AKI in the Elderly: A Literature Review

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Abstract:

Acute Kidney Injury (AKI) is a prevalent concern in the elderly population due to age-related changes in kidney structure and function, compounded by the increased prevalence of comorbid conditions. As the global population of individuals aged over 65 rises, understanding the mechanisms, risk factors, and outcomes associated with AKI in this demographic becomes imperative. The aging process leads to significant renal alterations, including a reduction in renal mass, loss of nephrons, and a decline in glomerular filtration rate (GFR), which greatly diminishes kidney function and resilience to injury.

Elderly individuals often present with multiple comorbidities such as hypertension, diabetes, and heart failure, increasing their risk for AKI. The incidence of AKI in older adults has been steadily rising, influenced by factors like insufficient hydration, nephrotoxic medication use, and surgical procedures. Moreover, AKI is frequently under-diagnosed and mismanaged in this age group, leading to inadequate treatment and poorer health outcomes. Patients with AKI experience not only a higher short- and long-term mortality risk but also diminished quality of life and increased likelihood of progressing to chronic kidney disease (CKD) or end-stage renal disease (ESRD). Education on prevention strategies—including promoting hydration, avoiding nephrotoxic agents, and proper medication management—is crucial. Given the complexities of AKI in the elderly, a tailored approach focusing on early detection, preventive measures, and supportive care is essential for improving outcomes in this vulnerable population.

Key Words: Acute Kidney Injury (AKI), Elderly, Risk Factors, Chronic Kidney Disease (CKD), Renal Aging

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Introduction

In recent years, there has been a significant increase in the global elderly population, which is projected to represent one-fifth of the world's population by 2030 [1]. This demographic shift presents substantial challenges for healthcare systems, with far-reaching health, economic, and social consequences worldwide. Aging is widely recognized as a complex process that involves a range of age-related chronic conditions and early organ degradation. These processes are regulated by various mechanisms, including genomic instability, telomere shortening, epigenetic changes, disrupted proteostasis, imbalanced nutrient sensing, mitochondrial dysfunction, and impaired autophagy [2]. At the cellular level, aging is marked by cellular senescence, an irreversible arrest of the cell cycle that halts cell division [3]. This aging process is associated with structural and functional decline in many major organs, including the kidneys.

The occurrence of acute kidney injury (AKI) is on the rise across all age groups; however, elderly individuals (those over 65 years) are particularly vulnerable to AKI. This vulnerability is due to age-related structural and functional kidney changes, reduced renal reserves, coexisting medical conditions, and a diminished capacity for recovery. Elderly patients with AKI face a higher risk of both short- and long-term mortality, and those who survive often develop chronic kidney disease (CKD), which can progress to end-stage renal disease (ESRD). In addition, elderly AKI patients frequently experience a decline in quality of life and reduced functional capacity, contributing to adverse health outcomes. Preventative measures, such as maintaining hydration and avoiding nephrotoxic substances, can help reduce the risk of AKI in this population. However, there are no specific treatments for AKI in elderly patients beyond supportive care. A comprehensive understanding of the

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underlying mechanisms, causes, clinical progression, complications, and prognosis of AKI in older adults is essential to reduce its occurrence and improve outcomes.

This discussion provides an overview of the changes in aging kidneys, risk factors for AKI in older adults, clinical characteristics, classification systems, disease progression, and outcomes in elderly AKI patients. Special attention is given to the differences between AKI in older individuals and the general population.

Methods of Search

To identify relevant literature on Acute Kidney Injury (AKI) in the elderly population, a systematic search in electronic databases like PubMed, Cochrane Library, Scopus, Web of Science and ClinicalTrials.gov was conducted. The following databases were included in the search: The search was performed using a combination of keywords and Medical Subject Headings (MeSH) terms. The primary search terms included: "Acute Kidney Injury", "AKI" in "Elderly", "Aged kidney", "Kidney in Older Adults", "Renal Failure.

These terms were combined using Boolean operators (AND, OR) to refine the search results. The following is an example of the string used in PubMed:

("Acute Kidney Injury" OR "AKI") AND ("Elderly" OR "Aged" OR "Older Adults" OR "Aged, 80 and over")

After initial searches, studies were screened for eligibility based on studies published in peer-reviewed journals, research involving subjects aged 65 years and older, studies focusing on the incidence, prevalence, etiology, or outcomes of AKI and original research articles, reviews, and clinical trials. Studies that do not specify age demographics or include younger populations, publications not written in English, case reports, editorials, and opinion pieces were excluded.

The selected articles were further evaluated for the quality of evidence using the appropriate tools (e.g., PRISMA, GRADE). Key data were extracted, including: Study design, sample size, patient demographics, definition and assessment of AKI and main findings related to AKI in the elderly.

Incidence of AKI in the elderly

The incidence of acute kidney injury (AKI) in older adults has been increasing consistently across various racial and geographic groups, with men showing particularly high rates[4]. While improved diagnostic sensitivity and the development of new biomarkers contribute to this trend, it is likely that the actual number of AKI cases is growing, representing a "silent epidemic." There is limited research on the prevalence of AKI among elderly populations. In China, however, a single-center study found that 14.8% of patients over 80 years old admitted to the hospital experienced AKI, with the majority of these cases linked to sepsis[5]. The wide range in AKI prevalence is influenced by the population demographics, underlying causes, and the criteria used to define AKI in different studies.

A number of additional studies have also highlighted that AKI is more common among the elderly, with a distinct correlation between increasing age and AKI occurrence[6]. This age-related trend appears in studies that rely on the International Classification of Diseases, Ninth Revision (ICD-9) codes for AKI, as well as in large databases that track creatinine values from both inpatient and outpatient settings[7].

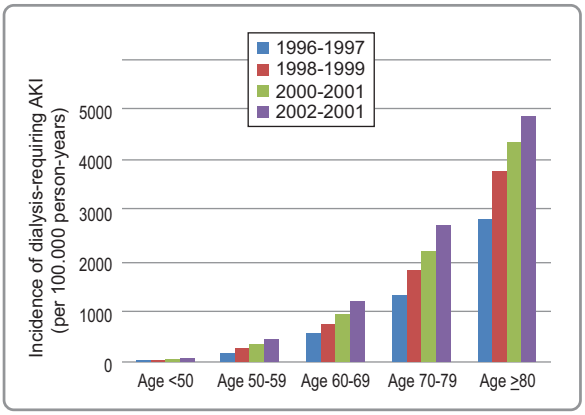

Figure 1: *Between 1996 and 2003, the incidence of dialysis-requiring AKI rose steadily across all age groups, with the highest absolute incidence seen among elderly individuals [8].*

An analysis of Medicare beneficiaries in the United States showed that the rate of AKI increases stepwise from 13.6 episodes (66–69 years) to 18.1 episodes (70–74 years) to 24.9 episodes (75–79 years) to 34.2 episodes (80–84 years) to 46.9 episodes (85 years and older) per 1000 patient-years, respectively[9]. This pattern holds true for both dialysis-requiring and nondialysis-requiring AKI. However, few studies specifically address AKI in

the elderly population, despite the continuous growth of this population and their higher chances of experiencing AKI[10].

