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Acute Kidney Injury in the Elderly: Epidemiology, Risk Factors and Outcomes

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Abstract

Structural and functional changes affecting the aging kidney predispose to an increased risk of Acute Kidney Injury (AKI) in the elderly, a condition which is becoming more and more relevant with the increase in life expectancy. The epidemiology of AKI in the elderly is not well assessed, because of the variable etiology, the coexistence of several comorbidities, the various clinical settings and geographical areas where the condition is managed, and the lack of uniform definition criteria. Currently, the use of the term AKI is suggested to mean any abrupt reduction in kidney function, while acute renal failure is just meant to indicate severe dysfunctions requiring renal replacement treatment. Comorbidities, common among elderly patients and several age-related conditions are risk factors for AKI. Moreover, also in elderly patients the presence of baseline proteinuria and reduced glomerular filtration rate are both powerful independent risk factors for AKI. Elderly patients with Chronic Kidney Disease (CKD) who develop AKI are at high risk for mortality, non-recovery from AKI and progression to more advanced stages of CKD and even to end-stage renal disease. As a consequence, the challenge for nephrologists is to find strategies to either prevent AKI or prevent the transition from AKI to CKD.

Keywords: Acute kidney injury; Elderly

Introduction

The elderly are the fastest growing age group of the general population. In Western Europe and in the United States, the number of subjects aged >60 years is projected to rise from 231 million in 2000 to 395 million in 2050 [1]. Recently, also in China a continuous growth of people older than 70 has been reported as a consequence of the increase in life expectancy [2].

Epidemiological data confirm that, as an effect of improvements in life expectancy and of aging population, the median age of patients suffering from Acute Kidney Injury (AKI), formerly indicated as Acute Renal Failure (ARF), is increasing too [3].

Therefore, in the elderly, the increasing incidence of AKI is higher worldwide and is a concern that is becoming more and more relevant. For example, in China, patients aged 80 years or older are the segment of population in which the incidence of AKI has recently been reported to increase most rapidly [2]. This has induced some authors to investigate the real proportion of the problem and whether the true epidemic in renal disease is AKI or Chronic Kidney Disease (CKD) [4-6]. Patients with AKI who are admitted in Intensive Care Units (ICUs) have a longer length of stay, higher hospital mortality and, in case of surviving, a 5-20% risk of dialysis-dependence [4]. In elderly patients, both CKD and AKI are often associated, but the recovery of kidney function is less complete than in patients affected by AKI alone [4].

While incidence of AKI has been progressively increasing over the recent past years, with older age, male gender and black race being associated conditions [7], its epidemiology in the elderly is far from being well assessed, due to the variable etiology, the coexistence of several comorbidities, the various clinical settings and geographical areas where the condition is managed, and the lack of uniform definition criteria [6].

This lack of standardized definitions and classification may have produced an incomplete understanding of the natural history of AKI and of the interactions between the kidney and other organ system failure [8].

Structural and Functional Changes Occurring in the Aging Kidney

The anatomical and physiological changes that occur in the kidneys with advancing age are not only the consequences of normal organ senescence but also of specific diseases, such as atherosclerosis or diabetes mellitus, which occur with greater frequency in the elderly [9].

The structural changes occurring in the normal aging of the kidney are listed in box 1 [10].

In particular, the concept of nephrosclerosis in the aging kidney has been recently reviewed by Glassock and Rule [9]. It is hypothesized that fibro-intimal hyperplasia occurring with aging in small arteries leads to glomerulosclerosis, followed by local tubular atrophy and interstitial fibrosis, and that such a constellation of findings contributes to the development of nephrosclerosis [11]. Nephrosclerosis, defined by 2 or more of these abnormalities, has been found to progressively increase with age: 2.7% for 18 to 29-year-olds, 16% for 30 to 39-year-olds, 28% for 40 to 49-year-olds, 44% for 50 to 59-year-olds, 58% for 60 to 69-year-olds, and 73% for 70 to 77-year-olds.

The sclerotic glomeruli of aging kidneys are smaller than the remaining functional glomeruli, in which a compensatory hypertrophy develops; both an increase in the proportion of small sclerosed glomeruli and an increase in the size of functional glomeruli may occur with age [12].

