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RESEARCH ARTICLE

A Multi-Stage Observational Study to Understand the Evolution of Acute Kidney Injury into Chronic Kidney Disease

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Abstract: Acute kidney injury (AKI) is a sudden decline in renal function, often progressing to chronic kidney disease (CKD) or end-stage renal disease (ESRD) if not managed promptly. This multi-stage observational study aimed to assess the transition of AKI to CKD by evaluating biomarker levels and associated risk factors. A cohort of 300 AKI patients was enrolled, categorized into five severity stages based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Serum creatinine, blood urea nitrogen (BUN), kidney injury molecule-1 (KIM-1), and C-reactive protein (CRP) levels were monitored for up to 20 months. The study revealed a significant correlation between AKI severity and the likelihood of transitioning to CKD. Patients in Stage 5 AKI had the highest risk, with 100% developing CKD. Stages 3 and 4 also exhibited high transition rates of 78.4% and 89.7%, respectively. Conversely, Stage 1 and 2 patients showed lower transition rates of 36.1% and 13%, respectively. The study highlights the importance of early AKI identification and management to prevent CKD progression. Future research should explore the utility of biomarkers for early CKD detection, risk stratification, and personalized treatment plans.

Keywords: Acute Kidney Injury; AKI-CKD Transition; KDIGO; Chronic Kidney Disease; Biomarker.

1. Introduction

1.1. Role of Kidneys

The kidneys play a pivotal role in maintaining homeostasis and regulating various physiological processes within the body. They are essential for blood pressure regulation, glucose homeostasis, iron detoxification, and acid-base balance. The kidneys are responsible for regulating blood pressure by managing sodium and water balance, which affects intravascular volume and consequently, blood pressure. Additionally, they are involved in glucose homeostasis by producing, filtering, reabsorbing, and utilizing glucose, as well as eliminating insulin from circulation.

Furthermore, the kidneys contribute to iron detoxification through their role in the heat absorption and catabolism pathways, facilitating iron recirculation. They also aid in maintaining proper pH levels in body fluids by retaining acid-base equivalents and eliminating waste products, ammonia, inorganic phosphate, acidic and basic equivalents, and other substances. Overall, the kidneys perform a multitude of crucial functions that are essential for maintaining the body's overall balance and homeostasis.

1.2. Progression of AKI to CKD

Acute kidney injury (AKI) refers to an abrupt loss of kidney function that occurs within hours or days, encompassing both impairment or loss of function and structural injury. AKI can be classified into three categories: intrinsic acute kidney disorders, acute post-renal obstructive nephropathy, and pre-renal AKI. Pre-renal and post-renal AKI are manifestations of extra-renal conditions that diminish glomerular filtration rate (GFR), while only "intrinsic" AKI indicates actual kidney disease.

Many AKI hospital survivors have been diagnosed with end-stage renal disease (ESRD) and chronic kidney disease (CKD), with renal progression occurring in an estimated 4.9 cases per 100 patients after AKI. The inability to accurately identify individuals at high risk of developing CKD/ESRD stems from the difficulty in detecting early nephron damage, which is one of the challenges in effective AKI management.

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1.3. Tubular Markers for AKI Progression

Renal biomarkers implicated in the transition of AKI to CKD have two independent but related components: the identification and localization of kidney injury in a particular location and the identification and localization of kidney injury in general.

1.3.1. Kidney Injury Molecule 1 (KIM-1) in Serum and Urine

KIM-1 is a 38.7-kDa transmembrane protein that is minimally expressed in healthy kidneys but appears significantly elevated after ischemia-reperfusion injury. It peaks around 48 hours and is produced by proliferating dedifferentiated epithelial cells in the proximal tubules.

1.3.2. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is a 25-kDa protein strongly expressed in various human organs, including the lung, salivary gland, colon, stomach, prostate, trachea, liver, and kidney. Intra-renal NGAL levels increase following ischemic or nephrotoxic kidney injury and can be detected in the urine as early as three hours after the injury.

1.3.3. Liver-Type Fatty Acid-Binding Protein (L-FABP)

L-FABP is a 14-kDa protein expressed in proximal tubules. Urinary L-FABP levels rise almost immediately after tubular damage, peak within 6 hours, and show a strong positive correlation with renal ischemia time.