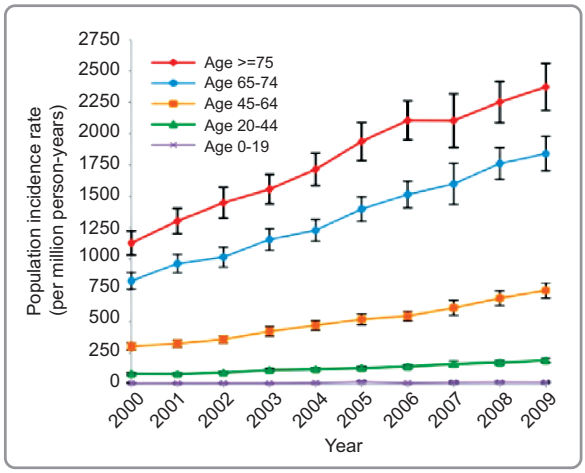

Figure 2: *Population incidence of dialysis-requiring AKI in the United States by age groups from 2000 to 2009. All age groups showed a similar pattern of increase in incidence but over 75 years population are the most sufferers*

A study of Medicare beneficiaries in the United States revealed that the rate of AKI increases incrementally with age, rising from 13.6 episodes per 1,000 patient-years for those aged 66–69, to 18.1 episodes for ages 70–74, 24.9 episodes for ages 75–79, 34.2 episodes for ages 80–84, and 46.9 episodes for individuals 85 and older 9. This trend is consistent for both dialysis-dependent and non-dialysis-dependent AKI cases. Despite the rapid growth of the elderly population and their heightened risk for AKI, there are relatively few studies focused specifically on AKI in older adults[10].

Kidney in aging

In the absence of specific diseases, aging leads to structural and functional changes in the kidneys, which result in a significant reduction in renal mass, fewer functioning nephrons, and an overall decline in kidney function. These changes in the aging kidney resemble those found in chronic kidney disease. As kidneys age, they undergo atrophy and become less efficient in their essential functions. This process is characterized by glomerulosclerosis, tubular atrophy, interstitial fibrosis, and atherosclerosis, collectively known as senile nephrosclerosis.

Kidney aging involves morphological, anatomical, and functional alterations that diminish the filtration process's efficiency, making the kidneys more prone to acute kidney injury (AKI), which can progress to azotemia or even uremic syndrome. Renal function begins to decline after the biological ages of 30–40[11]. The foundational studies of Davies and Shock in the 1950s introduced the concept of functional renal aging, noting that approximately 50% of kidney function remains by age 90 [12]. This decline in function is generally viewed as a normal physiological process, independent of other health conditions[13,14]. Renal aging has been linked to changes in vascular responses to mediators such as acetylcholine and angiotensin, yet efforts to reverse these effects have largely been unsuccessful [15]. The kidneys undergo a series of age-related changes; for instance, renal mass reduces to about 75–80% of its young adult size by age 80 to 90[16]. By age 70, between 30% and 50% of cortical glomeruli are lost due to ischemia, with many remaining glomeruli showing signs of sclerosis[17].

From an anatomical standpoint, age-related changes in the kidneys can be described at both microscopic and macroscopic levels. Microscopically, nephrons, the kidney's functional units, are often affected by glomerulosclerosis, vascular tuft collapse, thickening of the glomerular basement membrane, and intracapsular fibrosis[18].

Age-related changes in the kidney—due to factors like ischemia, hypoxia, and hypertension—include tubular atrophy, inflammation, interstitial fibrosis, glomerulosclerosis, vascular rarefaction, and arteriosclerosis, similar to the characteristics of chronic kidney disease[19]. Furthermore, aging kidneys show a reduction in nephron numbers, and the remaining nephrons often undergo hypertrophy[20]. An increase in both focal and global glomerulosclerosis is also common, with studies suggesting a rising prevalence of these conditions as age advances, even when no renal disease is present[21]. Other changes include a decrease in glomeruli number and size, thickening of the glomerular basement membrane, an increase in mesangial volume and matrix, and a wrinkling of capillary tufts[22]. The number of glomerular mesangial and endothelial cells increases until around age 50, maintaining a balanced ratio with glomerular volume [23]. After age 50, both cell types decrease in number, with a more significant reduction evident after age 70[24].

Glomerular podocytes are key structural components of the glomerular filtration barrier (GFB) and play a crucial role in maintaining glomerular permselectivity. These cells are terminally differentiated, neuron-like cells with limited capacity for division and regeneration. Injury or loss of podocytes directly damages the GFB, leading to proteinuria and kidney diseases characterized by progressive glomerulosclerosis. Podocytes are also central to age-related glomerular changes, such as global glomerulosclerosis, during kidney aging. Supporting this, an analysis of normal human kidney tissue revealed that podocyte nuclear density exceeds 300 per 106 ìm3 in individuals under 20, but drops to below 100 per 106 ìm3 by the age of 70-80, indicating a decline in podocyte density of approximately 0.9% per year. This decrease is likely due to either a reduction in podocyte numbers per glomerulus or an increase in glomerular volume.

Podocyte senescence, the primary cause of age-related podocyte loss, manifests in the aging kidney through hypertrophy, binucleation, detachment, the presence of cytoplasmic resorption droplets, and foot process effacement, along with increased SASP expression. These changes contribute to podocyte depletion and the development of age-related global glomerulosclerosis. Recent research suggests that podocytes may regenerate from other sources, such as parietal epithelial cells or bone marrow cells, although under normal conditions, podocyte regeneration and proliferation are likely minimal in aging kidneys.

Besides podocytes, glomeruli are made up of glomerular capillary endothelial cells and mesangial cells. With aging, the number of endothelial and mesangial cells increases, leading to mesangial matrix expansion and glomerular enlargement. However, the role of endothelial or mesangial cell senescence in kidney aging remains largely unexplored.

Expansion of the hyaline mesangial matrix leads to the closure of glomerular capillary loops and is linked with capillary tuft collapse and intracapsular fibrosis[25]. Conversely, a decline in podocyte numbers occurs with age. Podocytes also experience hypertrophy, often

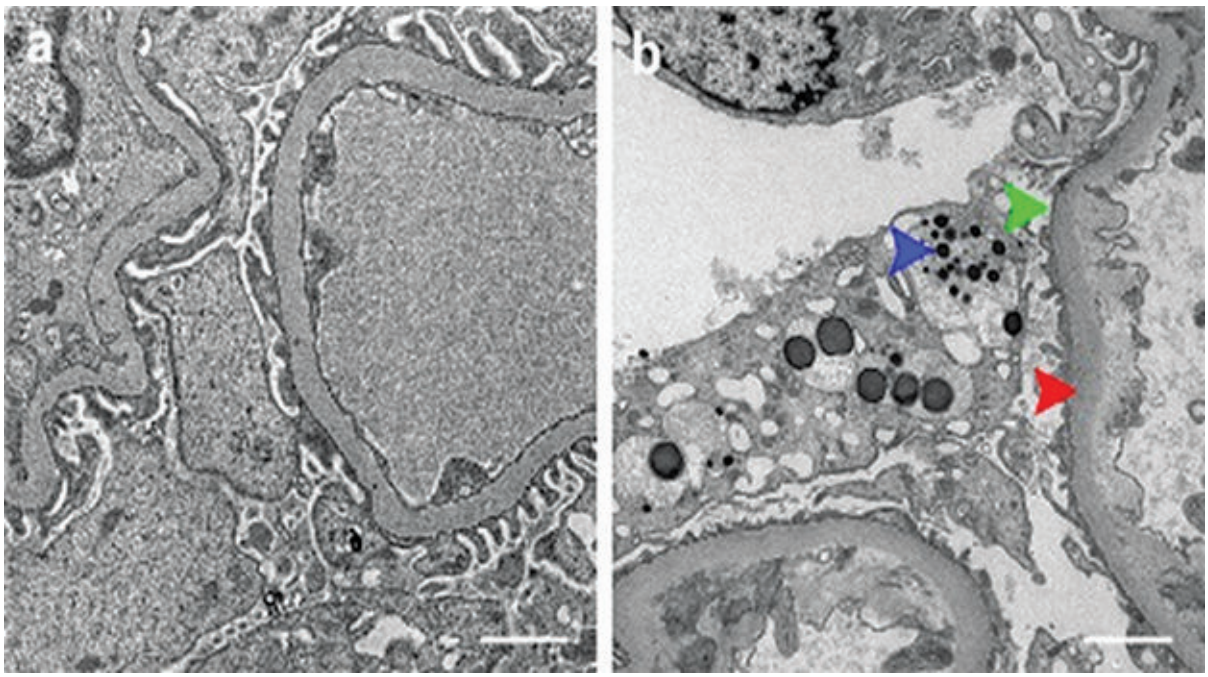

Figure 3: *Changes of glomerular podocytes in kidney ageing. Transmission electron micrographs show (a) the typical morphology of normal glomerular podocytes in the healthy young kidney. (b) ultrastructural changes of glomerular podocytes in the ageing kidney, characterized by variable foot processes effacement (green arrowhead), podocyte detachment, cytoplasmatic absorption droplets (blue arrowhead), concomitant with thickening of glomerular basement membrane (red arrowhead).*