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Parenchyma: reduced total mass

Glomeruli: decreased epithelial cells, increased mesangial cells, sclerosis

Afferent arterioles: hyalinosis

Glomerular capillaries: atrophy

Proximal tubules: decreased number and length

Distal tubules: diverticula and cysts

Interstitium: fibrosis

Arterial vessels: atherosclerosis and constriction

Box 1: Structural changes occurring in aging kidney [10].

Conversely, the functional changes occurring in aging kidney are the reduction of renal blood flow, the declining Glomerular Filtration Rate (GFR) and ultra-filtration coefficient, the reduction of both urine concentration and dilution capacity and sodium handling [10].

Such changes progressively alter renal sensitivity to vasoconstrictors and vasodilator agents, producing an imbalance of the two processes in which there may be a role for accumulation of endogenous inhibitor of nitric oxide synthetase asymmetric dimethylarginine (ADMA) [13] and reducing autoregulatory capacity and functional reserve [6,14,15]. This explains the increased risk of AKI in the elderly [2], especially in hypertensives [16], in which a faster decline of creatinine clearance with age has previously been reported [17].

Current Definitions of Acute Renal Failure and Acute Kidney Injury

Because of the problems due to the use of the serum creatinine, until recently there has been no general consensus on the definition of acute renal failure [18]. The poor accuracy of the serum creatinine in reflecting the actual GFR in case of non-steady state may explain this lack of consensus and the existence of more than 30 different definitions of acute renal failure in the literature. This great variety of definitions created much confusion and made it difficult to compare results from the several studies in this area. In 2004, the Acute Dialysis Quality Initiative (ADQI) group proposed the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria for diagnosis and stratification [19]. The RIFLE criteria refer to increasing degrees of renal function loss (defined on the basis of relative increases in serum creatinine from baseline or duration and severity of oliguria) and clinical outcome measures (persistent acute renal failure) to develop a consensus definition and classification of acute renal failure [10]. However, such stratification has some limitations, as those reported in the NEiPHROS-AKI survey [20] where the serum creatinine criteria strongly predicted ICU mortality, whereas the urine output did not [18]. The existence of these limitations moved the Acute Kidney Injury Network (AKIN) to propose several refinements to the RIFLE criteria, with the addition of the words 'Acute Kidney Injury' (AKI) to represent the entire spectrum of acute renal failure and with the addition of an absolute increase in serum creatinine of ≥ 0.3 mg/dL and a 48-hour period as the time over which the decline in kidney function has to occur [3,21]. AKIN proposed 3 different stages for AKI, related to the RIFLE criteria: stage 1 (Risk), stage 2 (Injury) and stage 3 (Failure), and removed RIFLE levels of Loss and End-stage renal disease, considered as outcomes rather than stages.

Currently, the use of the term Acute Kidney Injury (AKI) is suggested to mean any abrupt reduction in kidney function, while the meaning of Acute Renal Failure (ARF) is restricted to indicate severe dysfunctions requiring renal replacement treatment or other supportive interventions [3].

Epidemiology

The epidemiology of acute kidney injury around the world is still widely undefined because of the different criteria used for ascertainment and the various clinical settings and geographical areas where the condition is managed. In developed countries, in which elderly patients predominate, the epidemiology of AKI differs from that of developing areas [7].

Reported incidences of AKI in the elderly also vary according to the population studied, namely community, hospitalized or ICU patients.

In the USA, an incidence of AKI of 3.1% has been reported in a cohort of 233,803 elderly hospitalized patients evaluated in 2000 [22] and of 2.38% among Medicare beneficiaries of hospital discharges between 1992 and 2001 [7]. Among the patients of the community-based cohort of the Kaiser Permanente of Northern California, the incidence of non-dialysis requiring AKI was found to increase from 78 per 100,000 person-years in patients aged <50 to 3,545 per 100,000 person-years in patients aged 80 or more [3,23].

In Scotland, an incidence of AKI of 1,811 cases per million populations and an incidence of acute-on-chronic renal failure (ACRF) of 336 per million populations, respectively, have been reported; noteworthy, the median age was 76 years for AKI and 80.5 years for ACRF [24].

