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Original Paper

Clinical Course of Acute Kidney Injury in Elderly Individuals Above 80 Years

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Key Words
Acute Kidney Injury • Dialysis • Aging • Mortality • Length of Stay • Prognosis

Abstract
Background/Aims: Aging is associated with renal function decline and elderly patients are more vulnerable to acute kidney injury (AKI). The causes and prognosis of AKI according to new KDIGO definition that broadened the diagnosis and included more patients without dialysis dependence have not yet been compared between younger and elderly patients. ***Methods:*** In a retrospective analysis all patients with AKI admitted to a tertiary care Nephrology department (N=424) were included. Individuals were stratified by age (≤80 years, >80 years). Primary end-point was death or dialysis dependence at hospital discharge, secondary analyses addressed the need for dialysis, creatinine at discharge, mortality, and length of stay. ***Results:*** The distribution of AKI causes was different between the age groups. Circulatory AKI was the most important cause in both groups; however, septic or toxic AKI contributed relevantly in younger patients. Nevertheless, the number of patients reaching the primary end-point was similar (younger, 20.4%; older, 18.0%; OR 1.17, 95%CI, 0.703–1.948). While mortality tended to be higher in the older population, none of the secondary analyses indicated worse outcome for the older patients. ***Conclusion:*** The prognosis of AKI in elderly patients is not necessarily worse than in middle aged individuals. Nevertheless, older patients may be particularly vulnerable to circulatory or ischemic insults of the kidneys.

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Introduction

Acute kidney injury (AKI) is a frequent event and prognostically relevant for the patient. The US National Hospital Discharge Survey included all causes and clinical conditions and found that 19.2 cases of AKI occurred per 1.000 hospitalizations [1]. In the past, AKI was

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thought to be a fully reversible condition. However, recent data show this is not always true. Analyses of health care provider data show that episodes of AKI strongly enhance the risk to develop end-stage renal disease later on [2;3]. In addition, kidney failure is a risk factor for enhanced in-hospital mortality [4] and reduced life expectancy in those discharged after surviving AKI [5]. Current international recommendations on diagnosing AKI [6] broadened the diagnostic criteria and included more cases compared to the earlier literature. This is justified by the significant prognostic impact that even relatively "minor" deteriorations in GFR have [7;8].

The elderly are particularly vulnerable for renal insults. They often have comorbid conditions such as arterial hypertension, chronic heart failure or diabetes mellitus facilitating renal damage. The average use of medication potentially endangering kidney function rises with age. At the same time renal functional reserve declines [9]. It is therefore not surprising that epidemiological studies indicate an age-dependent increase of the risk to acquire AKI [10].

However, it is less clear whether established AKI also has a particularly unfavorable prognosis in the elderly. While a study showed that age enhances the amount of GFR lost by AKI [11] and a meta-analysis of 17 studies indicated that the elderly bear a higher risk of not recovering kidney function after AKI [12], several other studies could not show a clear difference in prognosis with age [13;14] Surprisingly, Hsu et al. found that patients with AKI at an age >80 years were less likely to receive dialysis treatment than younger individuals [10]. This finding might be biased by a different attitude towards providing dialysis to the elderly; however, differences in disease severity are another possible explanation.

The present study retrospectively evaluated all patients admitted to a tertiary Nephrology Department within a 36 month period who were diagnosed with acute kidney injury. These patients were divided into a group up to 80 years of age and a group beyond 80 years. Primary end-point of the chart analysis was a combination of death or permanent dialysis dependency at hospital discharge; secondary end-points were length of hospital stay and serum creatinine at discharge. The study tested the hypothesis that AKI has a more severe impact on the prognosis of older patients compared to younger individuals.

Patients and Methods

Patients

All charts of patients admitted to the Department of Nephrology, Halle University Hospital between Jan 1, 2009 and Dec 31, 2011 and coded with an ICD-10 N17.x code were retrospectively screened for inclusion in this study. Of 483 patients whose files were reviewed, 59 had to be excluded because they either were misclassified as acute kidney injury while suffering from progression of chronic kidney disease (n=17), because they had acute renoparenchymal disease such as systemic vasculitis (n=29), or because they did not fulfill KDIGO criteria [6] for the diagnosis of acute kidney injury (n=13). In all other cases, the diagnosis of AKI could be confirmed by chart review. The cause of AKI was adjudicated (circulatory insult, septic or toxic injury, or post renal disease) with supervision of an experienced nephrologist using all available information on the patients. The adjudication was done as follows: patients with ultrasound clues of urinary retention in whom catheterization led to improvement of kidney function were classified as 'post renal'. Patients with clinical clues of hypovolemia or shock in whom volume repletion and/or vasoconstrictive therapy led to improvement of kidney function were classified as 'circulatory'. Patients, in whom there was a clinical diagnosis of sepsis or severe infection together with a CRP level of at least 50 mg/l in the absence of post renal obstruction, were classified as 'septic'. Patients with a clinical diagnosis of contrast nephropathy or nephropathy due to intake of non-steroidal anti-inflammatory drugs (according to the assessment of the treating physician) were classified as 'toxic'. We chose very broad categories since it is often difficult to determine a single cause for AKI, particularly in the elderly. Comorbidity was quantified using the Charlson comorbidity index [15].