triggered by the intracellular uptake of protein droplets, foot process fusion, and detachment from the glomerular basement membrane, as observed through electron microscopy[26]. Tubular atrophy and interstitial fibrosis are the main tubular-interstitial pathological changes seen in aging kidneys[27]. It is believed that age-associated fibrointimal hyperplasia in smaller arteries promotes glomerulosclerosis, subsequently triggering localized tubular atrophy and interstitial fibrosis. During aging, the kidneys exhibit an increase in glomerular arteries, which bypass the afferent and efferent arterioles as a result of glomeruli loss. Comorbid conditions, such as hypertension and diabetes, can further intensify these age-related pathological changes in the elderly.

Vascular abnormalities in aging kidneys are linked to renal artery atherosclerosis, which can be caused by factors such as aging, ischemia, hypertension, obesity, and hypoxia in the kidney tissue. Notably, the prevalence of atherosclerosis in renal arteries increases significantly with age, from 0.4% in younger men to as high as 25% in older adults[28]. The pathological changes observed in the glomeruli, blood vessels, and tubulointerstitial areas due to aging are not unique to elderly kidneys; these changes are also common factors contributing to renal fibrosis seen in chronic kidney disease (CKD)[29].

A cross-sectional study conducted by the Mayo Clinic revealed that the prevalence of nephrosclerosis rises progressively with age, affecting 2.7% of individuals aged 18–29, 16% of those aged 30–39, 28% for ages 40–49, 44% for ages 50–59, 58% for ages 60–69, and reaching 73% in individuals aged 70–77[30].

Anatomical changes in the kidneys do not always correspond with functional changes. Less commonly observed features include smaller glomeruli, reduced glomerular density, and the presence of diverticuli[31]. Although kidney weight generally decreases after age 40–50, kidney volume does not decline at the same rate, primarily due to compensatory glomerular hypertrophy and an increase in sinus fat. Structural abnormalities visible on ultrasound or computed tomography, such as distorted renal contours, lobulated surfaces, and significantly reduced size, are more often linked to underlying comorbidities rather than the aging process itself[32]. Gross changes in aging kidneys typically involve parenchymal calcifications, simple renal cysts, and focal narrowing of renal arteries; however, these morphological changes do not necessarily indicate a decrease in kidney function.

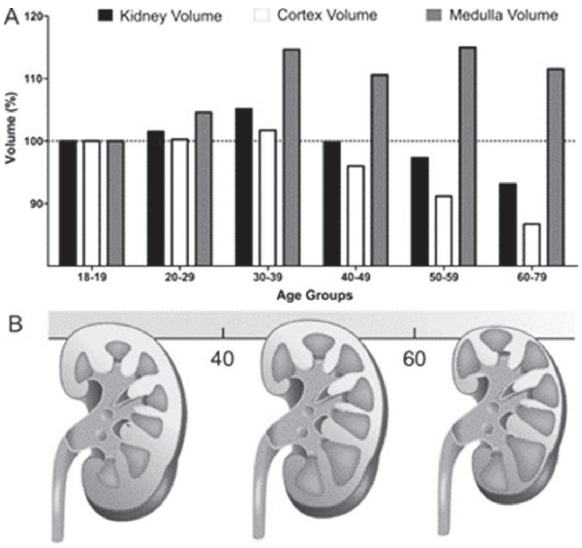

Figure 4: *(A) In a study of 1,281 living kidney donors, it was found that cortical volume decreases over time, while medullary volume increases, keeping the total kidney volume relatively stable until around age 50. Beyond this age, medullary volume ceases to increase, and total kidney volume starts to decline. The results were normalized to total, cortical, or medullary kidney volumes observed in the 18–19-year age group. (B) A schematic illustration depicts the changes in cortical and medullary volumes with aging (Adapted with permission from Kidney International)[33].*

Functional Changes in Kidneys during Aging and CKD

The functional changes in aging kidneys are marked by a decline in glomerular filtration rate (GFR), impaired tubular function, increased renal vascular resistance, and endocrine dysfunction. Age-related declines in GFR have long been recognized as an initial indicator of functional decline in aging kidneys[34]. Typically, estimated GFR (eGFR) begins to decrease around age 30 at a rate of 0.7–0.9 mL/min/1.73 m² per year in healthy individuals. The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) reported a GFR decline rate of 0.95 ± 2.23 mL/min/1.73 m² per year among 1,594 healthy participants aged 50–62 years[35]. The overall reduction in GFR, as measured by inulin clearance, begins around age 40 and accelerates between the ages of 60 and 70.

Uremic toxin accumulation increases with age and in patients with chronic kidney disease (CKD). Specifically, indoxyl sulfate (IS), a byproduct of tryptophan metabolism, shows an inverse relationship with kidney function, particularly in those with an eGFR below 60 mL/min[36]. Notably, elderly individual's aged 70–89 show elevated IS levels, averaging 1.56 ± 0.93 mg/L, which is comparable to levels seen in CKD stage 3 patients[37]. The rise in serum IS has been associated with glomerular sclerosis, increased oxidative stress, as well as both cardiac and renal fibrosis. Recently, attention has turned to the role of gut microbiota in elderly populations.

Microbes from older mice, unlike those from younger ones, have the ability to induce inflammation in germ-free mice, indicating that microbes may become more detrimental to the host with age[38]. These findings suggest that gut microbiota dysbiosis is linked to an increase in uremic toxins, which can accelerate kidney aging and the progression of chronic kidney disease (CKD).

Age-related tubular dysfunction is characterized by a reduced ability to concentrate urine, disrupted electrolyte balance, and a heightened susceptibility to acute kidney injury (AKI)[39]. The primary cause of tubular injury is renal interlobular arteriosclerosis, which leads to a decreased capacity to concentrate or dilute urine. Electrolyte imbalances manifest in various ways, including reduced urinary sodium excretion in the elderly, resulting in a greater risk of volume overload[40]. Furthermore, aging adversely affects potassium regulation. Urinary potassium levels are controlled by active transporters, such as Na-K ATPase, in the tubules and collecting ducts, which are crucial for responding to decreased GFR and lower urine outputt[41].

Renal tubules make up over 90% of the kidney's mass and are the most affected by aging. Signs of cellular senescence, such as nuclear expression of p16INK4a, are more prominent in renal tubular cells compared to other kidney cell types during the aging process. Experimental models have shown that various injuries can trigger cellular senescence and lead to fibrosis in renal tubular epithelial cells. As the kidney ages, the ability of these cells to regenerate after acute damage decreases, accompanied by increased cell senescence and an enhanced SASP (senescence-associated secretory phenotype). This impairs the repopulation of renal tubular cells and promotes maladaptive fibrotic repair, ultimately worsening the transition from acute kidney injury (AKI) to chronic kidney disease (CKD) and accelerating kidney aging.