In some studies carried out in Spain, an overall incidence of AKI of 209 cases per million population was reported [25], with an incidence of AKI 3.5 times higher in hospitalized patients older than 70 years than in younger patients and 5 times higher in those older than 80 years than in younger ones [26].

In Italy, an incidence of AKI 10 times higher among hospitalized patients aged 65 years or more that in younger counterpart has been reported [27].

In 2010, Fang et al. [28] reported an incidence rate of AKI of 4.10% in Chinese patients aged 60 to 80 years and of 6.17% in patients aged >80 years who were admitted to a University Hospital in Shangai.

More recently, Wen et al. [2] reported an incidence of AKI of 2.76% in patients aged 65 to 80 years and of 14.8% in patients aged ≥ 80 years who had been admitted to a tertiary metropolitan hospital in Beijing.

With regard to the epidemiology of AKI in ICU patients, in the BEST Kidney study, 5.7% of 29,269 critically ill patients had ARF during their ICU stay, and 4.3% were treated with Renal Replacement Therapy (RRT). Overall hospital mortality was 60.3%, and among survivors dialysis dependence at discharge was 13.8%; noteworthy, the median age of the patients with ARF was 67 years [29].

In the NEFROINT study, a prospective, observational, multicenter study designed to evaluate all incident admissions in 10 ICUs, the median age was 66 years; 42.7% of 576 patients evaluated had AKI

Authors	Reference	Incidence
Wen et al., China	[2]	2.76% (aged 65-80) 14.8% (aged >80)
Xue et al., USA	[7]	1.85% (aged <65) 2.86% (aged >85)
Ishani et al., USA	[22]	3.1%
Hsu et al., USA	[23]	78/100,000 person-yrs (aged <50) 3,545/100,000 person-yrs (aged ≥ 80)
Ali et al., Scotland	[24]	1,811 cases per million population
Liano and Pascual, Spain	[25]	209 cases per million population
Pasqual et al., Spain	[26]	3.5-times higher (aged >70) 5-times higher (aged >80)
Baraldi et al., Italy	[27]	10 times higher in aged ≥ 65 vs. ≤ 65
Fang et al., China	[28]	4.10% (aged 60-80) 6.17% (aged >80)
Uchino et al., multinational	[29]	5.7%
Garzotto et al., Italy	[30]	65,8%

Table 1: Incidence of acute kidney injury (AKI) in the elderly.

within 24 hours of ICU admission, while 23% developed new AKI later during their ICU stay [30].

Data on incidence of AKI from major studies are summarized in table 1.

Risk Factors for Acute Kidney Injury: Role of Comorbidities and Age-Related Factors

Comorbidities are common among elderly patients [6]. In an analysis conducted in 1999 on a sample of 1,217,103 Medicare beneficiaries aged 65 and older living in the US, 65% of the participants were found to have 2 or more chronic conditions, 43% had 3 or more chronic conditions and 24% had 4 or more chronic conditions [31].

Comorbidities and age-related factors can be summarized as follows: structural and functional changes in the kidney, multiple chronic comorbid conditions (CKD, cardiovascular disease, diabetes mellitus, abnormal lipid levels, vitamin D deficiency, sepsis, malnutrition), medication-related toxicity (non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, radiocontrast agents, nephrotoxic antibiotics), oxidative stress (with the following increase in reactive oxygen species, free radicals, and advanced glycation end products), hypovolemia and arterial hypotension, surgery (type of operation, duration of cardiopulmonary bypass) [32].

Currently, in the elderly other age-related factors, such as the telomere shortening [33], the Dicer and altered expression of specific associated microRNAs [34], the relationship between autophagy and heme-oxygenase-1 [35], Klotho deficiency [36], are thought to be involved in mechanisms predisposing to or modulating recovery from AKI [6].

