ) and 4.2 % for control group. Mortality rate of control group was significantly lower than that of groups 1 and 2 ( $p < 0.001$ ) (Table 2).

Complete recovery was achieved in 20.1 % of AKI-DO patients within 6 months following discharge. When groups were analyzed, complete recovery rate of group 1 was 33.1 %, whereas it was 2 % for group 2 ( $p < 0.001$ ) and 90.5 % for control group (Table 2).

Hospital expenditure was  $1715 \pm 871$  USD (United States dollar) for all patients in groups 1 and 2. The mean hospital costs for elderly and very elderly groups were found to be  $1383.3 \pm 529.6$  USD and  $2167 \pm 1213$  USD, respectively ( $p < 0.05$ ). Hospital cost for control group was  $120.7 \pm 90.3$  USD. Hospital cost for control group was significantly lower than for groups 1 and 2 ( $p < 0.001$ ) (Table 2).

## Causes of mortality

The main causes of death were sepsis (61 vs. 63 %), cardiovascular problems (23 vs. 22 %), and miscellaneous (16 vs. 15 %) in elderly and very elderly subjects, respectively ( $p > 0.05$ ).

## Related factor of AKI-DO

There was no association between serum creatinine and age ( $r = 0.043$ ;  $p = 0.379$ ). There was positive correlation between serum creatinine and serum potassium level, duration of hospital stay, number of comorbid diseases, presence of infection, need for hemodialysis, need for ICU, mortality, NSAID, ACEI, ARB, spironolactone, loop diuretics and contrast agents ( $r = 0.368$ ,  $r = 0.281$ ,  $r = 0.688$ ,  $r = 0.783$ ,  $r = 0.807$ ,  $r = 0.731$ ,  $r = 0.406$ ,  $r = 0.578$ ,  $r = 0.675$ ,  $r = 0.876$ ,  $r = 0.767$ ,  $r = 0.403$ ,  $r = 0.566$ , respectively,  $p < 0.001$  for all).

## Risk factors for AKI-DO

Risk factors for AKI-DO for elderly patients were as follows: NSAID (OR: 6.839, 95 % CI = 4.392–10.648), ACEI (OR: 7.846, 95 % CI = 5.161–11.928), ARB (OR: 6.466, 95 % CI = 4.813–8.917), contrast agents (OR: 8.850, 95 % CI = 5.857–13.372), HT (OR: 4.244, 95 % CI = 2.729–6.600), DM (OR: 2.303, 95 % CI = 1.411–3.761), heart failure (OR: 3.647, 95 % CI = 2.276–5.844), presence of infection (OR: 3.149, 95 % CI = 1.696–5.845) ( $p < 0.001$  for all).

Age and sex were not independent risk factors for AKI-DO ( $p > 0.05$ ). Risk factors for AKI-DO are shown in Table 3. Risk of AKI-DO due to specific substance combinations is shown in Table 4. Use of ACEI, ARB, NSAID, loop diuretics, spironolactone, radiocontrast agents increases risk of AKI-DO more in the presence of comorbid diseases like heart failure, HT, DM. Risk of AKI-DO in a diabetic patient for the use of ACEI, ARB, spironolactone, NSAID, radiocontrast agents or loop diuretics was as follows: OR: 20.25 (95 % CI = 8.89–82.11), OR: 26.83 (95 % CI = 4.92–146.15), OR: 21.54 (95 % CI = 2.46–5.84), OR: 14.50 (95 % CI = 5.16–30.35), OR: 12.50 (95 % CI = 4.88–31.99), OR: 3.34 (95 % CI = 5.63–9.93),

**Table 3** Risk factors for AKI-DO

	Odds ratio (OR)	95 % Confidence interval (CI)	
		Lower	Upper
NSAIDs	6.839	4.392	10.648
ACEI	7.846	5.161	11.928
ARB	6.466	4.813	8.917
Spirolactone	5.430	2.474	4.981
Radiocontrast agents	8.850	5.857	13.372
HT	4.244	2.729	6.600
DM	2.303	1.411	3.761
Heart failure	3.647	2.276	5.844
Presence of infection	3.149	1.696	5.845

AKI-DO acute kidney injury developing outside the hospital; NSAIDs nonsteroidal anti-inflammatory drugs; ACEI angiotensin-converting enzyme inhibitors; ARB angiotensin receptor blockers; HT hypertension; DM diabetes mellitus