Renal vascular abnormalities associated with aging include vascular remodeling, endothelial dysfunction, and increased vascular stiffness. The primary factor contributing to elevated renal microvascular resistance is arteriosclerosis, which significantly intensifies with age, particularly after 60. Another significant factor influencing kidney aging is the kidney's role in sympathetic regulation. With declining GFR and vascular injury, older individuals experience activation of the sympathetic nervous system, resulting in accelerated arterial stiffening[42]. The higher prevalence of anemia in older adults is often linked to decreased erythropoietin (EPO) production associated with tubular atrophy or tubulointerstitial scarringt[43]. Additionally, hormone levels related to kidney function change during the aging process. For instance, serum levels of 1,25-dihydroxyvitamin D decline in the elderly, while levels of 25-hydroxyvitamin D remain stable. This suggests a reduced conversion rate of 1,25-dihydroxyvitamin D, which may contribute to the development of osteoporosis in older adultst[44] .

A decline in mitochondrial energy production, which negatively affects active transport in the renal tubules, represents another functional change associated with aging kidneys. This decline impacts glucose reabsorption and results in increased protein levels in the urine, indicating tubular damage that is not directly related to the injury itself.

As individuals age, the rate of cellular apoptosis in the kidneys rises, leading to a reduction in functional nephrons. This loss contributes to decreased glomerular filtration rate (GFR) and creatinine clearance, reducing renal functional reserve and making the kidneys more susceptible to acute kidney injury (AKI). Older adults experience not only a higher rate of apoptosis but also produce fewer growth factors and exhibit downregulated cellular signaling. These factors result in slower cell division rates and, consequently, a weakened regenerative response following injury.

The reduction in nephron numbers disrupts sodium retention mechanisms, leading to altered urine concentration and increased volume depletion, which

may result in dehydration. Additionally, fewer nephrons increase the filtration load, potentially causing nephron hyperfiltration injury. Deficiencies in the acidification mechanism during physiological stress can lead to metabolic acidosis and a decrease in the production of renal 1-alpha-hydroxylase, causing changes in calcium metabolism and possibly triggering renal osteoporosis.

The structural and functional alterations associated with aging raise the risk of acute kidney injury (AKI). One hypothesis posits that diminished nitric oxide (NO) production in the kidneys of older adults contributes to this increased risk. Aging tubular cells may be more susceptible to ischemic damage due to declining antioxidant defenses and metabolic changes that heighten their vulnerability to injury. Furthermore, the kidneys lose their ability to autoregulate at higher blood pressures in older adults, although AKI can still occur in those who are normotensive.

In older patients, the kidneys exhibit impaired sodium conservation in response to acute reductions in sodium intake and a reduced ability to excrete large sodium loads rapidly. There is also a significant loss of maximum urine concentrating ability (declining from approximately 1200 to 800 mosm/L) and maximum urine diluting capacity (declining from about 50 to 100 mosm/L)[45]. The expression of aquaporins in the medulla decreases with age, further compromising kidney function. This reduced capacity for dilution increases the risk of hyponatremia in older patients, especially those following low-protein diets, such as the "tea and toast" diet often observed in some elderly individuals. Alterations in diluting capacity also contribute to thiazide-associated hyponatremia, which is more common in older adultst[46]. Additionally, there is a tendency toward hyperkalemia in this population due to hyporeninemic hypoaldosteronism.

Under normal circumstances, these changes can be functionally compensated for by adaptations in renal hemodynamics to maintain adequate GFR. However, when faced with pathophysiological challenges, the aging kidney often lacks sufficient functional reserve, making it more prone to clinically significant damaget[47].

Risk factors:

The increased incidence of acute kidney injury (AKI) among elderly individuals can be attributed to several factors:

A) The accumulation of comorbidities with age, such as renovascular disease and congestive heart failure, may elevate the risk of AKI.

B) These comorbidities often necessitate procedures, medications, or surgeries that can act as nephrotoxins and stress the kidneys

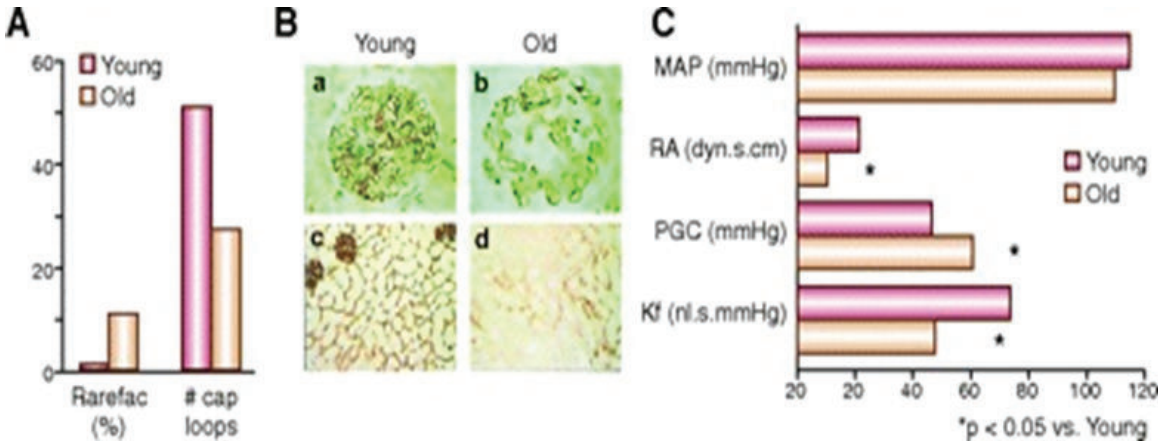

Figure 5: *The aging kidney in rats undergoes structural changes in the glomerular and peritubular capillaries (A and B) and functional changes in glomerular hemodynamics (C). a- Glomerular capillary loops in young rats are well preserved. b- Glomerular hypertrophy and decreased capillary loop numbers are observed in aging rats. c and d- Photomicrographs also show normal peritubular capillary architecture in young rat (c) and focal and patchy loss in peritubular capillary in aging rats (d)* [48].

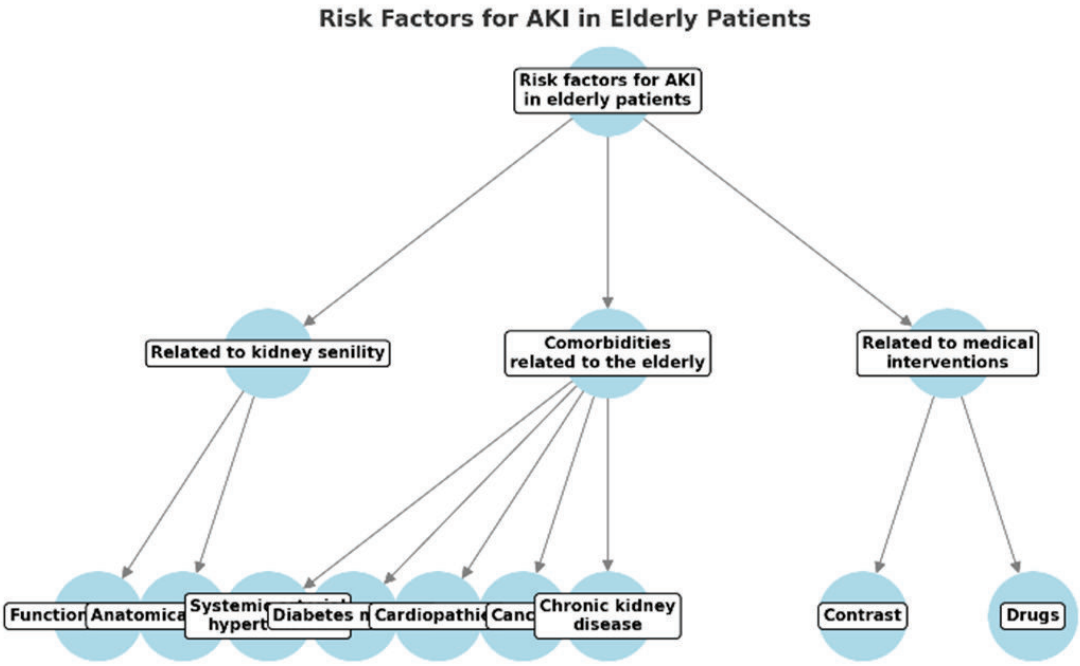

Figure 6: *The risk factors that make the elderly prone to develop AKI can be divided into three types [51]:*

C) Age-related structural and functional changes in the kidneys occur over time[49] .