Risk Factors for Acute Kidney Injury: Role of Proteinuria and Reduced Glomerular Filtration Rate

In 2008, Hsu et al. [37] compared 1,764 hospitalized adult members of Kaiser Permanente of Northern California who developed dialysis-requiring acute renal failure (mean age at hospitalization: 65.4 ± 14.1 years) with 600,820 hospitalized members who did not (mean age: 57.3 ± 17.2 years). The adjusted Odds Ratios (ORs) increased significantly and progressively from 1.95 to 40.07 for patients with stages 3 - 5 of CKD compared to patients with estimated GFR in stages 1 - 2 of CKD. Pre-admission baseline Diabetes Mellitus (DM), hypertension and proteinuria were also independent risk factors for AKI. In particular, patients with DM were at higher risk of AKI compared with their counterparts without DM in the same GFR category. The study showed

that the propensity to develop in-hospital AKI is another complication of CKD and that the risk markedly increases even in the upper half of stage 3 estimated GFR.

In 2010, Huang et al. [38] reported the results of a prospective analysis carried on a cohort of adult patients (mean age 65.7 ± 11.0 years) in Taiwan who underwent Coronary Artery Bypass Grafting (CABG) between 2003 and 2007. Proteinuria, measured with a dipstick, was defined as mild (trace to 1+) or heavy (2+ to 4+). Among a total of 1,052 patients, cardiac surgery-associated acute kidney injury (CSA-AKI) developed in 183 patients (17.4%) and required Renal Replacement Therapy (RRT) in 50 patients (4.8%). In a multiple logistic regression model, mild and heavy proteinurea were each associated with an increased Odds Ratio (OR) of CSA-AKI, independent of CKD stage and the presence of DM (mild, OR 1.66; heavy, OR 2.30). Heavy proteinuria was also associated with increased OR of postoperative RRT (OR 7.29). Thus, preoperative proteinuria could be considered a predictor of CSA-AKI among patients undergoing CABG.

In 2010, Grams et al. [39] prospectively analyzed a cohort of 11,200 participants in the Atherosclerosis Risk in Communities (ARIC) study for the association between baseline urine albumin-to-creatinine ratio (UACR) and estimated GFR (eGFR) with hospitalizations or death with AKI. During the 8.0 years of the average follow-up period, the incidence of AKI was 4.0 per 1000 person-years and hospitalizations for AKI were 492 (2.8% of a total of 17,265 hospitalizations). Noteworthy, the mean age of the AKI-patients was 64.7 years vs. 62.8 years of non AKI-patients. Using participants with UACRs <10 mg/g as a reference, the relative hazards of AKI, adjusted for age, gender, race, cardiovascular risk factors and categories of eGFR were 1.9, 2.2, and 4.8 for UACR groups of 11 to 29 mg/g, 30 to 299 mg/g and ≥ 300 mg/g, respectively. Similarly, the overall adjusted relative hazard of AKI increased with decreasing eGFR. Therefore, these data from a large, prospectively followed population-based cohort demonstrated that UACR and eGFR exhibit a strong, independent and graded association with incidence of AKI, also in older patients.

A similar association of proteinuria and GFR with AKI was reported in 2010 by James et al. [40] who used a large sample (920,985) of adults in Alberta, Canada, 10% of whom with a mean age of 67 to 78 years. The aim was to investigate how eGFR and proteinuria jointly modified the risk of AKI and of subsequent adverse clinical outcomes. During a median follow-up of 35 months, 6,520 participants (0.7%) were admitted with AKI and 615 (0.06%) with AKI requiring dialysis. Patients with normal eGFR values (≥ 60 mL/min per 1.73 m²) and mild proteinuria (urine dipstick trace to 1+) had 2.5 times the risk of hospital admission with AKI than did patients with no urinary protein; this risk was 4.4-fold increased for patients with heavy proteinuria (urine dipstick ≥ 2+). The authors concluded that the risk of admittance to hospital for patients with AKI increased with heavier proteinuria and reduced eGFR.

In 2011, Hsu and Hsu [41] reviewed the above 4 studies and stated that, on the whole, these data confirm that also in older patients the presence of baseline proteinuria and reduced GFR are both powerful independent risk factors for AKI, that even a very mild degree of proteinuria predicts increased risk of AKI, that the risk of AKI increases along the severity of baseline proteinuria, and that there is a graded association between reduced eGFR at baseline and risk of AKI, independently of proteinuria.