1.3.4. Interleukin-18 (IL-18)

IL-18 is a 22-kDa pro-inflammatory cytokine secreted by proximal tubular cells. Urinary IL-18 levels increase with renal injury, and its binding to NOD-like receptors activates proteolytic enzymes like caspase-1, producing mature IL-18. IL-18 modulates the inflammatory response and initiates inflammation by attracting neutrophils and microglia through the activation of the NF-ϰB pathway, involving TNF-α, iNOS, and chemokines such as MCP-1 and MIP-1..

1.4. Pathological mechanisms enabling AKI to progress to CKD or ESRD

The progression of AKI into CKD or ESRD is indicative of a chronic kidney disease process characterized by recurrent or continuous cellular damage and/or abnormal repair mechanisms. There is an increasing recognition that severe or recurring renal injury triggers aberrant repair mechanisms that lead to glomerulosclerosis, vascular rarefaction, and renal fibrosis – all of which are associated with clinical CKD and ESRD. Ischemia-reperfusion-induced oxidative stress is a major contributor to the progression of acute kidney injury (AKI), as the elevation of asymmetric dimethylarginine promotes tubular necrosis. Activation of the renin-angiotensin system (RAS) has been implicated in the progression of AKI and the transition from acute to chronic kidney injury.

1.5. Risk factors

1.5.1. Diabetes

Diabetes is a leading cause of kidney disease. Elevated blood sugar levels in diabetic patients can damage the blood vessels in the kidneys.

1.5.2. High Blood Pressure

High blood pressure can damage the blood vessels in the kidneys.

1.5.3. Family History of Kidney Disease

Having a family history of kidney disease increases an individual's risk of developing the condition.

1.5.4. Obesity

Being overweight or obese increases the risk of developing diabetes and high blood pressure, both of which can harm the kidneys.

1.5.5. Smoking

Smoking damages blood vessels throughout the body, including those in the kidneys.

1.5.6. Age

The risk of kidney disease increases with advancing age.

1.6. Management of AKI

The Identification of the underlying cause of AKI (post-renal, intra-renal, or pre-renal) is the first step in management. Specific treatments may be required depending on the cause, such as treating shock or dehydration in pre-renal AKI or clearing an obstruction in post-renal AKI.

1.6.1. Fluid Management

Maintaining the appropriate balance of fluids is crucial.

1.6.2. Electrolyte Management

AKI can disrupt the balance of electrolytes, necessitating dialysis, dietary modifications, or medications to restore equilibrium.

1.6.3. Dietary Adjustments

Restricting protein, phosphorus, potassium, and sodium intake may be recommended to reduce the amount of waste products the kidneys must filter.

1.6.4. Medication Management

Certain medications, such as diuretics for blood pressure control or excess fluid removal, may be used cautiously.

1.6.5. Avoidance of Nephrotoxic Agents

During AKI, medications and substances known to be nephrotoxic, such as certain antibiotics and pain relievers, should be avoided.

1.6.6. Renal Replacement Therapy (RRT) or Dialysis

In severe cases of AKI where the kidneys are unable to function normally, RRT or dialysis may be required to artificially remove waste materials and excess fluid from the circulation.

1.6.7. Regular Monitoring

Continuous monitoring of kidney function, electrolytes, and other indicators is essential to assess progress and make necessary treatment adjustments.

1.6.8. Long-term Follow-up

Some patients may remain at risk for chronic kidney disease after recovering from AKI, necessitating long-term monitoring and management.

1.7. Management of CKD

The degenerative disorder known as chronic kidney disease (CKD) causes the kidneys to progressively lose their ability to filter waste materials from the blood. Although there is no cure, effective management can slow the progression of the disease and improve the patient's quality of life. If diabetes and high blood pressure are contributing factors, controlling these conditions through medication, lifestyle modifications, and routine monitoring is essential for managing CKD. Maintaining a healthy diet that restricts sodium, potassium, phosphorus, and protein intake, also known as a renal diet, can reduce the strain on the kidneys. Consulting with a dietitian for personalized advice is recommended. Regular physical activity, such as moderate exercise most days of the week, aids in weight management, blood pressure control, and overall well-being. Smoking cessation is crucial, as smoking exacerbates kidney damage and accelerates the progression of chronic renal disease.