Various studies estimate that approximately 40% of AKI cases in older adults are due to acute tubular necrosis (ATN), while 30% are linked to prerenal causes[50]. Additionally, about one-quarter of AKI instances in older patients stem from obstructions. Furthermore, elderly individuals are more prone to chronic kidney disease (CKD), congestive heart failure, hypertension, renovascular disease, and diabetes, and they often undergo surgeries, particularly those related to cardiac and vascular issues.

1) Related to kidney senility,

2) Secondary to the elderly's comorbidities, and

3) Associated with medical intervention.

Causes of AKI in elderly

The low incidence of renal biopsy among elderly patients means that most of the identified causes of acute kidney injury (AKI) in this population rely on clinical judgment, resulting in limited data. One report indicated that ischemia (due to hypovolemia or hypotension) accounts for half of the AKI cases, followed by surgical causes at 33.3%, sepsis at 10%, and nephrotoxins at 3%[52]. Other larger studies have identified acute tubular necrosis as the most prevalent cause of AKI in elderly individuals, representing 39% of cases, while prerenal conditions are responsible for 30% of AKI instancesu[53].

Prerenal and intrinsic AKI

Prerenal azotemia is characterized by a functional decline in glomerular filtration rate (GFR) associated with renal underperfusion and is a primary cause of acute kidney injury (AKI) in both the general and elderly populations[54]. Traditionally linked to hypovolemia, prerenal AKI can also occur due to effective intravascular volume depletion related to conditions such as congestive heart failure (cardiorenal syndrome) and liver disease.

The body's normal response to volume depletion includes activating the renin-angiotensin-aldosterone system (RAAS), enhancing sympathetic nervous system activity, and stimulating vasopressin secretion. RAAS activation increases levels of angiotensin II, a potent vasoconstrictor that affects both afferent (pre-glomerular) and efferent (post-glomerular) arterioles. While the afferent vasoconstriction is typically balanced

by vasodilatory prostaglandins, the net effect is a predominance of efferent arteriolar constriction. This overall increase in arteriolar resistance leads to a reduction in renal blood flow, but the predominance of postglomerular constriction helps restore nearly normal intraglomerular pressure and maintain GFR, albeit with an increased filtration fraction (the ratio of GFR to renal plasma flow). Changes in intrarenal hemodynamics, along with the upregulation of angiotensin II, aldosterone, vasopressin, and sympathetic nervous activity, modify renal tubular function, promoting sodium, water, and urea conservation.

Prerenal AKI occurs when the decline in renal perfusion surpasses the ability of these counter-regulatory mechanisms to sustain near-normal GFR. Nonetheless, the adaptive responses that maximize sodium, water, and urea reabsorption continue to function, resulting in decreased urine volume, reduced urine sodium concentration, and increased urine osmolality.

The features of prerenal AKI include low urine sodium concentration (UNa < 500 mosm/kg) and an elevated blood urea nitrogen (BUN) to serum creatinine ratio (>20:1). However, in older adults, these indices may be less reliable due to age-related deficits in sodium and water conservation. Urine sodium levels may exceed 20 mEq/L, and urinary osmolality may be less than 500 mosm/kg, even in the presence of effective intravascular volume depletion. Additionally, an inability to concentrate urine adequately may lead to prerenal AKI, with urine volumes exceeding 500 mL/day. Diuretics can also contribute to prerenal AKI by impacting renal salt and water handling, further complicating these diagnostic indices.

The hallmark of prerenal azotemia is the rapid restoration of renal function following the normalization of kidney perfusion; thus, a trial of intravenous fluids may be necessary to confirm the etiology when diagnostic indices are unclear or inconsistent with the clinical context. Although often considered benign, prerenal AKI carries an increased risk of mortality, primarily related to the underlying comorbidities that contribute to its onset[7]. It is important to recognize that prerenal states significantly elevate the risk of developing intrinsic AKI. Pre-existing prerenal conditions heighten the risk of both ischemic and nephrotoxic insults. Moreover, prolonged or severe renal hypoperfusion that initially presents as functional prerenal AKI may evolve into intrinsic AKI (i.e., ischemic acute tubular necrosis) with structural damage to the renal tubules.

Elderly patients are at a higher risk for true volume depletion due to age-related changes in body composition, resulting in a lower total body water percentage relative to body weight, coupled with an increased burden of comorbidities. Medication use significantly impacts the development of prerenal AKI. Diuretics can exacerbate the predisposition to volume depletion, contributing to 25–40% of prerenal AKI cases in elderly patients[55] . Additionally, medications that influence renal hemodynamics can lead to prerenal AKI. Nonsteroidal anti-inflammatory drugs (NSAIDs), utilized by approximately 10–25% of older adults, inhibit the production of vasodilatory prostaglandins. NSAID use is associated with a threefold increased risk of AKI in the general population and a 13% absolute risk of prerenal AKI among a nursing home cohort with a mean age of 87 years[56]. The concurrent presence of chronic kidney disease, congestive heart failure, diabetes mellitus, hypertension, diuretic use, or angiotensin-converting enzyme inhibitors (ACEIs) further elevates this risk. Older adults are believed to have a higher baseline risk of AKI from NSAID use due to prolonged NSAID half-life, reduced body mass, and the previously mentioned age-related physiological changes that increase reliance on prostaglandin-dependent afferent arteriolar dilation.

Two additional classes of medications frequently prescribed to the elderly that pose a significant risk for prerenal AKI are ACEIs and angiotensin receptor blockers (ARBs). The usage of these agents has risen in patients with congestive heart failure and hypertension. Risk factors for developing AKI with ACEI or ARB use include volume depletion, pre-existing chronic kidney disease, bilateral renal artery stenosis (or unilateral renal artery stenosis with a solitary kidney), congestive heart failure, and concurrent diuretic use. While these medications are not contraindicated in older adults, they must be used cautiously. Follow-up serum chemistries should be conducted one to two weeks after initiating or adjusting the dose to monitor for AKI or hyperkalemia. An increase in creatinine greater than 30% from baseline should trigger further evaluation. While assessment for renal artery stenosis may be warranted, most cases of AKI induced by ACEIs or ARBs do not involve renal artery stenosis[57].

In the elderly, risk factors for ischemic acute tubular necrosis (ATN) include pre-existing chronic kidney disease, diabetes, atherosclerosis, active malignancy, and low serum albumin. Patients with impaired renal autoregulation are also at increased risk for developing ATN even in the absence of significant hypotension. This is typically seen in individuals with advanced age, hypertension, atherosclerosis, chronic kidney disease, or renal artery stenosisu[58,59].

Contrast-induced nephropathy (CIN) is a significant cause of AKI in hospitalized elderly patients. Older adults may be at greater risk for CIN due to a higher prevalence of chronic kidney disease, an important risk factor for this condition[60,61]. Additional risk factors include diabetic nephropathy, volume depletion, the amount of contrast agent used, and the use of high-osmolar (as opposed to low or iso-osmolar) contrast agents. Clinically, CIN is characterized by an acute rise in creatinine within 24 to 48 hours after the administration of contrast, peaking after three to five days and returning to baseline within seven to ten days. Typically, patients remain non-oliguric, and urinary sediment may show granular casts and renal tubular epithelial cells.