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Table 1. Demographic characteristics of the patients

Characteristics	
Age (median, range)	75.3 (19.0 – 98.9)
Gender (female n/%)	219/51,6 %
Kidney function prior to admission	normal: 105 (25 %) CKD ≥ 3: 288 (68 %) unknown: 31 (7 %)
Serum creatinine at admission (µmol/L, median, range)	308 (62 – 2326)
Serum urea at admission (mmol/L, median, range)	25.0 (2.2 – 77.1)
Charlson Comorbidity Index (median, range)	3 (0 – 13)

Classification of outcome

Patients were stratified into two age groups (≤80 years, >80 years). Severity of the acute kidney injury was categorized according to the stages 1-3 of the KDIGO recommendation [6]. Intense effort was put into the evaluation of renal function prior to the hospital stay (e.g. older charts, information from general physicians). Normal excretory renal function was assumed if a serum creatinine <89 µmol/L was documented in females or a serum creatinine < 103 µmol/l in males. If no information could be gained, previous kidney function was assumed to have been normal in order to determine the AKI stage. The need for intensive care treatment and/or renal replacement therapy, the need for dialysis at discharge, in-hospital mortality, length of hospital stay, and serum creatinine at discharge were obtained from full chart review. For multivariate analysis a combined end-point of death or dialysis dependence at hospital discharge was defined.

Statistics

Continuous variables are reported as median and range due to the lack of normal distribution for most of the parameters. Univariate comparison of gender and age groups was done by Wilcoxon test. Frequency comparisons were done by Fisher's exact test or chi-square test as appropriate. The influence of several clinical parameters on outcome of the patients was described by multivariable logistic regression analysis. Statistical calculations were done using Prism 5.0 (GraphPad Software, San Diego, CA, USA) and SPSS 20 (IBM, New York, NY, USA). An error probability of 0.05 was considered significant.

Results

Patient characteristics and influence of gender

Demographic characteristics of the 424 patients who were included in the analysis are given in table 1 and the age distribution is depicted in fig. 1. The average age of the female patients was higher (median, 79.1 vs. 71.3 years, p<0.0001) than that of male patients. The proportion of patients with impaired kidney function prior to the present hospitalization tended to be higher in females (female, 71% vs. male, 64 %, p=0.14). Nevertheless, females did not reach higher AKI stages than male patients (AKI 1 through 3, female 62 – 52 – 105 patients, male 51 – 37 – 117 patients, p=0.15). However, with regard to this categorization, the lower muscle mass in females might be a confounder, since they had lower admission serum creatinine levels compared to the male patients (median, females 283 µmol/L, males 336 µmol/L, p=0.0049). There were no gender differences with regard to Charlson comorbidity index, the need for ICU treatment, or in hospital mortality. Nevertheless, females less often received any dialysis treatment during the hospital stay (24 % vs. 36 % in males, p=0.011) and they less often remained dialysis dependent at hospital discharge (10 % vs. 19 % in males, p=0.015). A reason for the gender differences may be that females more often suffered from AKI caused by circulatory insult (61%) than men (48 %, p=0.01) while the latter more often had septic/toxic acute kidney injury.

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Table 2. Causes of AKI according to age groups. The contribution of septic and toxic causes of AKI to the total number of events was significantly higher in the younger patients (p=0.0097 by Fisher's exact test, septic/toxic AKI vs. all other causes).