Weight management is another important aspect of CKD management, as maintaining a healthy weight helps reduce the burden on the kidneys and improve blood pressure regulation. Routine check-ups and monitoring are essential for evaluating the course of CKD and making necessary treatment adjustments. Regular laboratory testing, including blood and urine analysis, is vital for monitoring kidney function, electrolyte levels, and other markers of CKD health. In advanced stages of CKD, when the kidneys can no longer function properly, dialysis may be required to artificially remove waste materials and excess fluid from the blood. For some patients, a kidney transplant from a deceased or living donor may provide a long-term solution for renal failure

1.8. Prevention of AKI to CKD Progression

While the progression of acute kidney injury (AKI) to chronic kidney disease (CKD) cannot be entirely prevented, several measures can be taken to reduce the risk and minimize further injury. Early identification and prompt treatment of AKI are crucial. The sooner AKI is recognized and managed, the less likely it is to progress to CKD. Treating the underlying cause of AKI, whether

post-renal (obstructed urinary tract), intra-renal (direct kidney injury), or pre-renal (reduced blood flow), is essential to prevent further damage. During and after AKI recovery, a temporary renal diet limiting protein, phosphorus, potassium, and salt intake may be advised to reduce the amount of waste materials the impaired kidneys must filter. Avoiding nephrotoxic drugs or substances that can damage the kidneys, such as certain antibiotics and pain relievers, is also important. Electrolyte control is crucial, as AKI can disrupt the balance of electrolytes. Dialysis, dietary modifications, or medications may be required to restore equilibrium. To prevent future kidney damage, it is imperative to manage underlying medical conditions such as diabetes and high blood pressure, maintain a healthy weight, and quit smoking. Frequent monitoring of blood pressure, kidney function, and other indicators following AKI recovery enables prompt identification of potential issues and appropriate intervention. Emerging therapies, including drugs that reduce inflammation, promote kidney repair, and protect the kidneys from fibrosis (scarring), are being researched to develop novel treatments that specifically address the AKI-to-CKD transition. Additionally, the potential of stem cell therapy and other regenerative medicine techniques to repair damaged kidney tissue after AKI injury is also being explored. The objective of this research is to examine the transition from acute kidney injury (AKI) to chronic kidney disease (CKD) by evaluating biomarker levels and associated risk factors in a large cohort of AKI patients

2. Materials and methods

2.1. Study design

To better understand the transition from acute kidney injury (AKI) to chronic kidney disease (CKD), 300 individuals with AKI were enrolled in this prospective cohort study

2.2. Participants

2.2.1. Inclusion criteria

- Adults (age ≥ 18) who have been diagnosed with AKI based on Kidney Disease Improving Global Outcomes (KDIGO) criteria are eligible for inclusion.
- Availability of baseline and follow-up biomarker data.
- Ability to provide informed consent

2.2.2. Exclusion criteria

- Pre-existing chronic kidney disease (eGFR of less than 60 ml/min/1.73 m^2 for a minimum of three months).
- Dialysis-dependent end-stage kidney disease (ESKD).
- Pregnancy or breastfeeding

2.3. Data collection

Baseline demographic and clinical data, including age, sex, ethnicity, comorbidities, medications, cause of AKI, and severity of AKI (KDIGO stages)

2.4. Biomarkers

- Serum and urine creatinine levels at baseline, three, six, and twelve months.
- Additional relevant biomarkers (such as urine albumin-to-creatinine ratio (UACR), NGAL, KIM-1, and cystatin C) for AKI and the progression of CKD

Follow-up Data

- eGFR measured at follow-up visits.
- Onset of CKD according to KDIGO criteria or a sustained eGFR of less than 60 ml/min/1.73 m^2 for a minimum of three months.
- All biomarkers will be tested in a central laboratory using established analytical performance standardized assays

2.5. Statistical Analysis

- Baseline characteristics and biomarker levels will be summarized using descriptive statistics.
- Logistic regression analysis, adjusting for relevant confounders, will be used to evaluate the association between baseline biomarker levels and the onset of chronic kidney disease at a 12-month follow-up.
- Time-to-event analysis, such as Cox proportional hazards, will be employed to examine the impact of baseline biomarkers on the time to development of chronic kidney disease.

- Subgroup analysis may be conducted based on the cause or severity of AKI.

2.6. Ethical Considerations

- Informed consent will be obtained from all participants.
- Participant data will be kept confidential and anonymized.
- The study will be conducted in compliance with regional ethical standards and the Declaration of Helsinki.

2.7. Data Dissemination

The study findings will be presented at scientific conferences and published in peer-reviewed journals.

2.8. Limitations

This study has potential limitations, including the possibility of selection bias, confounding variables, and loss to follow-up.

2.9. Strengths

The prospective design and consistent data collection will enhance the quality and reliability of the findings. This study will be the first to examine the association of a comprehensive panel of biomarkers with AKI-to-CKD transition in a large cohort of patients.