Vascular diseases associated with AKI are more common than in the general population and can be classified into large vessel and small vessel processes. Large vessel issues that may lead to AKI include renal artery thromboembolism, renal artery dissection, and renal vein thrombosis[62]. While all these conditions can cause renal infarction, AKI will only result if the lesions are bilateral, occur unilaterally in a solitary kidney, or affect a patient with significant pre-existing chronic kidney disease. Clinically, these disorders can present with sudden flank pain, hematuria, and oligoanuria, depending on severity, and are associated with elevated serum lactate dehydrogenase (LDH) levels. Risk factors for these conditions include trauma, nephrotic syndrome, and atrial fibrillation.

Small vessel involvement with atheroembolic disease is primarily a condition affecting the elderly, with a mean age of 71 in one study, and is associated with diffuse atherosclerosis. Atheroembolism may occur spontaneously but is more often triggered by vascular surgery, angiographic procedures, anticoagulation, or thrombolytic therapy. Destabilized atheromatous plaques can release cholesterol crystals into the small arteries of various organs, including the skin, central nervous system, extremities, gastrointestinal system, and kidneys, with the kidneys frequently affected due to their high blood flow. The cholesterol emboli are typically non-obstructive but provoke a strong inflammatory response that eventually occludes the vascular lumen. Patients may present immediately following vascular surgery or angiography, but symptoms often worsen days to weeks later, manifesting as declining renal function, livedo reticularis, and ischemic necrosis of the toes. Common laboratory findings include eosinophilia, eosinophiluria, proteinuria, and hypocomplementemia. The renal trajectory can be highly variable, often presenting as subacute kidney injury with progressive or fluctuating deterioration in renal function over several days to weeks. No specific treatment exists for atheroembolic disease; supportive care, including nutritional support (particularly with concurrent gastrointestinal involvement) and aggressive management of hyperlipidemia, is recommended. Anticoagulation is contraindicated, as it may precipitate further cholesterol embolizationv[63].

AKI in the elderly can also arise from acute or rapidly progressive glomerulonephritis. Diffuse proliferative forms of glomerulonephritis may be associated with infections and generally carry a favorable prognosis. However, rapidly progressive glomerulonephritis may be more prevalent in older adults and tends to have a poorer prognosis[64].

Clinically, patients often present with acute kidney injury (AKI), hypertension, hematuria, and proteinuria. Urinary sediment typically reveals dysmorphic red blood cells and red blood cell casts. Serological tests, including complement levels, antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies, cryoglobulin levels, and hepatitis B and C antibodies, can aid in identifying the underlying etiology; however, a kidney biopsy is usually necessary for a definitive diagnosis. Treatment approaches, which may involve high-dose glucocorticoids, immunosuppressive therapy, and plasmapheresis, will vary based on the specific cause. Although these treatments can carry potential toxicities, case series indicate that elderly patients with minimal comorbid conditions can tolerate and respond positively to therapy[65] .

Postrenal AKI

Postrenal or obstructive acute kidney injury (AKI) is more prevalent in the elderly compared to younger individuals, accounting for 9% to 30% of cases[66]. This type of AKI can be classified based on its location: affecting either the upper urinary tract (proximal to the bladder) or the lower urinary tract (with obstruction occurring at the bladder outlet or urethra). Obstruction in the lower urinary tract can impair renal function, while unilateral upper tract obstructions may lead to renal colic and unilateral hydronephrosis without affecting renal function if the contralateral kidney compensates. However, bilateral obstruction, obstruction of a solitary functioning kidney, or significant underlying chronic kidney disease can result in AKI. The most common causes of postrenal AKI in the elderly include benign prostatic hypertrophy (BPH), prostate cancer, retroperitoneal adenopathy or malignancies, pelvic neoplasms, and neurogenic bladder. Although BPH and prostate cancer are prevalent in older men, they only lead to obstruction in a minority of cases. In elderly women, pelvic and retroperitoneal malignancies are the primary causes of postrenal AKI[67].

Postrenal AKI can present with either complete or partial obstruction. Complete obstruction is characterized by anuria, while the patient may also experience flank and abdominal pain or suprapubic fullness. In cases of partial obstruction, patients may remain asymptomatic or report similar pain symptoms, along with voiding complaints such as frequency, urgency, hesitancy, hematuria, and nocturia. Urine output may vary from oliguria to polyuria or fluctuate between the two. Given its increased incidence among the elderly and its diverse presentations, clinicians should maintain a high index of suspicion for postrenal AKI. The diagnosis is particularly warranted in patients with BPH, lower urinary tract symptoms, diabetes, kidney stones, abdominal or pelvic malignancies, recent surgeries or radiation, retroperitoneal adenopathy, or medications that may cause urinary retention. Confirmation of lower tract obstruction can be achieved through ultrasonographic bladder scans or bladder catheterization. An elevated residual bladder volume (>100–150 mL) after voiding strongly suggests postrenal AKI; however, some elderly patients may experience chronic urinary retention with increased postvoid residual volume despite the absence of kidney dysfunction[68] .

Radiographic evaluation for upper tract obstruction typically starts with ultrasound imaging, which is both sensitive and specific for detecting obstruction. However, ultrasound results may be normal in patients with early obstruction or retroperitoneal processes that encase the kidneys and ureters, preventing ureteral dilation. Computed tomography (CT) scans can be useful in identifying the cause and location of the obstruction when ultrasound fails to reveal the lesion. Together, ultrasound, abdominal plain films, and CT scans are diagnostic in most cases. Intravenous pyelography has largely been replaced by CT imaging and is now rarely required. Antegrade or retrograde pyelography may still be beneficial in pinpointing the site and cause of obstruction and offers opportunities for therapeutic intervention. Laboratory findings in postrenal AKI are often nonspecific and may initially mimic prerenal AKI, later resembling intrinsic AKI.

The treatment for postrenal AKI focuses on the rapid detection and relief of obstruction. This can be achieved through the placement of a bladder catheter for lower tract issues or ureteral stents or percutaneous nephrostomy tubes for upper tract obstructions. Following relief of the obstruction, a significant post-obstructive diuresis may occur due to deficits in water and sodium reabsorption, alongside osmotic diuresis from retained solutes like urea. Close monitoring of the patient's volume status and electrolyte levels is crucial to prevent volume depletion or severe electrolyte disturbances. While intravenous fluids may be necessary, it's important to avoid aggressive fluid replacement, which could lead to further diuresis. If the obstruction is diagnosed and treated promptly, renal function is likely to improve. However, in patients with prolonged or severe obstruction, recovery of renal function may be delayed, incomplete, or absent[69]. A marked increase in urine output after correcting the obstruction does not always correlate with recovery of renal function, necessitating ongoing laboratory monitoring.

Clinical Features

The symptoms of acute kidney injury (AKI) can range from minimal clinical manifestations to severe conditions, heavily influenced by the patient's underlying health status and the specific cause of AKI. Symptoms may include oliguria or anuria, general weakness, malaise,

fatigue, confusion, nausea, vomiting, muscle cramps, and a metallic taste in the mouth. In severe cases, AKI can lead to coma or seizures[70]. Currently, there is a lack of studies addressing the key clinical differences in AKI presentation between elderly and younger patients. A small-scale study by Gong et al. found no significant differences between age groups regarding sex, laboratory test results, proteinuria/hematuria, or disease severity scores (Acute Physiology and Chronic Health Evaluation, APACHE), except for a longer hospital stay in the elderly group ($p = 0.038$). Several studies have indicated that aging diminishes the kidneys' ability to recover from AKI[71]. The proposed mechanism behind this decline may involve the age-related loss of specific tubular cells with regenerative capacity. Elderly patients with AKI tend to have worse outcomes compared to their non-AKI counterparts during hospitalization and have a poorer prognosis, with higher short-term and long-term mortality even after discharge from the initial admission[72].