	≤ 80 years	> 80 years	All patients
Circulatory insult	132 (48 %)	102 (68 %)	234 (55 %)
Septic/toxic AKI	104 (38 %)	38 (25 %)	142 (33 %)
Postrenal obstruction	17 (6 %)	2 (1 %)	19 (4 %)
Uncertain cause	21 (8 %)	8 (5 %)	29 (7 %)
Total	274	150	424

AKI causes and severity

The study population was separated into two groups up to 80 years and above 80 years of age. The younger had a median age of 69.2 (range, 19-79.9) years, the older of 84.6 (80.1-98.9) years. The older patients were more likely to be female than the younger ones (66% vs. 43%, p<0.001). The causes of AKI in younger and older patients are compared in table 2. The distribution of AKI causes was different between the age groups. The older patients more often suffered from circulatory AKI while there were more cases of septic/toxic AKI in the younger patients. The fraction of patients who already had impaired kidney function prior to the present incident was similar in both patient groups (younger vs. older, 70% vs. 78 %, p=0.12). Nevertheless, AKI tended to be slightly milder in the older patients (n.s., Figure 2). There was no difference in median serum creatinine at hospital admission between the age groups (median, younger, 308 µmol/L; older, 307 µmol/L, p=0.534). In addition, comorbidity as estimated by Charlson comorbidity index was similar between age groups (younger, mean 3.09, median 3 (0-13); older, mean 3.02, median 3 (0-9)).

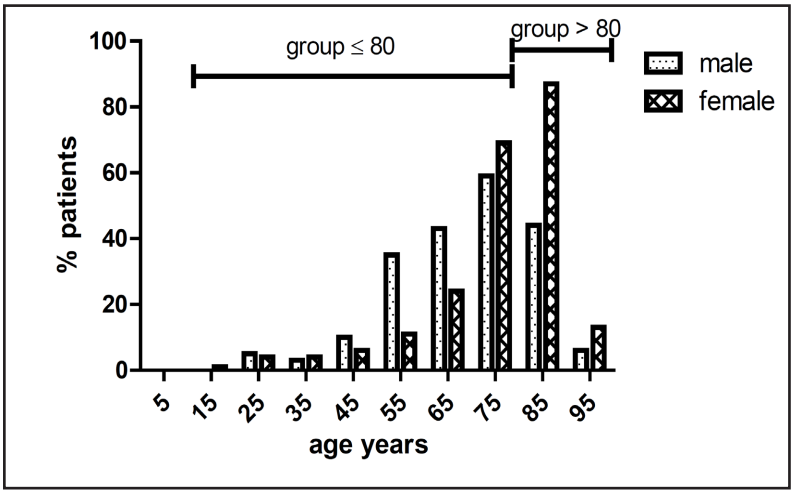


Fig. 1. Age distribution of the study group, separated by gender.

Outcome according to age

The primary end-point of death or dialysis dependence at hospital discharge occurred in 56/274 (20.4%) of the younger and 27/150 (18.0%) of the older patients (OR 1.17, 95% CI, 0.703 – 1.948, p=0.61). Table 3 compares the details of the outcome of AKI between age groups. Mortality tended to be slightly higher in the older patient group. In the younger group more patients received dialysis during their hospital stay and more patients remained on dialysis at hospital discharge. The in hospital stay was two days longer in the younger individuals and from both groups dialysis-free survivors reached the same degree of kidney function at discharge.

Additional sensitivity analysis was done to test if the cause of AKI mattered with regard to age-dependent outcome differences. Therefore, only patients with circulatory AKI were analyzed. This approach reduced patient numbers (n=234), and the results need to be interpreted with care, however, they may nevertheless give important hints. The analysis rendered

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Table 3. Outcome of AKI according to age groups (p for Fisher's exact test or Wilcoxon test as appropriate).

	≤ 80 years (n=274)	> 80 years (n=150)	OR (95% CI) younger vs. old	P
ICU admission	74 (27,5 %)	25 (17 %)	1.85 (1.12-3.07)	0.016
Any dialysis	97 (36%)	31 (21 %)	2.1 (1.32-3.35)	0.0019
In hospital mortality (n, %)	12 (4.5 %)	14 (9.5 %)	0.44 (0.2-0.99)	0.056
Dialysis at discharge (n, %)	44 (17%)	13 (9.5 %)	2.07 (1.07-3.98)	0.036
Length of hospital stay (days, median, range)	13 (2 – 121)	11 (1 – 81)	-	0.026
Creatinine at discharge in patients not on dialysis (µmol/L, median, range)	116 (27 – 587)	133 (46 – 979)	-	0.12

a more homogenous patient group and produced very similar results as in table 3. Still, there was no difference in the number of patients reaching the primary end point (younger, 21/132; older 10/102; OR 1.74 (0.78-3.88), p=0.24). Only the difference between both groups for dialysis dependence at hospital discharge increased (younger, 15/128; older 2/99; OR 6.44 (1.44-28.87), p=0.005). Further, the distribution of AKI stages across age groups remained the same as for the entire cohort.