Mortality

Acute kidney injury is associated with an extremely high mortality

rate, ranging from 37% [42] to 60% [30], with higher rates having been reported in critical care settings instead of non-critical care settings, as a possible consequence of multiorgan failure seen in the former. Furthermore, while declining rates in overall mortality have been recently reported [43], data on mortality in the elderly are conflicting [7,22-25,27,42-46].

With regard to the risk of long-term mortality after an episode of AKI, in their study on the cohort of 233,803 elderly hospitalized patients assessed in 2000, Ishani et al. [22] reported a 2-year combined mortality rate of 29.1% that was higher in patients with AKI and CKD than in those with AKI alone.

Lo et al. [42] studied the outcomes of 562,779 patients of Kaiser Permanente of Northern California who were hospitalized over an 8-year period and whose mean age at admission was 63.5 ± 14.8 years. The authors reported an in-patient death of 41.9% in subjects with dialysis-requiring ARF and of 1.14% in those with non-dialysis-requiring ARF; moreover, they found that, over the 6 years of follow-up an episode of dialysis-requiring ARF was independently associated with a more than two-fold increased long-term risk of death. However, such an increase in the risk of long-term mortality following AKI was not observed by Wald et al. [45,46].

AKI should now be recognized as a potent predictor not only of in-hospital mortality [47] but also of long-term morbidity and mortality [48]. Patients who, after admission to hospital, are discharged with AKI are 3 times more likely to die and 13 times more likely to reach ESRD in the year after hospital admission than patients who are admitted to hospital without AKI [49].

The increased mortality risk associated with AKI persists over time and after adjustment for post-discharge eGFR [40,50]. In the study carried out by James et al. [40], 27,959 of 920,985 participants (3%) died during the follow-up. Rates of all-cause mortality were higher in patients after hospital admission with AKI than in those without AKI. The prognostic significance of AKI varied according to baseline eGFR; however, heavy proteinuria was responsible for the high rates of death in participants with AKI and baseline eGFR ≥ 60 mL/min per 1.73 m². The authors concluded that long-term mortality increases after AKI at all levels of eGFR and proteinuria. However, they suggest that the risk of adverse outcomes attributable to AKI is not constant for all categories of baseline kidney function. In their study, the prognostic importance of AKI decreases as pre-existing kidney damage worsens. In other words, an AKI event in people with normal kidney function greatly increases their subsequent risk of ESRD and death; in people with stage 4 of CKD, an event of AKI adds a lower risk, but the baseline risk of adverse events is increased.

Therefore, it is believed that, on average, the severity of illness that is necessary to provoke AKI in a person with normal kidneys is greater than that required to provoke injury in a person with pre-existing kidney damage [51].

The role of only a modestly reduced eGFR in determining outcomes in aging subjects has been now been clarified as a result of large observational studies and meta-analyses [52]. The results show that younger patients with an eGFR of 45–59 ml/min per 1.73 m² are at increased risk of death, usually due to cardiovascular disease. This effect is softened by advancing age; therefore, older patients with an eGFR of 45–59 ml/min per 1.73 m² seem not to be at increased risk of death after correction for age [53,54]. Moreover, the existence of a 'U-shaped' effect, in which mortality is elevated in both higher and lower strata of eGFR, can be hypothesized [40,52,55].

Recently, Gong et al. [56] conducted a prospective study on 99 consecutive Chinese patients with AKI, aged 65 to 96 years (mean 77.8 ± 7.8 years), with the aim of investigating the clinical features and risk factors affecting mortality. The patients were divided into survivors and non-survivors, according to their outcomes, and factors including clinical characteristics and laboratory features were compared between the 2 groups. Significant differences between the 2 groups were found in concomitant diseases, Multiple Organ Dysfunction Syndrome (MODS), albumin, C-reactive protein and prealbumin levels. The mortality rate of the elderly patients with AKI was 42% vs. 24% of the non-elderly group. The clinical condition of 41 elderly AKI patients was complicated by the presence of MODS and 20 died of MODS. An increase in mortality rate from 39% to 100%, depending on the number of failed organs, was observed: 39% in patients with 2 organ dysfunctions, 50% in patients with 3 organ dysfunctions, 60% in patients with 4 organ dysfunctions, and 100% in patients with 5 organ dysfunctions. In the multivariate logistic regression analysis, concomitant disease (p=0.003) and MODS (p=0.001) were found to be independent risk factors for death of the elderly patients with AKI after adjusting for age, sex, pre-albumin, sepsis/infection, and serum creatinine.