Challenges

As people age, they experience a loss of muscle mass, which can lead to a lower baseline serum creatinine (sCr) level in the elderly compared to standard norms. This reduced baseline may mask a pathological increase due to kidney damage, resulting in underdiagnosis or delayed diagnosis. Additionally, low protein intake among older adults further lowers creatinine levels, contributing to this baseline reduction. Consequently, diagnosing acute kidney injury (AKI) based solely on sCr levels is often insufficient. Fluid overload or sepsis is more common in older patients, leading to a disproportionately lower rise in sCr[73,74] . Furthermore, the rate of sCr elevation in the elderly is generally much slower than in the general population, which can result in a delayed diagnosis of AKI[75]. While alternative markers such as cystatin C, interleukin-18, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1 could be considered, they are not routinely available in clinical settings.

The mortality rate among elderly patients with AKI is significantly high and may exceed that of other age groups. Most studies involving elderly ICU patients with AKI report mortality rates around 63.5%, with some estimates reaching as high as 76.2%[76]. This has a profound impact on overall patient outcomes.

The elderly population often presents with comorbidities like diabetes and hypertension, complicating treatment approaches and imposing economic burdens, particularly in developing countries. AKI is independently linked to long-term mortality in older adults; approximately 28% of patients over 65 do not regain renal function following an episode of AKI, which can lead to chronic kidney disease (CKD) due to insufficient compensatory mechanisms and regeneration[77]. Moreover, 18.9% of elderly patients with AKI progress to dialysis treatment, and 66.7% of this group may die within one year[78]. Even minor fluctuations in creatinine levels among elderly patients are associated with an increased risk of long-term mortality, with more significant changes correlating with a higher risk of death[79] .

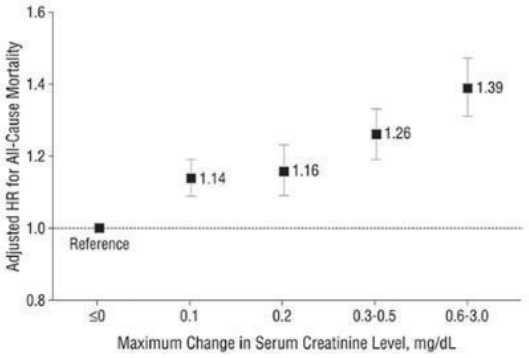

Figure 7: *Adjusted hazard ratios (HRs) and 95% confidence intervals for all-cause mortality according to maximum level of serum creatinine level increase during hospitalization.*

Currently, there are no established therapies to stop or reverse the age-related decline in glomerular filtration rate (GFR). Treatments designed to boost GFR by enhancing the filtration capacity of remaining functional nephrons may actually be detrimental, potentially causing pathological hyperfiltration in individual nephrons. For instance, studies in animals have shown that hypertrophy and hyperfiltration of functional glomeruli can lead to additional glomerulosclerosis, likely due to stress or injury to podocytes. Standard treatments for chronic kidney disease (CKD), such as angiotensin inhibitors and protein-restricted diets, do not reverse the GFR decline associated with aging, and their efficacy in older adults with age-related CKD remains uncertain[80]. A simulation study indicates that

angiotensin inhibitors provide only minimal benefits for this demographic.

Patients experiencing age-related reductions in GFR may require adjustments to their medication dosages. Furthermore, the decline in GFR related to aging disqualifies older adults from being living kidney donors.

Overall, the typical decrease in GFR associated with aging has little to no effect on life expectancy or the future need for dialysis, which is an essential point to communicate to older patients.

Management Strategies:

Unfortunately, while numerous effective strategies to prevent and treat acute kidney injury (AKI) have been established in experimental animal models, proven strategies for human patients remain limited. Consequently, prevention efforts for elderly patients emphasize acknowledging their heightened vulnerability to AKI. Key strategies include avoiding nephrotoxic agents, ensuring adequate fluid volume prior to known stressors, such as intravenous contrast or nephrotoxic medications, and utilizing off-pump coronary artery bypass surgery in high-risk individuals[81].

General approaches for the prevention of AKI

- Avoidance of nephrotoxins
  - Recognition of potential nephrotoxic agents
  - Recognition of high risk patients and clinical settings
  - Avoidance of concomitant use of multiple nephrotoxins
  - Use of lowest dose and for shortest time possible
  - If applicable, monitoring of drug dose
  - Frequent monitoring of renal function
  - Maintain euvolemia
- Minimization of nosocomial infection
- Extracellular fluid expansion
  - (maintain good urine output, stable hemodynamics)
- Avoid agents that impair renal blood flow autoregulation (NSAIDS, ACE inhibitors, ARBs)
- Pharmacologic interventions if applicable
- Use of computer surveillance systems
  - Identify high risk patients and medications
  - Determine correct dose for GFR

The general principles for managing acute kidney injury (AKI) in elderly patients are akin to those applied to other populations and focus on addressing life-threatening complications such as electrolyte imbalances, severe metabolic acidosis, fluid overload (including pulmonary edema), uremic bleeding, and uremic encephalopathy. Prompt correction of fluid deficits is essential to prevent further worsening of AKI. Once these deficits are addressed, clinicians must continuously monitor the patient's volume status to avoid excessive fluid expansion that could lead to pulmonary edema. Elderly patients are particularly vulnerable to fluid overload, making early interventions crucial to mitigate complications. Treatments for these patients can sometimes do more harm than good.

Effective medication management is vital, including dosage adjustments for renal and liver dysfunction, to appropriately address complications in elderly patients with AKI. Nutritional support for AKI patients, especially in the elderly, is another area that warrants further investigation. Sodium and fluid restrictions may be necessary, and close monitoring of electrolytes is essential. Potassium, phosphorus, and magnesium intake can be limited as needed, and phosphate binders might be required to manage hyperphosphatemia. While mild hypocalcemia and hyperuricemia may occur, they often do not need correction if asymptomatic. If significant acidosis develops ($pH < 7.2$), supplemental bicarbonate can be administered to maintain a safe pH level. Additionally, medication doses should be adjusted based on kidney function impairment, as serum creatinine levels may not accurately reflect true kidney function; thus, monitoring drug levels is advisable. Nutritional support should not be overlooked, as a patient's nutritional status is a critical predictor of prognosis in AKI, and elderly patients are particularly at risk for malnutrition.

Alongside these supportive measures, renal replacement therapy (RRT) may be necessary in severe cases of AKI. Indications for RRT include hyperkalemia, volume overload—especially when accompanied by pulmonary edema—severe acidosis, or overt uremia. RRT is often initiated prophylactically, before these complications arise. Recent studies suggest that the specific modality of RRT does not significantly influence outcomes, and the choice of dialysis modality should be guided by the available resources and expertise at

the local institutionx [3]. A recent large-scale multi-center randomized trial indicated that in critically ill patients, higher intensities of RRT did not lead to improved morbidity or mortality compared to more conventionally dosed RRT[82,84] .

The initiation of RRT in AKI is a debated topic, with discussions surrounding the timing of initiation (early versus late), dosages (high versus low), and methods of administration. Once AKI is confirmed, supportive measures such as hemodialysis should not be withheld solely based on age[85] . However, for elderly patients, it is important to incorporate shared decision-making regarding their life expectancy into the treatment plan. Advanced care planning can clarify patient preferences, and a time-limited trial of dialysis may also be considered. Current literature does not provide strong support for any particular modality or intensity of RRT for AKI[86].