Another sensitivity analysis excluded all patients with AKI 1 stage. This did not change any of the findings of table 3.

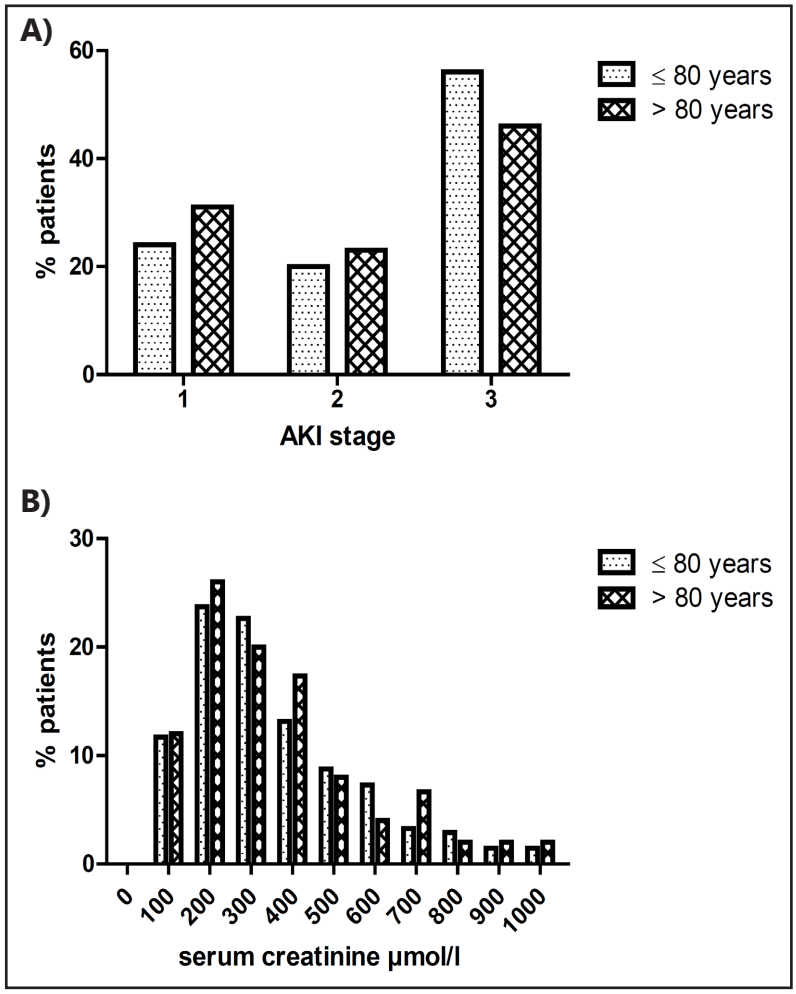


Fig. 2. A) Severity of AKI (KDIGO AKI stages) according to age group. B) Distribution of serum creatinine values at entry according to patient age group.

Multivariable logistic regression was done to detect the variables being predictive for adverse outcome. Therefore, the combined end-point of in hospital death or dialysis dependence at hospital discharge was used. Table 4 shows that gender, AKI stage, the Charlson comorbidity index, and preexisting renal dysfunction were predictive for adverse outcome while age was not.

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Table 4. Multivariable logistic regression analysis with combined end-point of adverse outcome (combination of death or dialysis dependence). Gender (reference category female), AKI stage (reference category 3 vs. all other), and preexisting renal dysfunction (CKD ≥ 3 vs. no/unknown) were included as dichotomic variables. Charlson comorbidity index (range 0 – 13) and age were included as continuous variables. The table lists the regression coefficient B with standard error (SE), the effect coefficient Exp(B), and the error probability p from Wald statistics.

	B	SE	Exp(B)	P
Gender	-0.619	0.271	0.538	0.022
Age	-0.005	0.009	0.995	0.615
AKI stage	1.012	0.277	2.750	<0.001
Charlson index	0.120	0.057	1.128	0.034
Preexisting renal dysfunction CKD ≥ 3	0.681	0.311	1.976	0.029

Discussion

Our data does not confirm the expectation that AKI necessarily has a worse prognosis in the elderly compared to younger individuals. In addition, age did not influence the severity of AKI either. This is even more surprising since the older group of patients tended to have a higher prevalence of preexisting kidney impairment. The older group needed both ICU treatment and dialysis treatment less frequently than their younger counterparts. The mortality was slightly higher, however, older survivors had a shorter length of hospital stay and less often stayed dialysis dependent at hospital discharge.