The presence of multiorgan failure had already been reported by Van Den Noortgate et al. [1] as one of the variables predicting in-hospital mortality in elderly patients with acute renal failure requiring dialysis post-cardiac surgery. Surprisingly, in this study, age was not found to influence the overall outcome both in older patient and in younger patients. According to the authors, this relatively beneficial outcome in the elderly might be the consequence of a different severity of the underlying disease. On the one hand, the aging kidney is less able to adapt to rapid hemodynamic changes and electrolyte balance, so AKI might develop more easily in the older patients. On the other hand, in the elderly, comorbid factors that are at the origin of AKI might be less preponderant or severe than in the younger population. After all, comorbid conditions probably more frequently lead to a fatal outcome than renal failure by itself.

With regard to malnutrition, the results of a meta-analysis of 17 observational clinical studies carried out by Wiedermann et al. [57] are noteworthy. Of the 17 studies, 11 evaluated the influence of serum albumin on AKI incidence and 6 evaluated the relationship between serum albumin and mortality among patients who developed AKI. In 3,917 patients evaluated, a substantial number of whom were aged 65 or more, the authors found that the lower serum albumin was an independent predictor both of AKI and of death after AKI development.

More recently, Oliva et al. [58] reported that low serum albumin is an independent predictor of mortality in Spanish chronic hemodialysis patients of over 75 years old.

In the older group with AKI evaluated by Wen et al. [2], MODS, heart failure and gastrointestinal bleeding were found to be independent risk factors for the 90-day mortality, while the presence of MODS, malnutrition, gastrointestinal bleeding, absolute increase in serum creatinine and the use of alfa-ketoacid were found to be independent variables predicting medium-term (at 1 year) survival/mortality. If classified according to the AKIN categories, patients with AKI stage 2 and 3 exhibited a significantly worse survival than patients with AKI stage 1 [59,60]. Comparing the 201 very old patients with *de novo* AKI (42.5%) and the 272 very old patients with AKI superimposed on CKD

Authors	Reference	Mortality
Wen et al., China	[2]	46.27% (at 90 days, de novo AKI) 29.04% (at 90 days, acute-on-chronic kidney injury)
Xue at al., USA	[7]	37.8% (in-hospital) 34.5-48.6% (90 days)
Ishani et al., USA	[22]	29.1% (2 years)
Ali et al., Scotland	[24]	32.7% (in-hospital) 41.4% (90 days) 49.8% (6 months)
Baraldi et al., Italy	[27]	33.3% (aged ≥ 65) 2.5% (aged ≤ 64)
Ukino et al., multinational	[29]	60.3%
Garzotto et al., Italy	[30]	21.7% (intensive care unit and in-hospital)
James et al., Canada	[40]	3% at 35 months
Lo et al., USA	[42]	41.9% (dialysis-requiring acute renal failure) 1.14% (non-dialysis-requiring acute renal failure)
Gong et al., China	[56]	42%
Sesso et al., Brazil	[59]	41% (in-hospital) 59% (community)
Kohli et al., India	[60]	60.9%

Table 2: Mortality from acute kidney injury (AKI) in the elderly.

(acute-on-chronic, A-on-C kidney injury) (57.5%), the former were found to be less old and to exhibit a higher percentage increase in serum creatinine and a higher mortality rate within 90 days (46.27% vs. 29.04%). This mortality rate was higher than the rate of 20-40% reported in previous reports on patients older than 65 years, and confirms age being a risk factor for in-hospital mortality in patients of this range of age.

Data on mortality for AKI are summarized in table 2.

Non-Recovery from Acute Kidney Injury

For a long time acute kidney injury has been considered a completely reversible syndrome. However, data from recent studies conducted on animals and humans indicate that AKI more than likely results in a permanent renal damage and can also affect other organs [61-63].