**Table 4** Risk factors of specific substance combinations use for AKI-DO

Specific substance combinations	Odds ratio (OR)	95 % Confidence interval (CI)	
		Lower	Upper
ACE + ARB	8.677	4.523	13.032
ACE + Spirolactone	10.964	5.655	21.257
ACE + NSAID	8.467	5.032	14.248
ACE + Radiocontrast agents	15.999	8.268	30.960
ACE + ARB + Spirolactone	12.943	5.270	15.179

AKI-DO acute kidney injury developing outside the hospital; ACEI angiotensin-converting enzyme inhibitors; ARB angiotensin receptor blockers; NSAIDs nonsteroidal anti-inflammatory drugs

respectively. Risk of AKI-DO in a patient with heart failure for the use of ACEI, ARB, spironolactone, NSAID, radiocontrast agents or loop diuretics was as follows: OR: 3.40 (95 % CI = 1.62–7.10), OR: 4 (95 % CI = 0.68–23.51), OR: 2.40 (95 % CI = 1.42–6.10), OR: 3.60 (95 % CI = 0.45–28.56), OR: 1.80 (95 % CI = 1.62–5.10), OR:

3.40 (95 % CI = 1.62–7.10), respectively. Risk of AKI-DO in a patient with hypertension for the use of ACEI, ARB, spironolactone, NSAID, radiocontrast agents or loop diuretics was as follows: OR: 24.15 (95 % CI = 6.59–44.50), OR: 2 (95 % CI = 1.07–3.71), OR: 3.19 (95 % CI = 1.250–2.750), OR: 3.59 (95 % CI = 1.75–4.14), OR: 3.69 (95 % CI = 2.75–5.14), OR: 2.69 (95 % CI = 1.75–4.14), respectively. All of the results are shown in Table 5.

Mortality risk at the end of 20th day after discharge was 0.519 times high. Mortality risk for patients with AKI-DO was increased at the end of 6th month after discharge (HR 1.721, 95 % CI: 1.451–2.043,  $p < 0.001$ ). Baseline cumulative hazard function is shown in Table 6.

## Discussion

Despite significant advances in healthcare technology over the past few years, the incidence of AKI-DO in elderly (65–75 year) and very elderly (>75 year) appears to be on increase. Although there are studies about AKI-DO in general population, data for elderly population are still insufficient. Retrospective studies which were held for AKI-DO in elderly might lead to inadequate or misleading data for short- and long-term clinical results of AKI-DO. Our study differs as it has a prospective design.

Incidence of AKI was 13.6/1000 patients/year for subjects aged 66–69 and 46.9/1000 patients/year for subjects aged older than 85 years [9]. Not enough studies have been carried out to find out incidence of AKI-DO. Furthermore, no study about clinical characteristics, hospital cost and outcome of AKI-DO has been published in our country.

We found the incidence of AKI-DO higher than the previously reported ones [10–12]. This may be related to the different risk factors among different populations.

Few studies in the published literature thoroughly attribute to the cause of AKI. Most common cause of AKI in elderly is acute tubular necrosis (53 %) [13]. However, Kaufman et al. reported that prerenal reasons were the most common etiologic factors of AKI-DO in African-Americans. Gastrointestinal diseases and inadequate oral intake were the most common prerenal factors [10]. In our study,

**Table 5** Risk for AKI-DO due to specific use of substances in the presence of specific diseases

	ACEI OR (95 % CI)	ARB OR (95 % CI)	Spirolactone OR (95 % CI)	NSAID OR (95 % CI)	Radiocontrast agents OR (95 % CI)	Loop diuretics OR (95 % CI)
DM	20.25 (8.89–82.11)	26.83 (4.92–146.15)	21.54 (2.46–5.84)	14.50 (5.16–30.35)	12.50 (4.88–31.99)	3.34 (5.63–9.93)
HF	3.40 (1.62–7.10)	4 (0.68–23.51)	2.40 (1.42–6.10)	3.60 (0.45–28.56)	1.80 (1.62–5.10)	3.40 (1.62–7.10)
HT	24.15 (6.59–44.50)	2 (1.07–3.71)	3.19 (1.250–2.750)	3.59 (1.75–4.14)	3.69 (2.75–5.14)	2.69 (1.75–4.14)