Although this is a retrospective evaluation, the younger and older patient groups seem to be quite comparable in terms of initial serum creatinine, severity of AKI, and comorbidity. There was a certain gender bias with more females in the older group. The multivariable analysis did not give any hint on worse prognosis in relation to patient age. Although the distribution of AKI causes was somewhat different between the younger and older patients, this also did not have an influence on outcome.

Most likely, the kidneys of elderly individuals are more vulnerable and prone to dysfunction than those of younger people. It is not fully established whether there is inevitable senescence of the kidneys or older people simply have had more time to acquire renal damage through hypertension, diabetes, or toxic effects – or both. Epidemiologic studies show that the prevalence of impaired renal function is strongly associated with age [16]. Histologic studies on clinically healthy living kidney donors suggest an age dependent increase in sclerotic alterations of the glomeruli [17]. This may be an explanation for a decrease in GFR and reduced functional reserve beyond 60 years [18].

Several studies have shown a relation between AKI and higher age. A population based evaluation of the incidence of AKI in Scotland indicated a median age of 76 years for the affected patients [19]. Patient age was a predictor of AKI in patients needing ICU treatment [20]. The same observation was made in a population based study including all types of hospitalizations [21].

At present few studies directly compared the outcome of AKI between age groups. Van den Noortgate et al. compared 42 patients < 70 years with 40 patients ≥ 70 years, all of whom required dialysis following cardiac surgery [13]. On the background of very high overall mortality, they did not find age related differences. The study did not include patients with AKI according to current definition but selected them for the need of dialysis treatment. A large registry evaluation [2] showed the strong impact of AKI on the risk of subsequent development of ESRD. The mean patient age of this sample from the Medicare registry was 79.2 years. Surprisingly, the risk of ESRD declined with any 5 years increment above 75. In their 1998 publication, Pascual and Liano reported on a truly geriatric patient group with AKI [14]. The definition of AKI was not consistent with current recommendations. Nevertheless, this study indicated that the prognosis was not different across age groups.

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Recently, a long-term follow-up of a randomized trial comparing high-intensity vs. low-intensity renal replacement therapy for AKI has been published [22]. While neither in the original trial nor in the follow-up treatment dialysis intensity predicted outcome, age and pre-existing renal dysfunction significantly mattered in terms of mortality. The initial trial enrolled ICU patients with dialysis dependent AKI, thus comparison with our patients is difficult. Further, the reference age category for the predictive value of age was <56 years old.

Studies on more specific causes of AKI also produced inconsistent results: Patients developing AKI after contrast media application were older than those not developing AKI (77 ± 7 vs. 73 ± 8 years) suggesting that age enhances susceptibility to acute kidney damage [23]. On the other hand, age did not influence the risk of renal damage by Vancomycin nephrotoxicity [24].

Adjudication of the causes of AKI is difficult [25], particularly in retrospective analysis. Therefore, the cause distribution has to be interpreted with caution. Our data are consistent with those reported by Pascual and Liano [14] since both studies indicate that circulatory or ischemic insults to the kidneys are the most important causes of AKI particularly in the elderly.

The obvious effect of gender on outcome of AKI was quite unexpected. Females were older but nevertheless had a better outcome of AKI. In contrast, Sidhu et al. [26] indicated that elderly women are at particularly high risk for nephrotoxic AKI after cardiac catheterization. The women in our study relatively often suffered from AKI due to dehydration and circulatory insult.

Limitations of this study: This is a retrospective analysis that selected patients through administrative coding. Most likely, not all patients who reached the KDIGO definition of acute kidney injury were also coded ICD N17.x and subsequently included in this analysis. Waikar et al. [27] compared ICD-9 coding with the incidence of dialysis dependent AKI and pointed out the low sensitivity of administrative coding. However, this effect most likely is not age-specific. Chao et al. [28] indicated that the AKI 1 stage might not be suitable for patients > 65 years of age. In contrast to younger populations, reaching AKI 1 criteria does not separate patients from those without AKI in terms of prognosis. This may reflect the lower muscle mass and the lower creatinine production in the elderly. However, our sensitivity analysis indicated that all findings are also true if only patients with AKI stages 2 and 3 are considered. The use of tubular damage markers for AKI such as NGAL (and others as reviewed in [29]) might have been useful, however, such data were not available.

Conclusions

In patients admitted to a tertiary care Nephrology Department for AKI, the course of renal failure and its prognosis is not very different between patients above 80 years of age and younger patients. Therefore, the elderly should receive at least the same attention to prevent and recognize AKI. Further, age alone should not be an argument to refrain from using all therapeutic measures, including dialysis.

Disclosure Statement

All authors declare to have no conflict of interest.

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