Elderly patients with CKD are at high risk of non-recovery from AKI and for progression to more advanced stages of CKD or even to ESRD [6].

In the study carried out by James et al. [40], 771 of 920,985 participants (0.08%) developed End-Stage Renal Disease (ESRD) during the follow-up, and 2,341 of 580,452 (0.4%) had a doubling of serum creatinine values. The authors concluded that the risk of clinically relevant kidney function loss was higher after AKI.

In a systematic review and meta-analysis of 17 studies published between 2000 and 2007, Schmitt et al. [62] reported data on recovery of kidney function by age and showed that in 31.3% of the surviving elderly patients kidney function did not recover, while it did in 26% of the younger patients (pooled relative risk, 1.28, p<0.05).

In the cohort of 233,803 hospitalized elderly patients evaluated by Ishani et al. [22], 3.1% survived to discharge with a diagnosis of AKI and 5.3 per 1000 developed ESRD; after adjustment for age, gender, race, DM and hypertension, the hazard ratio for developing ESRD was 41.2 for patients with AKI and CKD relative to those without kidney disease, 13.0 for patients with AKI and without previous CKD, and 8.4 for patients with CKD and without AKI. Thus, elderly patients with AKI, in particular those with previously diagnosed CKD, were reported to be at a significantly increased risk for ESRD, suggesting that episodes of AKI may accelerate progression of renal disease.

Therefore, large population-based studies have demonstrated that patients who survive an episode of AKI are at a considerable risk of progressing to advanced stages of CKD. The same studies demonstrate the continuity of disease from AKI to CKD to End-Stage Renal Disease (ESRD). In particular, Amdur et al. [63], using a US Department of Veterans Affairs database to ascertain the long-term renal function in 113,272 patients, showed that up to 20% of the patients with an in-patient diagnosis of Acute Tubular Necrosis (ATN) progressed to CKD stage 4 or greater within 18-24 months. However, within this population, a subset of patients appeared to nearly achieve a total recovery and not to progress to advanced stages of CKD. Therefore, it is likely that some patients who develop AKI are at higher risk for CKD progression than others.

Chawla et al. [64] hypothesized that patients surviving AKI who are at higher risk for progression to CKD can be well characterized. In order to identify and stratify AKI patients who are more likely to progress to CKD, the authors developed a prediction tool that was assessed on 5,351 elderly patients (mean age, 66.3 ± 12.3 years) hospitalized in the US Department of Veterans Affairs Healthcare System with a primary diagnosis of AKI. Especially those patients with AKI who required dialysis and then recovered were at high risk for progression to CKD. Hence, the severity of AKI was believed to be a robust predictor of progression to CKD. Noteworthy, among the demographic variables, age was associated with progression to CKD stage 4, with each year of age raising the odds ratio (OR) of entering CKD by 1% in univariate prediction model and by 1-2% in multivariate prediction models. Thus, advanced age could be useful to identify patients at risk for progression to CKD after an episode of AKI.

More recently, Coca et al. [61] conducted a systematic review and meta-analysis of 13 selected studies evaluating long-term renal and non-renal outcomes in patients with AKI, in order to estimate the risk for CKD, ESRD, death and other non-renal outcomes in patients with AKI vs. those without AKI, and in order to determine whether pre-existing renal injury, such as decreased baseline GFR or pre-existing proteinuria, modified these associations. Definitions of AKI varied substantially: need for RRT [42,45,65], increase in plasma creatinine of 0.3-0.5 or 0.6-3.0 mg/dL, ARF and acute tubular necrosis (ATN) [63]. Severity of AKI was graded as class 1-4 of AKI (class 1, 1%-24% increase in creatinine; class 2, 25%-49% increase in creatinine; class 3, 50%-90% increase in creatinine; class 4, >100% increase in creatinine) [66] or as mild, moderate and severe AKI. As much as 13 studies were selected for inclusion into the systematic review. Of these 13 studies, 4 were conducted on cohorts of patients aged more than 60 and 6 on cohorts of patients with more than 65 years of age.