ACEI angiotensin-converting enzyme inhibitors; ARB angiotensin receptor blockers; NSAIDs nonsteroidal anti-inflammatory drugs; DM diabetes mellitus; HF heart failure; HT hypertension

**Table 6** Baseline cumulative hazard function

Time (days)	At mean of covariates	
	Cumulative hazard	Survival
3	0.005	0.995
5	0.006	0.994
8	0.010	0.990
9	0.035	0.965
10	0.058	0.943
11	0.068	0.935
12	0.098	0.906
13	0.119	0.888
14	0.145	0.865
15	0.181	0.835
16	0.227	0.797
18	0.284	0.753
19	0.377	0.686
20	0.519	0.595

prerenal AKI was the most common type of AKI in both groups. The most striking causes for prerenal AKI were decreased oral intake, vomiting and diarrhea.

Heart failure, CKD, renovascular disease, osteoarthritis and surgical operations are more frequent in elderly people. Therefore, possibility of exposure to iodinated radiocontrast agents, renin–angiotensin system blockers or NSAID is higher [14]. These agents may negatively affect renal hemodynamics and cause a risk for the development of AKI [15, 16]. In addition to this, comorbid diseases like heart failure, DM, cirrhosis may decrease renal perfusion and may increase AKI risk [17]. Details about comorbid diseases in elderly patients with AKI-DO have not been studied in any of the previous studies [5, 6, 18–20]. To the best of our knowledge, although Schissler et al. [18] reported frequency of comorbidities in patients with AKI-DO, they did not declare whether they were independent risk factor for AKI-DO. Similarly, Dreischulte et al. [21] reported that combination of NSAID and renin–angiotensin aldosterone system blockers or combination of loop diuretics and aldosterone antagonists was risk factors for AKI-DO. In our study, NSAID, ACEI, ARB, radiocontrast agents, HT, DM, infections were found to be independent risk factors for AKI-DO as supporting the previous studies. Unlike other studies, we tried to analyze the risk of AKI-DO due to specific drug combinations like ACEI-ARB, ACEI-NSAID, ACEI-spirolactone in a prospective design. In our study, we concluded that risk of AKI-DO was higher with drug combinations than with a single-drug use. Unlike other studies, we showed that ACEI, ARB, NSAID, loop diuretics and radiocontrast agents increase the risk of AKI-DO in the presence of specific diseases like DM, HT, heart failure.

Our study and the other studies about AKI-DO had various differences [Supplementary Appendix 1].

Sex difference was not emphasized in most of the studies [5, 18, 19]. Only Talabani et al. [6], Wonnacott et al. [20] reported that incidence of AKI-DO in males was higher than in females. However, they did not explain the reasons behind this. They did not declare whether sex was an independent risk factor. However, in our study we found higher incidence of AKI-DO in elderly males than in elderly females. We also found that male gender was not an independent risk factor for AKI-DO. This may be related to the increased number of comorbid diseases in males and more common use of radiocontrast agents, NSAID, ACEI, ARB in males.

Only some of the AKI cases were reversible in elderly population [22]. In a recent meta-analysis, Schmitt et al. [22] reported that recovery of kidney function after AKI is approximately 28 % and it is less likely to occur when the patient is older than 65 years. In contrast to this, AKI was an important risk factor for CKD [18, 23–25]. A recent meta-analysis study consisting of 17 studies evaluated the patients with AKI and showed that the risk of non-recovery of kidney function is significantly higher in patients older than 65 years [26]. Talabani et al. reported that short-term (3 months) and long-term results (3 years) of AKI-DO were poor. They declared that only 58 % of AKI-DO patients were recovered completely after discharge. Mortality for the first 3 months was 69 % for AKI stage 2 or stage 3, whereas 3-year mortality was 35 %. Progressive increase in serum creatinine level was observed in 83 % of patients who had AKI on a background of CKD and 49 % of the patients who had AKI without a background of CKD.