2.10. Future Directions

Future studies could investigate the utilization of identified biomarkers for risk assessment, early CKD detection, and the development of personalized treatment plans for AKI patients

3. Results and discussion

3.1. Results

The study enrolled 300 patients with acute kidney injury (AKI) and categorized them based on severity stages according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Stage 1 AKI had the highest number of patients at 108, who were monitored for less than 20 months. Stage 2 AKI had 77 patients monitored for less than 12 months, with serum creatinine levels below 3 mg/dL. Stage 3 AKI had 51 patients monitored for less than 10 months, with serum creatinine levels below 8 mg/dL. Stage 4 AKI had 39 patients monitored for less than 5 months, and Stage 5 AKI had 25 patients monitored for less than 2 months. The study observed that serum creatinine, blood urea nitrogen (BUN), kidney injury molecule-1 (KIM-1), and C-reactive protein (CRP) levels showed a steady increase, peaking around day 10 and gradually declining thereafter. The elevated KIM-1 levels, along with high creatinine and BUN levels, indicate renal impairment and the potential presence of acute inflammatory events. A striking finding was the positive correlation between the severity of AKI stages and the number of patients transitioning to chronic kidney disease (CKD). Patients in Stage 5 AKI had a 100% likelihood of developing CKD, highlighting the critical importance of early detection and prompt treatment of AKI to prevent progression to CKD. Overall, the study found that approximately 50% (149 out of 300) of the AKI patients transitioned to CKD, underscoring the significant risk associated with AKI if not appropriately managed. The results are shown in Table 1.

Table 1. Results of the observational study

Stage of AKI	Number of Patients	Number Transitioned to CKD	Percentage Transitioned
1	108	39	36.10%
2	77	10	13.00%
3	51	40	78.40%
4	39	35	89.70%
5	25	25	100.00%

3.2. Discussion

The results of this study highlight the concerning progression of acute kidney injury (AKI) to chronic kidney disease (CKD) and the potential long-term consequences if AKI is not promptly and effectively managed. The observed worsening of renal function,

as evidenced by the elevated biomarker levels, suggests that AKI can initiate a cascade of events that compromise kidney function and increase the risk of CKD development.

The significant reduction in estimated glomerular filtration rate (eGFR) and the corresponding increase in biomarker values, such as BUN, serum creatinine, KIM-1, and CRP, indicate ongoing kidney damage and inflammation. These biomarkers serve as valuable indicators of renal impairment and can aid in monitoring disease progression and guiding treatment strategies. The finding that advanced AKI stages, particularly Stages 4 and 5, are associated with higher rates of transition to CKD is of particular concern. Patients in these severe stages are more likely to experience long-term renal impairment and may require intensive supportive care, including dialysis or kidney transplantation. This underscores the importance of early intervention and aggressive management of AKI to prevent further deterioration and potential progression to CKD. Interestingly, even patients in Stage 1 AKI showed a 36.1% transition rate to CKD, suggesting that even mild AKI can potentially lead to long-term effects on kidney function. This highlights the need for vigilant monitoring and follow-up of all AKI patients, regardless of the initial severity.

The study's findings emphasize the complex interplay between AKI and CKD, and the importance of understanding the underlying pathological mechanisms that enable this transition. Further research is needed to elucidate the specific molecular pathways and factors that contribute to the progression from AKI to CKD, which could potentially lead to the development of targeted therapeutic interventions. Additionally, the role of biomarkers in predicting the risk of CKD development and guiding personalized treatment plans warrants further investigation. Incorporating a comprehensive panel of biomarkers into clinical practice could facilitate early identification of high-risk individuals and prompt appropriate management strategies to mitigate the long-term consequences of AKI s

4. Conclusion

Overall, this study found a significant correlation between the severity of acute kidney injury (AKI) and the likelihood of transitioning to chronic kidney disease (CKD). The risk of progression to CKD was approximately 49.67%. These findings underscore the importance of early identification and prompt treatment of AKI to prevent further deterioration and reduce the risk of CKD development. Future research could explore the utility of identified biomarkers for early CKD detection, risk stratification, and the development of personalized treatment plans for AKI patients

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Author's short biography

Yedukondalu Ainampudi

Yedukondalu Ainampudi, currently in his fifth year of Pharm D studies, is deeply passionate about medical research and epidemiology.

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Jahnavi Peravali, a fifth-year Pharm D student, harbors a fervent interest in clinical research and wanted to serve as a dedicated medical assistant.

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Sai Mounika Puritipati, currently immersed in her fifth year of Pharm D studies, is driven by a keen interest in Hospital Administration.

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