In the studies carried out on AKI survivors older than 65 years, the following renal outcome rates and hazard ratios (HRs), at a mean follow–up of 20 to 75 months, have been reported: CKD, from 6.6-10.5 per 100 person-years for patients with mild and moderate-severe AKI, respectively, HR 2.33 [66], to 22 per 100 person-years, HR 6.64 [63]; ESRD, from 0.6 per 100 person-years, HR 3.26 [67], to 12.1 per 100 person-years, HR 2.33 [68].

Regardless of the heterogeneity of the statistical data, the results of this meta-analysis show that the risks for both CKD and ESRD, as

well as the adjusted HRs, increased in a graded manner with mild AKI, moderate AKI and severe AKI.

Change effects due to reduced baseline GFR and to proteinuria before AKI should also be considered.

In the 2 studies reporting the risk for CKD after AKI in subjects with both reduced and normal baseline GFR [40,42], the relative risk (hazard ratio, HR) for CKD was higher in patients who did not have a decreased baseline GFR (adjusted HR 38.8,) than in those with a decreased baseline GFR (adjusted HR 24.4). As already seen for mortality rate, the role of only a modestly reduced eGFR in determining the progression of CKD in aging subjects has been the subject of several investigations which showed that older patients with an eGFR of 45-59 ml/min per 1.73 m^2 are less likely than younger patients to progress to end-stage renal disease, and when progression does occur it is slower than in younger patients [53,69].

Similarly, in the 2 studies reporting the risk for ESRD both in patients with and without decreased baseline GFR, the relative risk for ESRD was higher in subjects with AKI who did not have decreased baseline GFR.

Moreover, in one of the two studies cited (i.e. that of James et al.) [40], patients with AKI who had a pre-existing proteinuria (and a normal baseline GFR) had a lower relative risk for CKD (defined as doubling of creatinine or ESRD) (HR 9.7) compared with patients without proteinuria (HR 30.0). Moreover, James reported the association between the different severity grades of AKI (mild, moderate and severe) and the increased occurrence of non-renal outcomes such as congestive heart failure and cardiovascular disease [40].

According to Coca et al. [61], their meta-analysis gives the opportunity to assess the absolute and relative risk associated with these outcomes (CKD and ESRD) after AKI. They consider potentially counterintuitive the fact that patients with normal GFR before AKI have a higher relative risk for the development of ESRD if compared with those developing AKI in a decreased baseline GFR setting. They cite as an example the study of Wald et al. [45] and state that, although the absolute risk of ESRD in subjects without previous AKI and without a decrease in baseline GFR was of 9.8% - while it was almost doubled (to 18.4%) in subjects with AKI and reduced baseline GFR-, the relative risk for ESRD was higher in the subjects with normal GFR, because of the extremely low probability of ESRD in subjects without previous AKI or reduced baseline GFR [61].

In conclusion, AKI is an important cause of ESRD because it can lead to an acceleration of the normal age-related decline in GFR. Moreover, patients suffering from repeated or prolonged injuries are predisposed to CKD since, although tubular regeneration may occur after AKI, cellular plasticity may be lost and the inflammatory processes occurring during repair and regeneration phases can lead to paracrine stimulation of myofibroblasts. The consequent development of progressive tubulo-interstitial fibrosis accelerates progression of CKD to ESRD [70]. On the other hand of this AKI-CKD nexus [71], the reduction of the renal mass of CKD, similarly to diabetic and aging-related pathology, predisposes patients to AKI. The literature on the reciprocal relationship between AKI and CKD in elderly patients that is the way in which these conditions predispose to each other, has been recently reviewed by Coca et al. [72]

According to the authors, the plethora of data indicating that not only does AKI often lead, but also predisposes to CKD, is a concern for public health. In fact, since approximately 40 million people in the US were aged >65 in 2010, since the incidence of AKI in this elderly population is approximately 3,000 per 100,000 person-years [23], since 75% will survive to discharge after AKI, and since the incidence of stage 4 or worse of CKD after AKI is approximately 120 per 1,000 person-years [63], then approximately 100,000 elderly people per year in the US are developing new CKD after an episode of AKI. So, if is true that biomarkers are transforming our understanding of AKI [73], the challenge for the nephrology community is that of finding strategies to either prevent AKI or prevent the transition from AKI to CKD [72].

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