Talabani et al. [6] reported that patients who were hospitalized had more complete recovery and less mortality in comparison with outpatients. Der Mesropian et al. [19] performed a study in veterans with AKI-DO and AKI-DI, and they reported that 6 % of patients with AKI-DO had serum creatinine level doubled after 3 years following discharge. Schissler et al. declared that AKI-DO was associated with increased mortality, hospital stay, development of CKD in their study with 422 veterans with AKI-DO. In the same trial, mortality of AKI-DO patients was found to be 11.5 %. However, mortality rates after discharge were not determined [18]. Wonnacott et al. reported that CKD developed in 39.4 % of AKI-DO (mean age:  $74.4 \pm 15.4$ ) during 14 months following discharge. In addition to this, mortality rate was 45 % (43.7 % of them died in the hospital). It was interesting that most of these patients who died had stage 1 AKI. On the other hand, mortality and hospitalization rates were lower in patients with stages 2 and 3 AKI in the same study. They emphasized that AKI stage 1 was not benign as it was associated with increased mortality [20].

A Canadian study showed that absolute rates and adjusted hazard ratios for CKD were higher in 65 years or older patients with AKI-DO as compared to subjects younger than 65 years [27]. In our study, we found the mortality rates and rate of CKD development significantly higher in elderly and very elderly patients in comparison with control group. Control group with normal serum creatinine was aged above 65 years like the patient group. This may lead to more accurate statistical results. Mortality rate increased 1.7 times during the 6 months following discharge. Unlike the other studies, there was association between serum creatinine and mortality. Mortality rate of patients with increased serum creatinine was higher. Our study included 6 months data after discharge, and this was the main difference of our study. Talabani et al. [6] included all the patients who were hospitalized and outpatients, whereas we included only the patients who were hospitalized. For this reason, mortality rates belonged only to the patients who were hospitalized. Patients with CKD usually have comorbid diseases like HT, heart failure, DM. For this reason, they usually use multiple drugs. Patients with CKD may need HD, and rehospitalization may be required [28]. That is why unlike other studies we prefer to exclude CKD patients.

Schissler et al. reported that although there was no difference between the serum peak creatinine levels of AKI-DO and AKI-DI, mean hospital stay for AKI-DI was  $15.8 \pm 17.1$  days, whereas it was  $8.9 \pm 9.2$  days for AKI-DO. There was no association between serum creatinine level and duration of hospital stay [18]. In contrast to this trial, serum creatinine levels and duration of hospital stay were higher in very elderly patients when compared to elderly patients in our study. We found significant association between serum creatinine and duration of hospital stay. Duration of hospital stay was higher in the group with normal serum creatinine in elderly and very elderly when compared to control group.

Wonnacott et al. [20] carried out a study including AKI-DO and AKI-DI patients (mean age:  $74.4 \pm 15.4$  years), and the need for ICU was found 4.7 % for AKI-DO patients. In our study, 33.8 % of the patients needed ICU. Need for ICU in our study was much higher than the study results of Wonnacott et al. In their study, 80 % of the patients were in AKI stages 1 and 2. However, in our study mean serum creatinine level was 5.91 mg/dl for group 1 and 6.68 mg/dl for group 2. We found close association between need for ICU and serum creatinine level.

Schissler et al. [18] reported that only some of the patients with AKI-DO needed dialysis (5.5 %). Similarly, Wonnacott et al. [20] reported that 3.5 % of the patients with AKI-DO needed HD. In our study, 32.6 % of the patients with AKI-DO needed HD. Increased need for HD in our study might be related to the late admission of patients to the hospital (in late stages of AKI). However, in

the studies which were carried out by Schissler and Wonnacott most of the patients were in early stages of AKI.

Although there were many studies about the cost of AKI-DI [3, 29–31], there are no studies about hospital cost of AKI-DO elderly patients. We found the mean hospital cost of the elderly and very elderly groups as  $1383.3 \pm 529.6$  and  $2.167 \pm 1.213$  USD, respectively. Hospital cost was higher when compared to control group. The results may show high economic burden for our country.

## Limitations

Our study was a single-center and observational study, and long-term results of AKI-DO were not observed. In our study, the number of comorbid diseases is lower in control group and this may be a disadvantage. We only found out clinical outcomes following 6 months after discharge in our study. Longer follow-up period may be more appropriate for long-term results.

## Conclusions

Acute kidney injury developing outside the hospital is associated with increased mortality and morbidity and increased rehospitalization. The incidence of AKI-DO requiring hospitalization is higher in very elderly patients than in elderly ones. Cost of AKI-DO is high. Incidence of AKI-DO was higher in elderly males than in elderly females. Medications like ACEI, ARB, NSAID and radiocontrast agents are risk factors for AKI-DO. Therefore, clinicians should be cautious when prescribing such medications.

## Compliance with ethical standards

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

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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