AKI in the Elderly and Mortality

Elderly patients with acute kidney injury (AKI) face a high short-term mortality rate, ranging from 20% to 45%. This rate varies depending on whether the AKI is hospital-acquired (associated with higher mortality) or community-acquired (linked to lower mortality)[87,88]. Additionally, intrinsic AKI carries a poorer prognosis compared to prerenal or postrenal causes. Despite a rise in accompanying comorbidities, overall outcomes have improved in recent years. The short-term mortality associated with AKI in the elderly has continued to decline, reflecting a similar trend in the broader AKI population[89].

Long-term mortality rates remain elevated among patients with AKI, with age being a significant factor[90] Specifically, patients with AKI exhibit 90-day, 6-month, 1-year, and 5-year survival rates of approximately 46–74%, 55–73%, 57–65%, and 65–70%, respectively[91]. Elderly patients with AKI generally experience even higher long-term mortality rates compared to younger individuals, although the extent of this increased risk varies[92]. One report indicated no significant differences in mortality risk between dialysis-dependent patients with AKI after cardiac surgery who were aged 70 years or older and those younger than 70 years. The long-term survival impact of AKI may be moderated by the presence of additional comorbidities, potentially skewing the results.

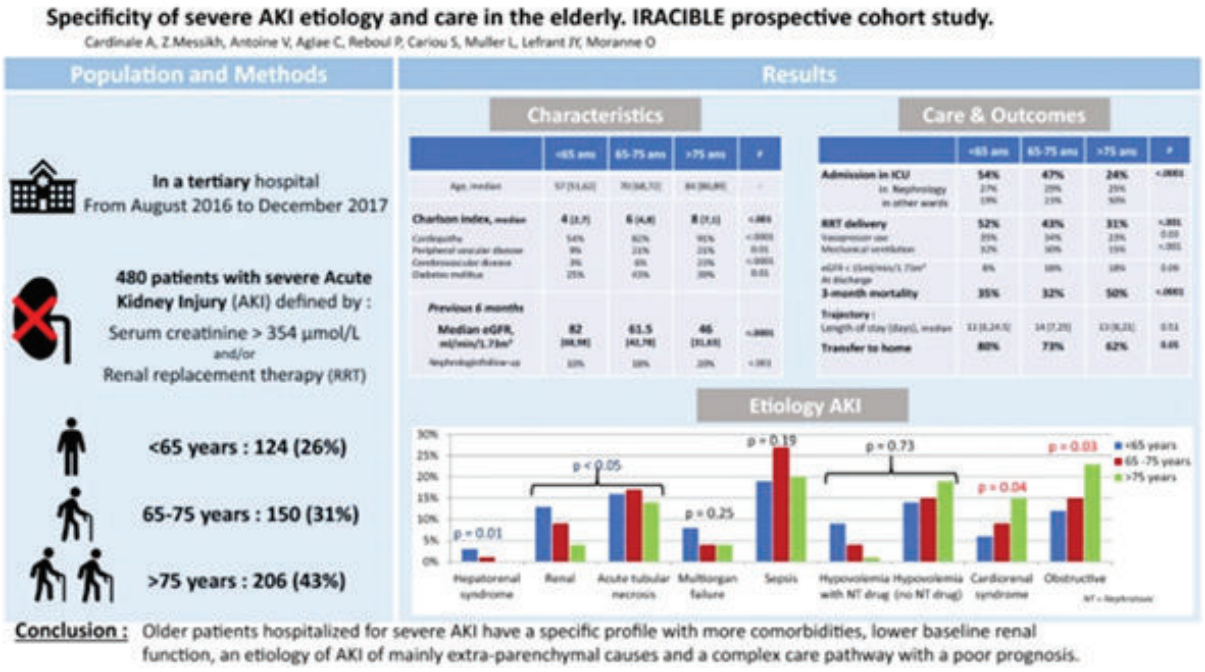

Figure 8: *Older patients hospitalized for severe AKI have more comorbidities, lower baseline renal function, of mainly extra-parenchymal causes and with an overall poor prognosis [5]*.*

Recovery of Renal Function after AKI

A systematic review and meta-analysis have demonstrated that recovery of kidney function after AKI is approximately 28% less likely in patients over 65 years of age[93]. It remains unclear whether this observation is due to the direct effects of advanced age on renal function or the increased prevalence of comorbidities (including baseline chronic kidney disease, CKD) in older adults. Long-term recovery is also less probable in this population, with AKI in the elderly often leading to the development of CKD. The diminished likelihood of renal recovery in older patients may stem from aging-related impairments in kidney repair capacity.

The ability of renal epithelial cells to proliferate declines with age, as does the functionality of progenitor and stem cells essential for tubular repair[94] . Therefore, it may not be straightforward to determine whether age itself is an independent predictor of poor prognosis, as other comorbid conditions may play a more significant role in influencing the risk of unfavorable outcomes[95].

Progression to CKD and ESRD

Acute kidney injury (AKI) is no longer viewed as entirely reversible, and the progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD) is frequently reported. The diagnosis of AKI during hospitalization is associated with a 3–20-fold increased risk of subsequent CKD in the following months to years[96,97]. A recent meta-analysis emphasized that patients over 65 years diagnosed with AKI have a significantly higher likelihood of not recovering renal function compared to younger individuals (relative risk 1.28; $p < 0.01$)[98] .

Mechanisms explaining the increased risk of CKD following AKI can be inferred from experimental models and include diminished proliferative capacity of tubular epithelial cells, lower rates of cellular turnover, reduced expression of growth factors, and a decreased ability to recruit progenitor cells to injury sites for repair[99] .

Quality of Life after Recovery

The quality of life (QoL) following AKI is rarely examined in the literature, and none of the existing studies focus on the elderly population. One small-scale study indicated that AKI survivors have lower physical health summary scores but comparable mental health scores when compared to the general population, as assessed by the 36-Item Short Form Health Survey (SF-36)[100] . Another study suggested that there was no significant decrease in QoL after three years of follow-up in survivors of AKI requiring dialysis, based on the Medical Outcomes Study (MOS-SF20) questionnaires[101]. Conversely, a separate study identified lower overall health-related QoL in dialysis-dependent AKI survivors after 2.4 years of follow-up[102]. A Finnish nationwide survey corroborated these findings, using EuroQoL instruments[103].

Conclusion

The elderly are at a heightened risk for acute kidney injury, and the incidence of AKI within this population is increasing over time. This rise can be attributed to various factors, including the increased susceptibility of the kidneys to stressors and insults as individuals' age. While short-term survival rates for AKI appear to be improving, even among the elderly, this group is particularly vulnerable to AKI due to comorbidities, polypharmacy, and various interventions that may harm renal function. Furthermore, AKI in elderly patients is often identified more slowly or even masked, which raises the risk of complications and adverse outcomes. The occurrence of AKI is linked to an elevated risk of mortality as well as long-term negative effects, such as CKD or ESRD, in older adults. Healthcare providers must enhance their awareness of AKI and its devastating impacts on the elderly, allocating more resources to reduce the incidence of AKI in this vulnerable population.

Important Points

- Elderly individuals are at a greater risk for developing acute kidney injury (AKI).
- Specific hemodynamic, metabolic, molecular, and structural changes contribute to the increased vulnerability of the aging kidney to injury [104].
- Certain causes of AKI, such as postrenal obstructive disease, ischemic acute tubular necrosis (ATN), and hemodynamically mediated AKI, are more prevalent in older adults.
- Multiple underlying factors often contribute to the onset of AKI.
- Diagnostic and therapeutic challenges in AKI remain consistent between elderly patients and the general population.

- The likelihood of renal recovery after AKI is generally diminished in older adults [105].

Author's contribution

Mrittika Mostafi searched and collected most of study materials and assisted in writing the chapters on pathophysiology. The principal author contributed rest of the chapters.

Conflict of interest and financial declaration

There is no financial involvement from any source and there is nothing to declare

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